INSTITUT NATIONAL D'ASSURANCE
MALADIE-INVALIDITE
SERVICE DES SOINS DE SANTE
Comité d' évaluation des pratiques
médicales en matière de médicaments

PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

Systematic literature review: full report

Consensus conference
November 21st 2013
Auditorium Lippens (Royal Library)
Brussels

This literature review was performed by vzw Farmaka asbl and was followed-up by a reading committee.

Researchers

Hera Decat MD, *vzw Farmaka asbl*
Griet Goesaert MD*, vzw Farmaka asbl*
Hilde Habraken Lic, *vzw Farmaka asbl*
Thérèse Leroy Lic, *vzw Farmaka asbl*
Karijn Van den Maagdenberg, Dr. Ir., *vzw Farmaka asbl*
Gerben Vandermeiren MD, *vzw Farmaka asbl*
Sofie Wouters Lic*, vzw Farmaka asbl*

Reading committee
Henrard Gilles, MD, ULg, Liège
Haentjens Patrick, MD, PhD, VUB, Brussel
Van Meerhaeghe Alain, MD, CHU, Charleroi
Verhoeven Veronique, MD, PhD, UA, Antwerpen

Administrative and IT support

Stijn Dumon, *vzw Farmaka asbl*

Translation
Miles NV
Sophie Vanderdonck vzw Farmaka asbl

TABLE OF CONTENTS

Abbreviations

ACL: anterior cruciate ligament
AE: adverse events
ALT: alanine aminotransferase
AR: absolute risk
ARD absolute risk difference
ARR: absolute risk reduction
ARI: absolute risk increase
ASA: acetyl salicylic acid
AST: aspartate aminotransferase
AT: serum alanine aminotransferase and aspartate aminotransferase.
BID: twice daily
CES: compression elastic stocking
CI: confidence interval
CO: crossover RCT
DB: double blind
DUS: duplex ultrasound
DVT: deep vein thrombosis
GCS: graduated compression stockings
HIT: heparin induced thrombocytopenia
HR: hazard ratio
INR: international normalized ratio
IPC: intermittent pneumatic compression
ITT: intention-to-treat analysis
LMWH: low molecular weight heparin
MA: meta-analysis
n: number of patients
N: number of studies
NA: not applicable
NR: not reported
NS: not statistically significant
NT: no statistical test
OA: oral anticoagulation
OL: open label
OR: odds ratio
PA: pulmonary angiogram
PE: pulmonary embolism
PG: parallel group RCT
PO: primary outcome
PP: per protocol analysis
PTS: post-thrombotic syndrome
QD: once daily

RCT: randomized controlled trial
RR: relative risk
SB: single blind
THA: total hip arthroplasty
THR: total hip replacement
TKA: total knee arthroplasty
TKR: total knee replacement
UFH: unfractionated heparin
ULN: upper limit of the normal range
VKA: vitamin K antagonists
VTE: venous thromboembolism

1 Methodology

1.1 Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference on 'Prevention and treatment of venous thromboembolism' which will take place on November 21 2013.

1.1.1 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are

Question – Vraag 1
Quels sont les facteurs de risque de thrombose veineuse profonde et d'embolie pulmonaire?
Welke zijn de risicofactoren voor een diepe veneuze trombose en longembolie?

Question – Vraag 2
Comment pose-t-on le diagnostic de thrombose veineuse profonde / embolie pulmonaire en 2013 ?
Hoe wordt de diagnose van diepe veneuze trombose / longembolie in 2013 gesteld?

Question – Vraag 3
Quel est le traitement d'une thrombose veineuse profonde / embolie pulmonaire en première ligne de soins ?
Hoe wordt een diepe veneuze trombose / longembolie in de eerstelijnsgezondheidszorg behandeld?
- *quel est le traitement initial ?*
  welke startbehandeling wordt toegepast?
- *quelle est la durée optimale du traitement initial?*
  wat is de optimale duur van de startbehandeling?
- *quand faut-il hospitaliser ?*
  wanneer moeten patiënten in het ziekenhuis worden opgenomen?
- *quel médicament utilise-t-on pour la prévention de la récidive et pour quelle durée ?*
  welk geneesmiddel wordt er gebruikt om een recidief te voorkomen en hoe lang?
- *comment faut-il prévenir ou traiter le syndrome postphlébitique ?*
  hoe wordt het postflebitissyndroom voorkomen of behandeld?

Question – Vraag 4
Quand et comment traiter une thrombose veineuse superficielle?
Wanneer en hoe wordt een oppervlakkige veneuze trombose behandeld?

Question – Vraag 5
Quel est le traitement préventif après un premier évènement TEV ?
Wat is de preventieve behandeling na een eerste voorval van VTE?
Quelle est sa durée ?
Wat is zijn duur?
Quel est le traitement préventif après récidive(s) de TEV ?
Wat is de preventieve behandeling na herhaling(en) van VTE?

Quelle est sa durée ?
Wat is zijn duur?
Quel est le traitement d'un syndrome post-phlébitique ?
Wat is de behandeling van een postflebitissyndroom?

Question – Vraag 6
Un traitement préventif d'une TEV est-il indiqué en cas de :
Is een preventieve behandeling van een VTE aangewezen in geval van een:
- *chirurgie orthopédique majeure ?*
  majeure orthopedische ingreep?
- *autre chirurgie majeure (non oncologique) ?*
  andere majeure (niet-oncologische) ingreep?
- *arthroscopie du genou ?*
  artroscopie van de knie?
- *immobilisation plâtrée ?*
  immobilisatie met gipsverband?
- *alitement pour raison médicale ?*
  bedrust om medische redenen?
- *voyage avec immobilisation prolongée ?*
  reis met langdurige immobilisatie?

Quand et comment ?
Wanneer en hoe moet dit gebeuren?

Question – Vraag 7
Un traitement préventif d'une TEV est-il indiqué et si oui lequel
Is een preventieve behandeling van een VTE aangewezen en zo ja, welke:
- *en chirurgie oncologique ?*
  in geval van oncologische heelkunde?
- *chez le patient oncologique hors chirurgie*
  bij kankerpatiënten die niet heelkundig behandeld worden?

Pour quelle durée ?
Hoe lang wordt er behandeld?

Question – Vraag 8
Gestion d'un traitement anticoagulant / antithrombotique en première ligne de soins
Management van een behandeling met anticoagulantia / antitrombotische middelen in de eerstelijnsgezondheidszorg
- *interactions importantes, médicamenteuses et non médicamenteuses (listes de référence), y compris automédication ?*
  ernstige medicamenteuze en niet-medicamenteuze interacties (referentielijsten), met inbegrip van zelfmedicatie?
- *arrêt en fonction de quels interventions chirurgicales et dans quel délai ?*
  stopzetting in functie van welke heelkundige ingrepen en binnen welke termijn?
- *surveillance biologique nécessaire (initiale et termes à prévoir)*
  de biologische parameters die moeten opgevolgd worden? (Wanneer starten en hoe lang opvolgen?)
- *quels facteurs / interventions pour améliorer l'observance thérapeutique et la sécurité d'emploi ?*
  mogelijke factoren / interventies om de therapietrouw en de gebruiksveiligheid te verbeteren?

1.1.2 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss selected guidelines regarding jury questions numbers 1, 2, 3, 5 and 6.

- To search for systematic reviews, meta-analyses, RCTs (and large observational studies for rare safety endpoints) for the following populations, comparisons and endpoints:

1.1.2.1 Populations

The following populations are to be evaluated.

1. Patients presenting with VTE (lower limb DVT or PE) (Excluded: other DVT locations)

2. Patients who are at risk of developing VTE, because of	
Surgery	Major orthopaedic surgery • Elective hip replacement • Elective knee replacement • Hip fracture surgery
	Non-major orthopaedic surgery • Knee arthroscopy • Lower limb cast (also non-surgery) (Excluded: all other orthopaedic surgery)
	General surgery • Gastrointestinal • Gynaecological • Laparoscopic • Thoracic • Urological Surgery in cancer patients (Excluded: cranial, spinal, day-care, plastic, ENT, oral, maxillofacial, cardiac, vascular surgery, caesarean section)
Medical condition (with immobilisation)	• General medical patient • Stroke • Cancer (Excluded: acute coronary syndrome, spinal injury, non-cancer palliative care, critical care, pregnancy, major trauma)
Travel with prolonged immobilisation	

1.1.2.2 Interventions

Only products with a registered indication in Belgium will be considered. These are listed here:

Pharmacological	
○ **Antiplatelet**	Acetylsalicylic acid
○ **Anticoagulants**	
○ **Heparin** ○ Unfractioned heparin (UFH) ○ Low molecular weight heparin (LMWH)	 Dalteparin Enoxaparin Nadroparin Tinzaparin
○ **Vitamin K antagonists (VKA)**	Acenocoumarol Fenprocoumon Warfarin
○ **Thrombin inhibitors**	Dabigatran (new antico)
○ **Factor Xa inhibitors**	Apixaban (new antico) Rivaroxaban (new antico) (excluded: fondaparinux)
Non-pharmacological	
○ **Graduated compression stockings** (GCS) (Excluded: other compression or motion devices, vena cava filter)	

1.1.2.3 Comparisons

The following comparisons are to be reported

a. Patients presenting with VTE

- Initial treatment
  - Pharmacological interventions

	PLacebo	UFH	LMWH	VKA	New antico
UFH					
LMWH					
VKA					
New antico					

  - Other comparisons
    - Ambulatory versus hospital care

- Long-term treatment (secondary prevention)
  - Pharmacological interventions

	PLacebo	UFH	LMWH	VKA	New antico
UFH					
LMWH					
VKA					
New antico					
Antiplatelet					

- Other comparisons
    - Longer duration versus shorter duration

- Prevention of postthrombotic syndrome
    - GCS versus no GCS
    - Short (below knee) GCS versus long (thigh length) GCS
    - Longer duration versus shorter duration of GCS

b. Patients at risk of VTE

- Pharmacological and non-pharmacological interventions

	PLacebo	GCS	UFH	LMWH	VKA	New antico	ASA
UFH							
LMWH							
VKA							
New antico							
LMWH+GCS							
VKA+GCS							
New antico + GCS							
ASA							

- Other comparisons
    - Longer duration versus shorter duration treatment

1.1.2.4 Endpoints

The following endpoints are to be reported:

- All cause mortality
- Deep-vein thrombosis (DVT) symptomatic / non symptomatic
- Pulmonary embolism (PE) symptomatic/non-symptomatic
- Major bleeding events
- Minor bleeding events
- post-thrombotic syndrome (PTS)
- Patient preference, quality of life, ease of use

1.1.2.5 Study criteria

- Efficacy
    - Design
        - RCT
        - At least single blind when blinding is possible.
    - Duration of RCT: no duration stated.
    - Minimum number of participants: minimum 40 per study arm. For studies with multiple treatment arms, we looked at the number of participants in comparisons relevant to our search.
    - Phase III trials (no phase II trials)

- Safety
    - Information from the selected RCTs
    - Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI), Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG), European Medicines Agency (EMA), Meyler's Side Effects of Drugs (15th edition), Martindale: The complete drug reference (36th edition), Farmacotherapeutisch Kompas.
    - Additional information from large observational studies.

1.1.2.6 Guidelines

Only guidelines that report levels of evidence/recommendation are to be selected.
Only guidelines from 2009 onwards are to be selected.
Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation.
Similarities and discrepancies between guidelines are to be reported.
The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

1.2 Search strategy

1.2.1 Principles of systematic search

Relevant literature was searched in a stepwise approach.

- Firstly, sources that report and discuss data from systematic reviews, meta-analyses and original trials, like Clinical Evidence were consulted. Guidelines were consulted to look up additional relevant references.
- In a second step we have searched for large systematic reviews from reliable EMB-producers (NICE, AHRQ, the Cochrane library) that answer our research questions. One or more systematic reviews were selected as our basic source. From these sources, references of relevant publications were screened manually.
- In a third step, we conducted a systematic search for randomised controlled trials (RCTs), meta-analyses and smaller systematic reviews that were published after the search date of our selected systematic reviews.

The following electronic databases have been searched

- Medline (PubMed)
- Cochrane Library

A number of other sources were consulted additionally: relevant publications, indices of magazines available in the library of vzw Farmaka asbl: mainly independent magazines that are a member of the International Society of Drug Bulletins (ISDB) such as Geneesmiddelenbulletin (The Netherlands), Folia Pharmacotherapeutica (Belgium), La Revue Prescrire (France), Drug & Therapeutics Bulletin (UK), Therapeutics Letter (Canada), Geneesmiddelenbrief (Belgium), Arzneimittelbrief (Germany),…

Guidelines were searched through the link “evidence-based guidelines” on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to ‘guideline search engines’, like National Guideline Clearinghouse and G-I-N.

1.2.2 Search strategy details

As a source document, the following systematic reviews or meta-analyses were selected

- National Clinical Guideline Centre. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing Clinical Guideline Methods, evidence and recommendations. June 2012. http://www.nice.org.uk/nicemedia/live/13767/59711/59711.pdf

- National Clinical Guideline Centre - Acute and Chronic Conditions Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. Methods, evidence and guidance. 2010. http://www.nice.org.uk/nicemedia/live/12695/47920/47920.pdf

A search strategy was developed in Pubmed to find relevant RCTs that appeared after the search date of above publications (http://www.ncbi.nlm.nih.gov/pubmed/).
In some cases, when the selected systematic reviews were not sufficient (e.g. no search for all drugs), an additional search was conducted for RCTs that appeared before the search date of the selected systematic review.

The following search strategy was used:

(((((Thromboembolism OR Thrombophlebitis OR Venous Thrombosis OR vein thrombosis[TIAB] OR dvt OR vte OR Pulmonary Emboli*) AND (Heparin* OR UFH OR LMWH OR dalteparin OR Enoxaparin OR nadroparin OR tinzaparin OR Danaparoid OR vitamin K antagonist* OR anticoagula* OR acenocoumarol OR phenprocoumon OR warfarin OR pentasaccharide* OR indirect factor Xa inhibit* OR direct thrombin inhibitor* OR dabigatran OR apixaban OR rivaroxaban) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB]) AND ("2011"[PDat] : "2013/07/01"[PDat]))
OR ((post-thrombotic syndrome OR postthrombotic syndrome) AND (prevention OR treatment) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB]) AND ("2011"[PDat] : "2013/07/01"[PDat]))
OR ((Thromboprophyla* OR ((prophylaxis OR prevention) AND venous thrombosis*)) AND (Heparin* OR UFH OR LMWH OR dalteparin OR Enoxaparin OR nadroparin OR tinzaparin OR Danaparoid OR vitamin K antagonist* OR anticoagula* OR acenocoumarol OR phenprocoumon OR warfarin OR pentasaccharide* OR indirect factor Xa inhibit* OR direct thrombin inhibitor* OR dabigatran OR apixaban OR rivaroxaban) AND (surgery OR surgical OR hip OR knee OR "General Surgery"[Mesh] OR "Orthopedic Procedures"[Mesh] OR medical patient* OR stroke OR cancer OR immobil* OR restricted mobility OR "mobility limitations" OR "plaster cast" OR "casts, surgical"[Mesh] OR arthroscopy OR "Arthroscopy"[Mesh] OR travel*) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB]) AND ("2008"[PDat] : "2013/07/01"[PDat]))) NOT (animals[MESH] NOT humans[MESH])
OR ((Thromboembolism[TIAB] OR Thrombophlebitis[TIAB] OR Venous Thrombosis[TIAB] OR vein thrombosis[TIAB] OR dvt[TIAB] OR vte[TIAB] OR Pulmonary Emboli*[TIAB]) AND (home therap*[TIAB] OR inpatient[TIAB] OR outpatient[TIAB]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB]) AND ("2002/04"[PDat] : "2013/07/01"[PDat])))

1.3 Selection procedure

Inclusion criteria used to select relevant *meta-analyses and systematic reviews*:

- Research question in selected publication matched research question for this literature review
- Systematic search
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes

Inclusion criteria for *randomised controlled trials (RCTs)* are mentioned in chapter 1.1. with relevant interventions, endpoints and study criteria.

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

Some publications were excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English

1.4 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.
The GRADE system[3,4,5] assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency*		- 1	Important inconsistency
Directness**		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision***		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of assciation (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

*** Consistency** refers to the similarity of estimates of effect across studies. if there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the (inevitably somewhat arbitrary) decision about whether important inconsistency exists.

**** Directness:** there are two types of indirectness of evidence. The first occurs when considering, for example, use of one of two active drugs. Although randomised comparisons of the drugs may be unavailable, randomised trials may have compared one drug with placebo and the other with placebo. Such trials allow indirect comparisons of the magnitude of effect of both drugs. Such evidence is of lower quality than would be provided by head to head comparisons of the drugs.
The second type of indirectness of evidence includes differences between the population, intervention, comparator to the intervention, and outcome of interest, and those included in the relevant studies.

*****Imprecision**: When studies include relatively few patients and few events and thus have wide confidence intervals, a guideline panel will judge the quality of the evidence to be lower.

In this literature review the criterium 'pubication bias' and the criteria specifically intended for observational studies (see table above) have not been assessed. This adapted version of GRADE therefore evaluates the following criteria:

Study design	+ 4	RCT
Study quality	- 1	Serious limitation to study quality
	- 2	Very serious limitation to study quality
Consistency	- 1	Important inconsistency
Directness	- 1	Some uncertainty about directness
	- 2	Major uncertainty about directness
Imprecision	- 1	Imprecise or sparse data
SUM	4	HIGH quality of evidence
	3	MODERATE quality of evidence
	2	LOW quality of evidence
	1	VERY LOW quality of evidence

In assessing the different criteria, we have applied the following rules.

.

Study design

In this literature review, all studies are RCTs (inclusion criterium). "Study design" is therefore not reported specifically in this report.

Study quality

To assess the methodological quality of RCTs, we considered the following criteria.
Randomization: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
Allocation concealment: : If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
Blinding: Who was blinded? Participants/personnel/assessors
If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection without double dummy)?.
Missing outcome data:
Follow-up, description of exclusions and drop-outs, ITT
Selective outcome reporting

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:

Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.
For example:

- Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
- A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: statistical heterogeneity

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

If we include systematic reviews or meta-analyses that include studies with <40 patients per study-arm (for a cross-over study: <40 patients in the complete study), a point is deducted for imprecision. For meta-analyses and in comparisons with only one study: a point is deducted when power is inadequate (depends also on the sample size).

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

1.5 Synopsis of study results

The complete report contains per research question

- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English)

The synopsis report contains per research question

- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

1.6 How to interpret outcome measures in the evidence tables

Outcomes are reported as follows:

- **Event rate (absolute risk**) for intervention group and comparator group.
  For binary outcomes such as number of patients with an adverse event, the event rates (n/N; numerator = total number of patients with an event, denominator = total number of patients) are shown with percentages.
  Event rates are also presented for meta-analyses. Please note: the event rates reported for meta-analyses, are 'crude rates' (n/N; numerator = total number of events, denominator = total number of patients across studies, presented with percentages). They are not the results of a meta-analysis (so no weighting was done) and are only reported to give a general idea of absolute risk.

- **Relative risk,** with 95% confidence interval (as calculated by the authors of the trial or meta-analysis)

- **Absolute effect or absolute risk difference**, with 95% confidence interval: for some RCTs and some meta-analyses.
  The absolute effect that is reported for some meta-analyses, is provided by the authors of the meta-analysis. This absolute differences in event rates was calculated using the GRADEpro software by applying the calculated relative risk from the meta-analysis to the total event rate in the control arm of the pooled results.
  This is meant to give an illustrative estimate of the absolute difference in event rates.

References

1. Clinical Evidence. A compendium of the best available evidence for effective health care. Website: http://clinicalevidence.bmj.com
2. Minerva is a journal for evidence-based medicine published in Belgium. Website: www.minerva-ebm.be
3. GRADE working group. http://www.gradeworkinggroup.org
4. GRADE working group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
5. Guyatt G, Oxman A, Kunz R et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6

2 Critical reflections of the literature group and the reading committee

Patient populations included in the trials

- **Trials on treatment of VTE**

Trials include either

- Patients with acute DVT, excluding patients with PE
- Patients with acute PE (with or without DVT)
- Patients with acute VTE (DVT and/or PE)

The reported meta-analyses in this document pool all of these studies. DVT and PE are manifestations of the same disease process. There may however be a difference in risk of mortality or even in risk of recurrent VTE in patients with DVT only compared to patients presenting with PE, because DVT and PE represent a different degree of severity of the same disease process (see also below: meta-analyses included in this literature review).

- **Treatment of distal DVT**

Very few trials exist on the treatment of distal DVT and most did not meet inclusion criteria due to size, interventions used or reported endpoints. Some trials on VTE treatment specifically exclude distal DVT, while others allow them into the trial but do not report separately on this subgroup.

- **Treatment of asymptomatic PE/subsegmental PE**

No trials were included that focus on subsegmental PE or asymptomatic PE.
With the apparition of new imaging techniques, more patients are diagnosed with (less severe cases of) PE. It is unclear whether these cases need the same treatment as clinically apparent, 'major' PE. The absence of placebo-controlled trials adds to this uncertainty. (See also appendix Critical reflections – historical background).

- **Meta-analyses included in this literature review: possible limitations**

The aim of a meta-analysis is to obtain a more precise estimate of effect, by pooling trials. However, populations of the included trials can be very different (heterogenous). For example,

- in treatment of VTE, some trials may include only DVT patients while others include only PE patients, or some trials may include patients with a first VTE event, while others include patients with a first or a second event.
- In trials on prevention in surgery, clinical heterogeneity may be present when pooling trials of different surgical procedures or surgical sites.
- In medical patients, different trials may include different medical conditions and different grades of immobility
- in cancer patients, different cancers or different stages of cancer progression may be pooled.

The main problem in these situations is that different populations may present a different risk of (recurrent) VTE. An estimate of effect from a meta-analysis of these trials may be of limited use to the clinician when faced with a specific patient with a specific condition.
When performing a meta-analysis, the presence of statistical heterogeneity can be examined. Potential sources of heterogeneity might be explored by performing sensitivity analyses or

categorical meta-analysis. However, even when statistical test find no major heterogeneity, the included populations may still be clinically heterogenous.

Comparisons

- **Trials on treatment of acute VTE**

Very few trials compare active treatment to placebo in acute VTE. This would off course pose ethical problems.
Few trials concentrate on the *initial* treatment of VTE only and most published trials on initial treatment are comparisons to UFH, which was excluded from this review.
Most trials examine the *continuation phase* of treatment and start randomizing patients after a common initial treatment for VTE.
Trials with new anticoagulants compare the new anticoagulant to 'conventional treatment'. All are constructed as non-inferiority trials. The trials with apixaban and rivaroxaban are designed to compare interventions in both the initial phase and continuation phase of treatment. However, in these trials, the majority of patients had received up to 24 or 48 hours of initial treatment with LMWH, heparin or fondaparinux prior to randomisation. Therefore, no conclusions can be drawn as to the efficacy of apixaban and rivaroxaban compared to 'standard' treatment in the first two days of treatment.
The trials with dabigatran start after a common initial anticoagulant therapy of all patients, thus studying only the continued treatment.

- **Trials on prevention in surgery or non-surgical medical patients**

Placebo-controlled trials exist. Most are old.
Newer anticoagulants are studied in comparison to enoxaparin. All of these trials are non-inferiority trials, except when longer duration of the new anticoagulant is compared to shorter duration enoxaparin. The clinical relevance of comparing two different durations of two different drugs is not apparent.

Outcomes

Most trials on treatment of VTE report on recurrent symptomatic VTE as an outcome.
Most trials in the prevention of VTE in surgical or medical patients report both symptomatic and asymptomatic VTE (mostly asymptomatic DVT, by screening all included patients). The rate of asymptomatic DVT is usually much higher than the rate of symptomatic events and the clinical relevance of asymptomatic DVT is not clear.
If asymptomatic DVT is a component of a composite outcome, it will have a large impact on the statistical significance of this outcome. It is however methodologically unsound to construct a composite outcome that combines both unfrequent but serious events and frequent but clinically less important events. Unfortunately, the trials with the new anticoagulants all report a composite primary outcome that combines both asymptomatic and symptomatic VTE and mortality.
In most trials, when a DVT is detected, the patient is removed from the trial and treated. This may prevent a natural evolution to PE (which of course is a good thing), leading to an underestimation of the eventrate of PE in a clinical situation.

Trial quality

- **Sponsoring**

Most trials were sponsored by pharmaceutical companies. All trials with the new anticoagulants were sponsored.

- **Non-inferiority trials**

Non-inferiority trials are constructed to test whether the newer drug is not inferior in efficacy when compared to an active 'conventional' treatment. To test this, a margin of non-inferiority is chosen: a threshold below which it can be established that the new drug is not worse than its comparator. Conducting and reporting of non-inferiority trials should be done according to certain standards (1-3).
The choice of the non-inferiority margin is important: a very wide margin will prove statistical non-inferiority more easily but casts doubt on the actual efficacy and clinical benefit. A valid choice of margin should be based on previous placebo-controlled trials of the comparator. This is not always the case. In a lot of the included non-inferiority trials, the basis for the choice of the non-inferiority margin is not specified.

In studies on treatment of VTE, very few placebo-controlled trials exist. Treating VTE patients with placebo would not be considered ethical nowadays. It is therefore difficult to establish a reliable non-inferiority margin. This is the case for non-inferiority trials of LMWH versus warfarin (see appendix: Critical reflections – historical background) and for trials comparing new anticoagulants versus LMWH or vitamin K antagonists in the treatment of VTE.
If the effect of the comparator drug versus placebo is unclear, we remain uncertain whether a new drug is truly better than placebo.

In a non-inferiority trial, the statistical analysis should consist of both a per protocol analysis and an intention to treat analysis (1, 2).
This is almost never the case in the trials that are included in this review. Often only 1 statistical analysis is done, mostly on a 'modified ITT' population, excluding certain patients from analysis. This is a huge problem in the surgical and medical patient prevention studies: often >25% of patients are excluded from analyses (mostly because of lack of diagnostic test on asymptomatic DVT).

To conclude, the reading committee feels that there is an important lack of evidence in the treatment of VTE, which can hopefully be resolved by future trials. The more the disease spectrum of pulmonary embolic disease widens to include less severe cases, the more we are uncertain whether the benefit of a treatment really outweighs the risk.

3 Guidelines

3.1 Criteria for guideline selection

In order to be included, the guideline had to be of recent date (not older than 5 years) and had to report levels of evidence and/or grades of recommendation.
The following guidelines fulfilled these criteria:

3.2 Selected guidelines

Comprehensive guidelines

NICE 2012	National Institute for Health and Care Excellence . Venous thromboembolic diseases (CG144), 2012 http://guidance.nice.org.uk/CG144/NICEGuidance/pdf/English
NICE 2010	National Institute for Health and Care Excellence . Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital(CG92), 2010 http://publications.nice.org.uk/venous-thromboembolism-reducing-the-risk-cg92
SIGN 2010	Scottish Intercollegiate Guidelines Network . Prevention and management of venous thromboembolism, 2010 http://www.sign.ac.uk/pdf/qrg122.pdf

ISTH 2013	Farge D, Debourdeau P, Beckers M et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. J Thromb Haemost 2013; 11: 56–70.

Guidelines on diagnosis

ACCP 2012 Diagnosis	Bates SM, Jaeschke R, Stevens SM et al. Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines 2012. CHEST 2012; 141(2)(Suppl):e351S–e418S.

Guidelines on therapy

ACCP 2012 Therapy	Kearon C, Akl EA, Comerota AF, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines 2012. CHEST 2012; 141(2)(Suppl):e419S–e494S.

Guidelines on prevention

ACCP 2012 Orthopedic prevention	Falck-Ytter Y, Francis CW, Johanson NA et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines

	2012. CHEST 2012; 141(2)(Suppl):e278S–e325S. http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112404.pdf
ACCP 2012 Surgical prevention	Gould MK, Garcia DA, Wren SM et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines 2012. CHEST 2012; 141(2)(Suppl):e227S–e277S. http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112297.pdf
ACCP 2012 Nonsurgical prevention	Kahn SR, Lim W, Dunn AS et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines 2012. CHEST 2012; 141(2)(Suppl):e195S–e226S. http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112296.pdf
ACP 2011	Qaseem A, Chou R, Humphrey LL et al. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline, American College of Physicians. Ann Intern Med. 2011;155:625-632.

3.3 Score systems used in guidelines

3.3.1 Score sytems uses for diagnosis of DVT

Original three level Wells score or criteria for assessment of suspected DVT

Wells score or criteria	
Criteria	**Score (points)**
Active cancer (treatment ongoing or within last six months or palliative)	1
Calf swelling >3 cm compared to other calf (measured 10 cm below tibial tuberosity)	1
Collateral superficial veins (non-varicose)	1
Pitting oedema (greater in the symptomatic leg)	1
Swelling of entire leg 1	1
Localised tenderness along distribution of deep venous system	1
Paralysis, paresis, or recent plaster castimmobilisation of lower extremities	1
Recently bedridden >3 days, or major surgery in past four weeks	1
Alternative diagnosis at least as likely as DVT subtract 2	- 2
Interpretation: For evaluation (low v moderate v high)	
Score of 0 or less.	low probability of deep vein thrombosis
Score of 1 or 2	moderate probability of deep vein thrombosis.
Score of 3 or higher	high probability of deep vein thrombosis.

Philip S Wells, David R Anderson, Janis Bormanis, Fred Guy, Michael Mitchell, Lisa Gray, Cathy Clement, K Sue Robinson, Bernard Lewandowski. Value of assessment of pretest probability of deepvein thrombosis in clinical management. Lancet 1997; 350: 1795–98

Revised two-level DVT Wells Score

Clinical Feature	**Points**
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2
Clinical probability simplified score	
DVT 'likely'	2 points or more

DVT 'unlikely'	1 point or less

Philip S. Wells, M.D., David R. Anderson, M.D., Marc Rodger, M.D., Melissa Forgie, M.D., Clive Kearon, M.D., Ph.D., Jonathan Dreyer, M.D., George Kovacs, M.D., Michael Mitchell, M.D., Bernard Lewandowski, M.D., and Michael J. Kovacs, M.D. Evaluation of d-Dimer in the Diagnosis of Suspected Deep-Vein Thrombosis N Engl J Med 2003;349:1227-35

3.3.2 Score systems used for diagnosis of PE

Two-level PE Wells score

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate greater than 100 beats per minute	1.5
Immobilisation (for more than 3 days) or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified score	
PE *likely*	More than 4 points
PE *unlikely*	4 points or less

Geneva score

Parameter	Score (points)
Age	
- **60-69 y**	1
- **>80 y**	2
Previous DVT or PE	2
Recent surgery within four weeks	3
Heart rate >100 beats per minute	1
PaCO2 (partial pressure of CO2 in arterial blood):	
<35 mmHg	2
35-39 mmHg	1
PaO2 (partial pressure of O2 in arterial blood):	
<49 mmHg	4
49-59 mmHg	3
60-71 mmHg	2
72-82 mmHg	1
Chest X-ray findings	
- **Band atelectasis**	1
- **Elevation of hemidiaphragm**	1
The score obtained relates to probability of PE:	
<5 points indicates a low probability of PE	
5-8 points indicates a moderate probability of PE	
>8 points indicates a high probability of PE	

Revised Geneva score:

The revised Geneva score uses eight parameters, but does not include figures which require an arterial blood gas sample to be performed.

Parameter	Score (points)
Age 65 years or over	1
Previous DVT or PE	3
Surgery or fracture within one month	2
Active malignant condition	2
Unilateral lower limb pain	3
Haemoptysis	2
Heart rate:	
ƒ75 to 94 beats per minute	3
ƒ95 or more beats per minute	5
Pain on deep palpation of lower limb and unilateral oedema	4
The score obtained relates to probability of PE:	
0-3 points indicates low probability (8%)	
4-10 points indicates intermediate probability (28%)	
11 points or more indicates high probability (74%)	

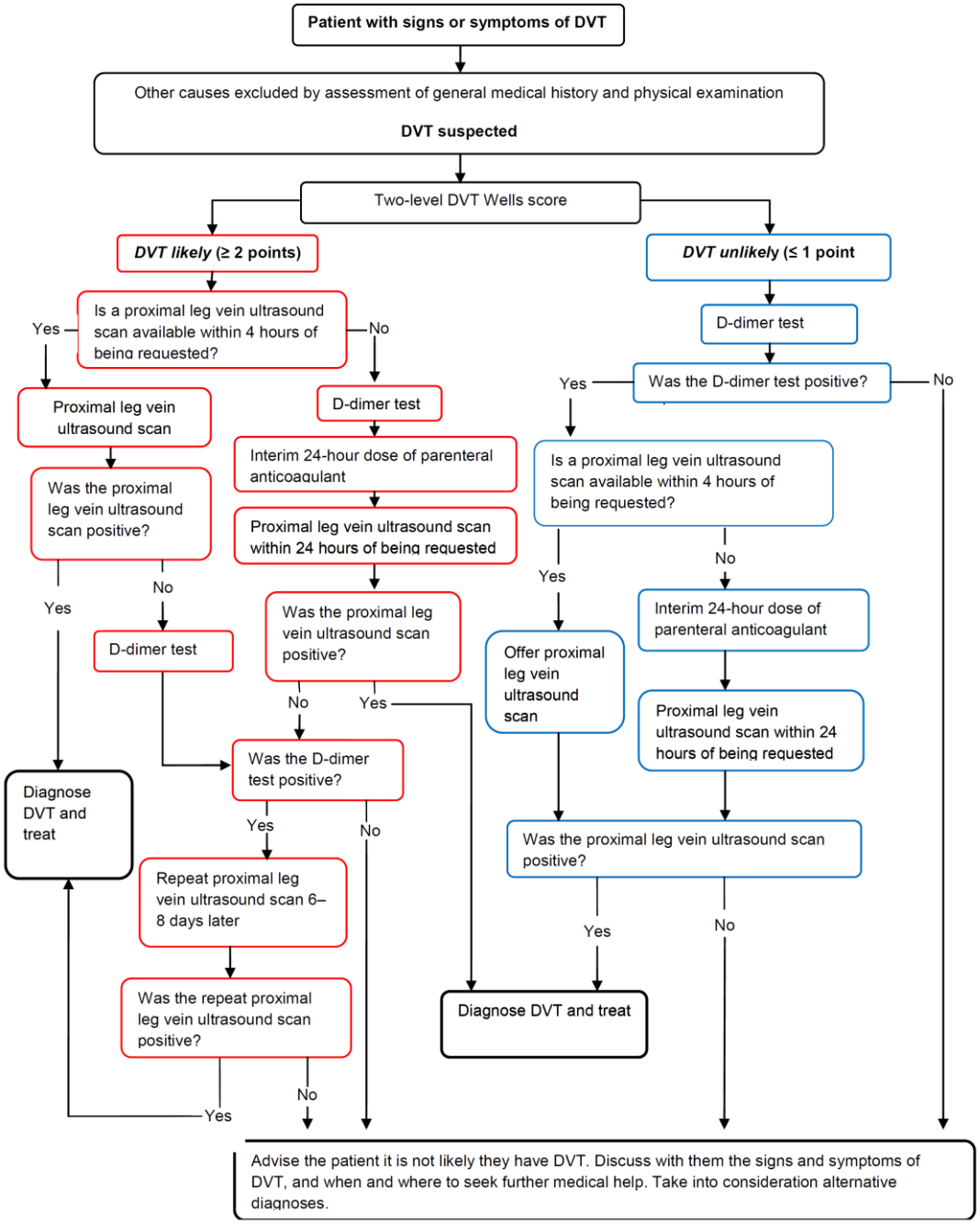
3.4 Summary of guidelines – comprehensive guidelines

3.4.1 NICE 2012	**Levels of evidence:** A. high quality evidence: we are very confident that the true effect lies close to that of the estimate of the effect B. moderate quality evidence: we are moderately confident in the effect of estimate; the true effect is likely to be close to the estimate of the effect but there is a possibility that it is substantially different C. low quality evidence: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect D. very low quality evidence: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect
	Included populations, interventions, outcomes: - adults with a suspected or confirmed DVT or PE (including following groups requiring special consideration: people with cancer, people who misuse intravenous drugs, residents of nursing homes and people with physical disabilities who have restricted movement following a VTE and people with learning disabilities who require long-term medication taken at home) - diagnostic and pharmacological interventions - VTE related mortality, all cause mortality, recurrent VTE rates, quality of life, chronic thromboembolic pulmonary hypertension, fatal bleed, intracranial haemorrhage, post thrombotic syndrome
	Members of development group, target population: - physicians and patient representatives - primary, secondary and tertiary healthcare settings
	*** Risk factors** Major risk factors for VTE include a prior history of DVT, age over 60 years, surgery, obesity, prolonged travel, acute medical illness, cancer, immobility, thrombophilia (an abnormal tendency for the blood to clot) and pregnancy. Recommendations: *** Diagnosis of deep vein thrombosis** If a patient presents with signs or symptoms of deep vein thrombosis (DVT), carry out an assessment of their general medical history and a physical examination to exclude other causes. (Consensus) If DVT is suspected, use the two-level DVT Wells score to estimate the clinical probability of DVT. (Grade: moderate) Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score *either*: - a proximal leg vein ultrasound scan (Grade: moderate) carried out within 4 hours of being requested and, if the result is negative, a D-dimer test (Grade: low) *or* - a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested. Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan. Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score a D-dimer test and if the result is positive offer *either*:

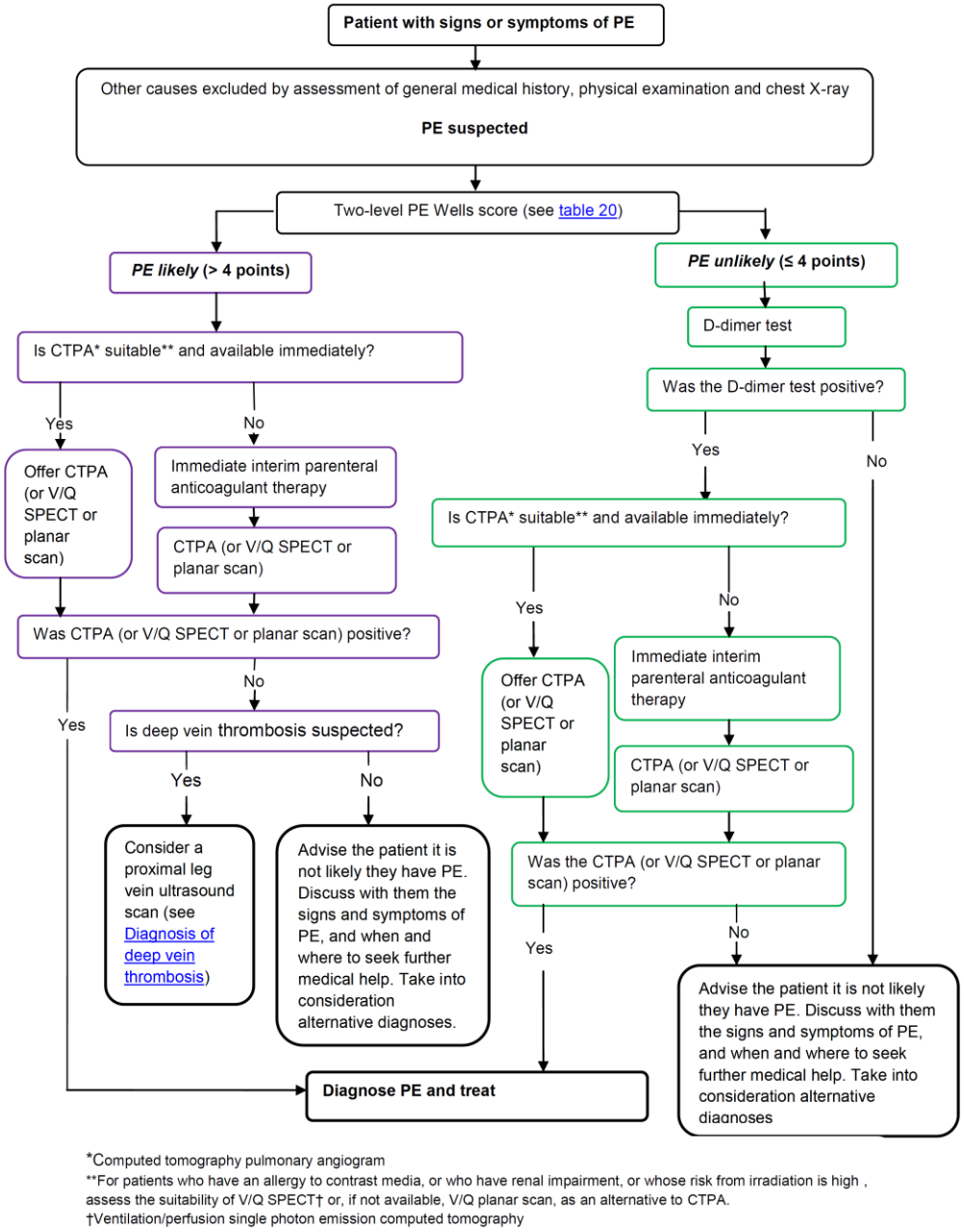
	- a proximal leg vein ultrasound scan carried out within 4 hours of being requested *or* - an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested. Diagnose DVT and treat patients with a positive proximal leg vein ultrasound scan. Take into consideration alternative diagnoses in patients with: - an *unlikely* two-level DVT Wells score *and* - a negative D-dimer test *or* - a positive D-dimer test and a negative proximal leg vein ultrasound scan. - a *likely* two level DVT Wells score *and* - a negative proximal leg vein ultrasound scan and a negative D-dimer test *or* - a repeat negative proximal leg vein ultrasound scan. Advise patients in these two groups that it is not likely they have DVT, and discuss with them the signs and symptoms of DVT and when and where to seek further medical help. *** Diagnosis of pulmonary embolism** If a patient presents with signs or symptoms of PE, carry out an assessment of their general medical history, a physical examination and a chest X-ray to exclude other causes. (Consensus) If PE is suspected, use the two-level PE Wells score to estimate the clinical probability of PE. Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score *either*: - an immediate computed tomography pulmonary angiogram (CTPA) *or* - immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately. Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected. Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score a D-dimer test and if the result is positive offer *either*: - an immediate CTPA *or* - immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately. For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high: - Assess the suitability of a ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scan (Grade: low-moderate) or, if a V/Q SPECT scan is not available, a V/Q planar scan (Grade: very low), as an alternative to CTPA. (Grade: very low) - If offering a V/Q SPECT or planar scan that will not be available immediately, offer immediate interim parenteral anticoagulant therapy. Diagnose PE and treat patients with a positive CTPA or in whom PE is identified with a V/Q SPECT or planar scan. Take into consideration alternative diagnoses in the following two groups of patients: - Patients with an *unlikely* two-level PE Wells score and *either* - a negative D-dimer test *or*

	- a positive D-dimer test and a negative CTPA. - Patients with a *likely* two-level PE Wells score and *both* - a negative CTPA *and* - no suspected DVT. Advise these patients that it is not likely they have PE and discuss with them the signs and symptoms of PE, and when and where to seek further medical help. If a patient presents with signs or symptoms of both DVT (for example a swollen and/or painful leg) and PE (for example chest pain, shortness of breath or hemoptysis), carry out initial diagnostic investigations for either DVT or PE, basing the choice of diagnostic investigations on clinical judgment. (Consensus) *** Pharmacologic interventions** Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs (Grade: low), with the following exceptions: - For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m_2) offer unfractionated heparin (UFH) with adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay. - For patients with an increased risk of bleeding consider UFH. (Grade: very low-low) - For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy. Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]) is 2 or above for at least 24 hours, whichever is longer. Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months. At 6 months, assess the risks and benefits of continuing anticoagulation. Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment. (Grade: low-moderate) Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment. (Grade: very low-low) Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment. (Grade: low-moderate) *** Mechanical interventions** Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications, and: - advise patients to continue wearing the stockings for at least 2 years - ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions. - advise patients that stockings need to be worn only on the affected leg or legs. (Grade: moderate)

Decision model DVT (NICE 2012)



Decision model PE (NICE 2012)



*Computed tomography pulmonary angiogram
**For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high , assess the suitability of V/Q SPECT† or, if not available, V/Q planar scan, as an alternative to CTPA.
†Ventilation/perfusion single photon emission computed tomography

3.4.2 NICE 2010	**Levels of evidence:** 1++ high-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias 1+ well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias 1- meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias 2++ high-quality systematic reviews of case-control or cohort studies, high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal 2+ well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal 2- case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal 3 non-analytic studies (case reports, case series,…) 4 expert opinion, formal consensus
	Included populations, interventions, outcomes: - surgical patients, inpatients with acute medical illness (e.g. myocardial infarction, stroke, spinal injury, severe infection or exacerbation of chronic obstructive pulmonary disease), trauma inpatients, patients admitted to intensive care units, cancer inpatients, people undergoing long-term rehabilitation in hospital, patients admitted to a hospital bed for day-case medical or surgical procedures - aspirin (low-dose and high-dose), dabigatran, rivaroxaban, fondaparinux, heparin (UFH/LMWH), adjustable-dose vitamin K antagonists (VKA-adj), graduated compression / anti-embolism stockings (GCS), intermittent pneumatic compression / foot impulse devices (IPCD/FID), placebo, combinations - all cause mortality, deep-vein thrombosis (DVT), pulmonary embolism (PE), major bleeding events, secondary outcomes: post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTEPH), heparin-induced thrombocytopenia (HIT), neurological events, quality of life, survival, length of stay
	Members of development group, target population: - physicians and patient representatives - primary, secondary and tertiary healthcare settings

	Risk assessment
	Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
	• surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
	• acute surgical admission with inflammatory or intra-abdominal condition
	• expected significant reduction in mobility
	• have one or more of the risk factors :
	  • Active cancer or cancer treatment
	  • Age over 60 years
	  • Critical care admission
	  • Dehydration
	  • Known thrombophilias

	• Obesity (BMI over 30 kg/m2) • One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions) • Personal history or a first degree relative with a history of VTE • Use of hormone replacement therapy • Use of oestrogen-containing contraceptive therapy • Varicose veins with phlebitis. Recommendations: *** General surgery (gastrointestinal, gynaecological, laparoscopic, thoracic and urological)** Offer VTE prophylaxis to patients undergoing *gastrointestinal surgery* who are assessed to be at increased risk of VTE: (level 1+ or 1++) Start mechanical VTE prophylaxis at admission. Choose any one of: - anti-embolism stockings (thigh or knee length) - foot impulse devices - intermittent pneumatic compression devices (thigh or knee length) Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility. Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose any one of: - fondaparinux sodium - LMWH - UFH (for patients with renal failure). Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days). Offer VTE prophylaxis to patients undergoing *gynaecological, thoracic or urologic surgery* who are assessed to be at increased risk of VTE: (level 1+ or 1++) Start mechanical VTE prophylaxis at admission. Choose any one of: - anti-embolism stockings (thigh or knee length) - foot impulse devices - intermittent pneumatic compression devices (thigh or knee length) Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility. Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of: - LMWH - UFH (for patients with renal failure). Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days). Offer VTE prophylaxis to patients undergoing *bariatric surgery*: (level 1+ or 1++, extrapolation from studies investigating other general surgery because no studies specific to bariatric surgery were found) Start mechanical VTE prophylaxis at admission. Choose any one of:

	- anti-embolism stockings (thigh or knee length) - foot impulse devices - intermittent pneumatic compression devices (thigh or knee length) Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility. Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of: - fondaparinux sodium - LMWH - UFH (for patients with renal failure). Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days). Extend pharmacological prophylaxis to 28 days postoperatively for patients who have had major cancer surgery in the abdomen or pelvis. (level 1+ or 1++) *** Elective hip replacement** Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing *elective hip replacement surgery* : (level 1+ or 1++) Start mechanical VTE prophylaxis at admission. Choose any one of the following based, on individual patient factors: - anti-embolism stockings (thigh or knee length), used with caution - foot impulse devices - intermittent pneumatic compression devices (thigh or knee length) Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility. Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of: dabigatran etexilate, starting 1-4 hours after surgery fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established LMWH, starting 6–12 hours after surgery rivaroxaban, starting 6-10 hours after surgery) UFH (for patients with renal failure), starting 6–12 hours after surgery. Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used. *** Elective knee replacement** Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing *elective knee replacement surgery*. (level 1+ or 1++) Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors: - anti-embolism stockings (thigh or knee length), used with caution - foot impulse devices - intermittent pneumatic compression devices (thigh or knee length) Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

	Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of: dabigatran etexilate, starting 1-4 hours after surgery fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established LMWH, starting 6–12 hours after surgery rivaroxaban, starting 6-10 hours after surgery UFH (for patients with renal failure), starting 6–12 hours after surgery. Continue pharmacological VTE prophylaxis for 10-14 days, according to the summary of product characteristics for the individual agent being used. **<u>* Hip fracture surgery</u>** Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing *<u>hip fracture surgery</u>*: (level 1+ or 1++) Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors: - anti-embolism stockings (thigh or knee length), used with caution - foot impulse devices - intermittent pneumatic compression devices (thigh or knee length). Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility. Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of: - fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding - LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery. - UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery. Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used. *Remark:* Fondaparinux sodium is not recommended for use preoperatively for patients undergoing hip fracture surgery. If it has been used preoperatively it should be stopped 24 hours before surgery and restarted 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding. Regard hospitalised patients as being *at risk of bleeding* if they have any of the following risk factors: - Active bleeding - Acquired bleeding disorders (such as acute liver failure) - Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2) - Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours - Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours - Acute stroke - Thrombocytopenia (platelets < 75 x 109/l) - Uncontrolled systolic hypertension (230/120 mmHg or higher)

	- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease). **<u>* Other orthopaedic surgery</u>** Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having <u>orthopaedic surgery</u> (other than hip fracture, hip replacement, knee replacement) based on an assessment of risks and after discussion with the patient. (level 1+ or 1++) Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors: - anti-embolism stockings (thigh or knee length), used with caution - foot impulse devices - intermittent pneumatic compression devices (thigh or knee length). Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility. Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of: - LMWH - UFH (for patients with renal failure). Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility. Do not routinely offer VTE prophylaxis to patients undergoing upper limb surgery. If a patient is assessed to be at increased risk of VTE refer to recommendation from other orthopaedic surgery. (level 4) **<u>* Lower limb plaster casts</u>** Consider offering pharmacological VTE prophylaxis to patients with lower limb plaster casts after evaluating the risks and benefits based on clinical discussion with the patient. Offer LMWH (or UFH for patients with renal failure) until lower limb plaster cast removal. (level 1+ or 1++) **<u>* General medical patients</u>** Regard medical patients as being at increased risk of VTE if they: have had or are expected to have significantly reduced mobility for 3 days or more, or are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors (see risk factor surgery and trauma) Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE. Choose any one of: - fondaparinux sodium - LMWH - UFH (for patients with renal failure). Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE. (level 1+ or 1++) Consider offering mechanical VTE prophylaxis to medical patients in whom pharmacological prophylaxis is contraindicated. Choose any one of: - anti-embolism stockings (thigh or knee length) - foot impulse devices

	- intermittent pneumatic compression devices (thigh or knee length) (no studies were found, extrapolation from RCTs in surgical populations, level 1-) **<u>* Stroke patients</u>** Do not offer anti-embolism stockings for VTE prophylaxis to patients who are admitted for stroke. Until the patient can have pharmacological VTE prophylaxis, consider offering a foot impulse or intermittent pneumatic compression device. (level 1+ or 1++) Consider offering prophylactic-dose LMWH (or UFH for patients with renal failure) if: - a diagnosis of haemorrhagic stroke has been excluded, *and* - the risk of bleeding (haemorrhagic transformation of stroke or bleeding into another site) is assessed to be low, *and* - the patient has one or more of: major restriction of mobility, previous history of VTE, dehydration and/or comorbidities (such as malignant disease). Continue until the acute event is over and the patient's condition is stable. (level 1+ or 1++) ***<u>Cancer</u>** Offer pharmacological VTE prophylaxis to patients with cancer who are assessed to be at increased risk of VTE. Choose any one of: - fondaparinux sodium - LMWH - UFH (for patients with renal failure). Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE. (level 1+ or 1++) Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant. (level 1+ or 1++)

3.4.3 SIGN 2010	**Grades of recommendation:** A. At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results B. A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+ C. A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++ D. Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+ Good practice points: recommended best practice based on the clinical experience of the guideline development group
	Levels of evidence: 1++ high quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias 1+ well conducted meta-analyses, systematic reviews or RCTs with a low risk of bias 1- meta-analyses, systematic reviews or RCTs with a high risk of bias 2++ high quality systematic reviews of case control or cohort studies; high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal 2+ well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal 2- case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal 3 non-analytic studies (case reports, case series) 4 expert opinion
	Included populations, interventions, outcomes: - adult patient groups at risk of VTE - mechanical methods of prophylaxis, antiplatelet agents, unfractionated and low molecular weight heparins, heparinoids, fondaparinux, hirudins, dextrans, vitamin K antagonists, new oral agents - outcomes not mentioned in detail
	Members of development group, target population: - physicians - medical practitioners including general practitioners, nurses, pharmacists and dentists
	Risk factors *Table 1: Risk factors for venous thromboembolism* **Age** Incidence of first VTE rises exponentially with age. In the general population: <40 years – annual incidence of 1/10,000 60-69 years – annual incidence of 1/1,000 >80 years – annual incidence of 1/100 May reflect immobility and coagulation activation38,39 **Obesity** 2 to 3-fold VTE risk if obese (body mass index >30 kg/m2) May reflect immobility and coagulation activation **Varicose veins** 1.5 to 2.5-fold risk after major general/orthopaedic surgery Low risk after varicose vein surgery **Family history of VTE** A history of at least one first degree relative having had VTE

	at age <50 years or more than one first degree relative with VTE history regardless of age is an indicator of increased risk of first VTE (but not of recurrent VTE) **Thrombophilias** Low coagulation inhibitors (antithrombin, protein C or S); Activated protein C resistance (eg factor V Leiden); High coagulation factors (I, II, including prothrombin G20210A, VIII, IX, XI); Antiphospholipid antibodies; High homocysteine: 1.5 to 2.5-fold VTE risk; Elevated lipoprotein(a) >300mg/l: 1.8-fold risk of VTE **Other thrombotic states** Cancer: compared with general population overall 5 to 7-fold risk of first VTE and increased risk of recurrent VTE. Risk varies with type of cancer. Further increased risk associated with surgery, chemotherapy, use of erythropoeisis stimulating agents and central venous catheters Heart failure, recent myocardial infarction/stroke Metabolic syndrome: 2-fold increased risk of VTE Severe acute infection Chronic HIV infection Inflammatory bowel disease, nephrotic syndrome Myeloproliferative disease, paraproteinaemia, Bechet's disease, paroxysmal nocturnal haemoglobinuria Sickle cell trait and sickle cell disease **Combined oral contraceptives, hormone replacement therapy and anti-oestrogens** Combined oral contraceptives (COCs): compared with non-users, COC users have 3 to 6-fold increased risk. Compared with users of COCs containing second generation progestogens, users of COCs containing third generation progestogens have a further 1.7- fold increase in VTE risk.61 2.5-fold increased risk of postoperative VTE in COC users No evidence that progestogen-only oral contraceptives are associated with increased VTE risk but high-dose progestogens used to treat gynaecological problems associated with 6-fold increased VTE risk Oral oestrogen hormone replacement therapy (HRT) users have 2.5-fold increased VTE risk but not transdermal oestrogen HRT users Heritable thrombophilia further increases VTE risk in COC and oral oestrogen HRT users Raloxifene and tamoxifen associated with a 2 to 3-fold increased VTE risk **Pregnancy, puerperium** Approximately 10-fold increased risk during pregnancy compared with non-pregnant and 25-fold increased risk compared with nonpregnant/non-puerperal during puerperium68 Pregnant and puerperal women with thrombophilia have increased risk of VTE compared to pregnant and puerperal women without an identified thrombophilia **Immobility** For example, bed rest >3 days, plaster cast, paralysis: 10-fold increased VTE risk; increases with duration **Immobility durin travel** 2 to 3-fold increased risk **Hospitalisation** Acute trauma, acute illness, surgery: 10-fold increased VTE risk **Anaesthesia** 2 to 3-fold increased risk of postoperative VTE in general compared with spinal/epidural **Central venous catheters** Compared with subclavian access, femoral route 11.5-fold increased risk of VTE Slightly increased risk of central venous catheter (CVC) thrombosis in patients with prothrombin G20210A or factor V Leiden compared to risk in CVC patients with wild type prothrombin and factor V

Table 2: Risk factors for recurrent venous thromboembolism (in patients not on long term anticoagulation)

Previous unprovoked VTE

Recurrence rate 5% per year after an unprovoked VTE

Male sex Compared with women, men have an increased relative risk (RR) of recurrent VTE (RR 1.6, 95% confidence interval (CI) 1.2 to 2.0). The higher relative risks reported in some studies may be
explained by sex-specific factors present at the time of the first VTE events

Obesity Hazard ratio (HR) 1.6 (95% CI 1.1 to 2.4)

Thrombophilias Risk of recurrent VTE is not increased in patients with either heterozygous or homozygous factor V Leiden or prothrombin gene G20210A81 but may be increased in patients with antithrombin

Recommendations:

*** Thromboprophylaxis in surgical patients**

General surgery:

Patients undergoing abdominal surgery who are at risk due to the procedure or personal risk factors should receive thromboprophylaxis with mechanical methods unless contraindicated and either subcutaneous low molecular weight heparin, unfractionated heparin or fondaparinux. (A)

Orthopedic surgery:

Patients undergoing total hip replacement or total knee replacement surgery should receive pharmacological prophylaxis (with low molecular weight heparin, fondaparinux, rivaroxaban or dabigatran) combined with mechanical prophylaxis unless contraindicated.(A)

Extended prophylaxis should be given. (A)

*** Thromboprophylaxis in medical patients**

When the assessment of risk favours use of thromboprophylaxis, unfractionated heparin, low molecular weight heparin or fondaparinux should be administered. (A)

Patients with cancer are generally at high risk of venous thromboembolism and should be considered for prophylaxis with low molecular weight heparin, unfractionated heparin or fondaparinux whilst hospitalised. (A)

*** Diagnosis of venous thromboembolism**

A validated clinical decision rule should be used in the initial assessment of outpatients presenting with suspected deep vein thrombosis or pulmonary embolism. (B)

The results of the initial assessment should be used to determine the diagnostic strategy. (Good practice point)

Patients who have a negative or inadequate initial scan but who have a persisting clinical suspicion of deep vein thrombosis or whose symptoms do not settle should have a repeat ultrasound scan. (C)

*** Travel-related thrombosis**

The risks and possible benefits of any intervention should always be discussed with the patient before travelling. (Good practice point)

Travellers should be advised to remain as ambulant as safely possible before, during and after journeys. Leg exercise whilst seated may be recommended. (D)

The use of AES for prevention of VTE during and after long-haul travel is not

	routinely recommended. When used, care should be taken to ensure an appropriate fit. (D) Appropriate monitoring of the INR and dosage adjustment is recommended prior to travel for patients taking warfarin. (Good practice point) In people deemed to be at especially high risk of travel-related VTE, pharmacological prophylaxis can be considered. LMWH has been used for this purpose. (Good practice point) ***Initial treatment venous thromboembolism** *Pulmonary embolism:* Patients with suspected PE should be treated with therapeutic doses of heparin or fondaparinux until the diagnosis has been deemed very unlikely. (A) Once confirmed the heparin or fondaparinux should be continued until the INR is at least 2.0 on a vitamin K antagonist, and for at least 5 days. (D) Patients with intermediate-risk PE should not routinely receive thrombolytic therapy. (D) Patients with intermediate-risk PE should be monitored in hospital and be considered for thrombolysis should they deteriorate. (Good practice point) Patients with low-risk PE can be considered for outpatient management or early discharge. (Good practice point) Patients with high-risk PE should be managed in a coronary care unit or high dependency unit. (Good practice point) *Lower limb deep vein thrombosis:* Patients with suspected DVT should be treated with therapeutic doses of LMWH or fondaparinux until the diagnosis has been deemed very unlikely or confirmed. (A) In confirmed DVT the heparin or fondaparinux should be continued until the INR is at least 2.0 on a vitamin K antagonist, and for at least 5 days. (D) Intravenous UFH may be an appropriate alternative in certain circumstances, e.g. if thrombolysis is being considered, in the immediate postoperative period or where there is particular risk of bleeding. (B) Patients with cancer and VTE should be offered treatment with LMWH *(rather than vitamin K antagonist)* for three to six months and reviewed thereafter. (A) *** Further management of venous thromboembolism** *Choice of anticoagulant:* Low molecular weight heparin rather than warfarin should be considered in venous thromboembolism associated with cancer. (A) *Duration of anticoagulation:* After a first episode of proximal limb deep vein thrombosis or pulmonary embolism, treatment with a vitamin K antagonist should be continued for at least three months. (A) Uninterrupted, long term continuation of vitamin K antagonist therapy after a first episode of venous thromboembolism may be appropriate in some patients and can be based on individual assessment, including: - an unprovoked first event - the site and severity of the first event - the presence of persistent comorbidities, e.g. cancer - the presence of persistent antiphospholipid antibodies - male sex

	- bleeding risk on anticoagulant treatment - patient compliance and preference. (Good practice points) Measurement of D-dimer concentration one month after discontinuation of a course of VKA therapy after a first episode of unprovoked VTE can be considered for the identification of patients who may benefit from resumption of VKA therapy and continuation in the long term. (A) After recurrent VTE, long term treatment with a VKA is recommended but the nature of the recurrence (provoked or unprovoked), the elapsed time between episodes and risk of bleeding should be considered in reaching this decision. The use of long term VKA should be subjected to periodic review, to include anticoagulant control, bleeding episodes and altered risk of bleeding. (Good practice point) *Graduated compression stockings:* After deep vein thrombosis affecting a lower limb, the use of well fitted below-knee graduated elastic compression stockings for two years should be encouraged to reduce the risk of post-phlebitic syndrome. (A) *** Outpatient management of acute VTE** Outpatient therapy of DVT may be considered for selected patients with appropriate support services in place. (B) Validated prognostic models to identify patients at low risk of adverse outcomes may be incorporated into treatment algorithms for the management of patients with PE to identify those suitable for outpatient management or early discharge. (B)

3.4.4 ISTH 2013	**Grades of recommendation:** 1. strong recommendation; desirable effects clearly outweigh undesirable effects 2. weak recommendation; desirable effects probably outweigh undesirable effects *Best clinical practice:* judgment was based on the professional experience and consensus of the international experts within the working group, in the absence of any clear scientific evidence en because of undetermined balance between desirable and undesirable effects
	Levels of evidence: A. high quality evidence B. moderate quality evidence C. low quality evidence D. very low quality evidence
	Included populations, interventions, outcomes: - cancer patients - subcutaneous low-dose heparin (LMWH, UFH), mechanical devices - total mortality up to 120 days after randomization, symptomatic DVT, all PEs, fatal PEs, all bleeding events, major bleeding events, effects on skin (for mechanical prophylaxis)
	Members of development group, target population: - physicians - internists, family physicians, other clinicians

	Recommendations: *** Initial treatment of established VTE** Low-molecular-weight heparin (LMWH) is recommended (Grade 1B). Fondaparinux and unfractionated heparin (UFH) can also be used (Grade 2D) Thrombolysis may only be considered on a case-by-case basis (Best clinical practice). Periodic reassessment of contraindications to anticoagulation is recommended and anticoagulation should be resumed when safe (Best clinical practice). *** Early maintenance (10 days to 3 months) and long-term (beyond 3 months) treatment of established VTE** LMWH for a minimum of 3 months is preferred over vitamin K antagonists (VKA) (Grade 1A). Idraparinux is not recommended (Grade 2C). After 3-6 months, LMWH or VKA continuation should be based on individual evaluation of the benefit-risk ratio, tolerability, patient preference and cancer activity (Best clinical practice). *** Treatment of VTE recurrence in cancer patients under anticoagulation** Three options can be considered (Best clinical practice): 1) switch from VKA to LMWH when treated with VKA 2) increase in LMWH dose when treated with LMWH 3) vena cava filter insertion *** Prophylaxis of postoperative VTE in surgical cancer patients** Use of LMWH o.d. or low dose of UFH t.i.d. is recommended. Pharmacological prophylaxis should be started 12-2h preoperatively and continued for at least 7-10 days. There are no data allowing conclusion that one type of LMWH is superior to another (Grade 1A). There is no evidence to support fondaparinux as an alternative to LMWH (Grade 2C). Use of the highest prophylactic dose of LMWH is recommended (Grade 1A). Extended prophylaxis (4 weeks) after major laparotomy may be indicated in cancer patients with a high risk of VTE and a low risk of bleeding (Grade 2B). The use of LMWH for VTE prevention in cancer patients undergoing laparoscopic surgery may be recommended as for laparotomy (Best clinical practice). Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated (Grade 2C). *** Prophylaxis in hospitalized medical patients with cancer and reduced mobility** We recommend prophylaxis with LMWH, UFH or fondaparinux (Grade 1B). For children or adults with acute lymphocytic leukemia treated with L-asparaginase, depending on local policy and patient characteristics, prophylaxis may be considered in some patients (Best clinical practice). *** Prophylaxis in patients receiving chemotherapy** In patients receiving chemotherapy, prophylaxis is not recommended routinely (Grade 1B). Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic (Grade 1B) or lung (Grade 2B) cancer treated with chemotherapy and having a low risk of bleeding. In patients treated with thalidomide or lenalidomide combined with steroids and/or chemotherapy, VTE prophylaxis is recommended. In this setting, VKA at low or therapeutic doses, LMWH at prophylactic doses and low-dose aspirin have shown similar effects. However, the efficacy of these regimens remains unclear (Grade 2C). Special situations include brain tumors, severe renal failure (CrCl <30ml/min), thrombocytopenia and pregnancy. Guidances are provided in these contexts but are not included in this summary.

3.5 Summary of guidelines - guidelines on diagnosis

3.5.1 ACCP 2012 Diagnosis	**Grades of recommendation:** 1. strong recommendation; benefits clearly outweigh risk and burdens or vice versa 2. weak recommendation; benefits closely balanced with risks and burden
	Levels of evidence: 1. Strong recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence 2. Weak recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence
	Included populations, interventions, outcomes: - patients suspected to have deep vein thrombosis - venography, D-dimer, MRI, CT scan venography, venous US - DVT, PE, death, bleeding in treated patients
	Members of development group, target population: - cardiologists - health care providers, nurses, pharmacists, physicians
	Recommendations: - In patients with a suspected first lower extremity DVT, we suggest that the choice of diagnostic tests process should be guided by the clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients (Grade 2B) . - In patients with a low pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a moderately sensitive D-dimer, (ii) a highly sensitive D-dimer, or (iii) compression ultrasound (CUS) of the proximal veins rather than (i) no diagnostic testing (Grade 1B for all comparisons) , (ii) venography (Grade 1B for all comparisons), or (iii) whole-leg ultrasound (US) (Grade 2B for all comparisons) . We suggest initial use of a moderately sensitive (Grade 2C) or highly sensitive (Grade 2B) D-dimer rather than proximal CUS. - If the D-dimer is negative, we recommend no further testing over further investigation with proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons) . If the proximal CUS is negative, we recommend no further testing compared with (i) repeat proximal CUS after 1 week, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons) . - If the D-dimer is positive, we suggest further testing with CUS of the proximal veins rather than (i) whole-leg US (Grade 2C) or (ii) venography (Grade 1B) . If CUS of the proximal veins is positive, we suggest treating for DVT and performing no further testing over performing confirmatory venography (Grade 2C) . - In patients with a moderate pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a highly sensitive D-dimer or (ii) proximal CUS, or (iii) whole-leg US

	rather than (i) no testing (Grade 1B for all comparisons) or (ii) venography (Grade 1B for all comparisons) . We suggest initial use of a highly sensitive D-dimer rather than US (Grade 2C) . - If the highly sensitive D-dimer is negative, we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons) . If the highly sensitive D-dimer is positive, we recommend proximal CUS or whole-leg US rather than no testing (Grade 1B for all comparisons) or venography (Grade 1B for all comparisons) . - If proximal CUS is chosen as the initial test and is negative, we recommend (i) repeat proximal CUS in 1 week or (ii) testing with a moderate or highly sensitive D-dimer assay over no further testing (Grade 1C) or venography (Grade 2B) . In patients with a negative proximal CUS but a positive D-dimer, we recommend repeat proximal CUS in 1 week over no further testing (Grade 1B) or venography (Grade 2B) . - In patients with (i) negative serial proximal CUS or (ii) a negative single proximal CUS and negative moderate or highly sensitive D-dimer, we recommend no further testing rather than further testing with (i) whole-leg US or (ii) venography (Grade 1B for all comparisons) . - If whole-leg US is negative, we recommend no further testing over (i) repeat US in one week, (ii) D-dimer testing, or (iii) venography (Grade 1B for all comparisons) . If proximal CUS is positive, we recommend treating for DVT rather than confirmatory venography (Grade 1B) . If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment (Grade 2C) . - In patients with a high pretest probability of first lower extremity DVT, we recommend either (i) proximal CUS or (ii) whole-leg US over no testing (Grade 1B for all comparisons) or venography (Grade 1B for all comparisons) . - If proximal CUS or whole-leg US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B) . - In patients with a negative proximal CUS, we recommend additional testing with a highly sensitive D-dimer or whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B for all comparisons) or venography (Grade 2B for all comparisons) . We recommend that patients with a single negative proximal CUS and positive D-dimer undergo whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B) or venography (Grade 2B) . In patients with negative serial proximal CUS, a negative single proximal CUS and negative highly sensitive D-dimer, or a negative whole-leg US, we recommend no further testing over venography or additional US (Grade 1B for negative serial proximal CUS and for negative single proximal CUS and highly sensitive D-dimer; Grade 2B for negative whole-leg US) . - We recommend that in patients with high pretest probability, moderately or highly sensitive D-dimer assays should not be used as standalone tests to rule out DVT (Grade 1B) . - If risk stratification is not performed in patients with suspected first lower extremity DVT, we recommend one of the following initial

	tests: (i) proximal CUS or (ii) whole-leg US rather than (i) no testing (Grade 1B), (ii) venography (Grade 1B) , or D-dimer testing (Grade 2B) . - We recommend that patients with a negative proximal CUS undergo testing with a moderate- or high-sensitivity D-dimer, whole-leg US, or repeat proximal CUS in 1 week over no further testing (Grade 1B) or venography (Grade 2B) . In patients with a negative proximal CUS, we suggest D-dimer rather than routine serial CUS (Grade 2B) or whole-leg US (Grade 2C) . We recommend that patients with a single negative proximal CUS and positive D-dimer undergo further testing with repeat proximal CUS in 1 week or whole-leg US rather than no further testing (Grade 1B for both comparisons) . - We recommend that in patients with (i) negative serial proximal CUS, (ii) a negative D-dimer following a negative initial proximal CUS, or (iii) negative whole-leg US, no further testing be performed rather than venography (Grade 1B) . - If proximal US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B) . If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment (Grade 2C) . - In patients with suspected first lower extremity DVT, we recommend against the routine use of CT venography or MRI (Grade 1C) . - In patients suspected of having recurrent lower extremity DVT, we recommend initial evaluation with proximal CUS or a highly sensitive D-dimer over venography, CT venography, or MRI (all Grade 1B) . - If the highly sensitive D-dimer is positive, we recommend proximal CUS over venography, CT venography, or MRI (Grade 1B for all comparisons). - In patients with suspected recurrent lower extremity DVT in whom initial proximal CUS is negative (normal or residual diameter increase of <2 mm), we suggest at least one further proximal CUS (day 7 ± 1) or testing with a moderately or highly sensitive D-dimer (followed by repeat CUS [day 7 ± 1] if positive) rather than no further testing or venography (Grade 2B) . - We recommend that patients with suspected recurrent lower extremity DVT and a negative highly sensitive D-dimer or negative proximal CUS and negative moderately or highly sensitive D-dimer or negative serial proximal CUS undergo no further testing for suspected recurrent DVT rather than venography (Grade 1B) . - If CUS of the proximal veins is positive, we recommend treating for DVT and performing no further testing over performing confirmatory venography (Grade 1B for the finding of a new non-compressible segment in the common femoral or popliteal vein, Grade 2B for a ≥4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result) . - In patients with suspected recurrent lower extremity DVT and abnormal but non-diagnostic US results (e.g., an increase in residual venous diameter of , 4 but _ 2 mm), we recommend further testing with venography, if available (Grade 1B) ; serial proximal CUS (Grade 2B) or testing with a moderately or highly sensitive D-dimer with

	serial proximal CUS as above if the test is positive (Grade 2B) , as opposed to other testing strategies or treatment. - In patients with suspected recurrent ipsilateral DVT and an abnormal US without a prior result for comparison, we recommend further testing with venography, if available (Grade 1B) or a highly sensitive D-dimer (Grade 2B) over serial proximal CUS. In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a negative highly sensitive D-dimer, we suggest no further testing over venography (Grade 2C) . In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a positive highly sensitive D-dimer, we suggest venography if available over empirical treatment of recurrence (Grade 2C) . - In patients suspected of having upper extremity DVT, we suggest initial evaluation with combined modality US (compression with either Doppler or color Doppler) over other initial tests, including highly sensitive D-dimer or venography (Grade 2C) . - In patients with suspected upper extremity DVT in whom initial US is negative for thrombosis despite a high clinical suspicion of DVT, we suggest further testing with a moderate or highly sensitive D-dimer, serial US, or venographic-based imaging (traditional, CT scan, or MRI), rather than no further testing (Grade 2C) . - In patients with suspected upper extremity DVT and an initial negative combined-modality US and subsequent negative moderate or highly sensitive D-dimer or CT or MRI, we recommend no further testing, rather than confirmatory venography (Grade 1C) . We suggest that patients with an initial combined negative modality US and positive D-dimer or those with less than complete evaluation by US undergo venography rather than no further testing, unless there is an alternative explanation for their symptoms (Grade 2B), in which case testing to evaluate for the presence an alternative diagnosis should be performed. We suggest that patients with a positive D-dimer or those with less than complete evaluation by US but an alternative explanation for their symptoms undergo confirmatory testing and treatment of this alternative explanation rather than venography (Grade 2C) .

Decision models ACCP 2012 Diagnosis
After assessment of pre-test probability

If pre-test probability is low:

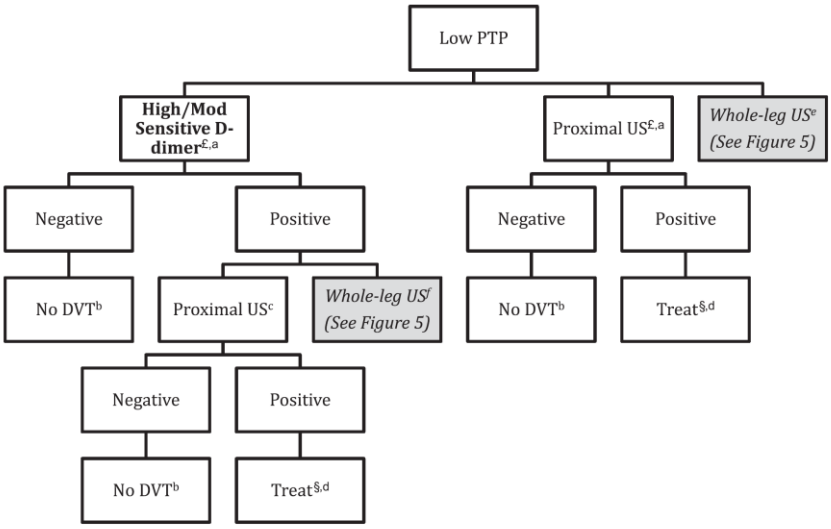


FIGURE 1. [Section 3.2] Recommendations for evaluation of suspected first lower extremity DVT: patients with low pretest probability (PTP) for DVT. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. Venography is not generally indicated in the figure, as it is not routinely used. §See Kearon et al.[11] £Beginning with moderately sensitive D-dimer (Grade 2C) or highly sensitive D-dimer (Grade 2B) is suggested over beginning with US. [a]Grade 1B vs no testing and vs venography; Grade 2B vs whole-leg US. [b]Grade 1B vs further testing. [c]Grade 1B vs venography; Grade 2C vs whole-leg US. [d]Grade 2C for treating DVT vs confirmatory venography. [e]Grade 2B for high/moderate sensitivity D-dimer or proximal US over whole-leg US. [f]Grade 2C for proximal US over whole-leg US. PTP = pretest probability; US = ultrasound.

If pre-test probability is moderate:

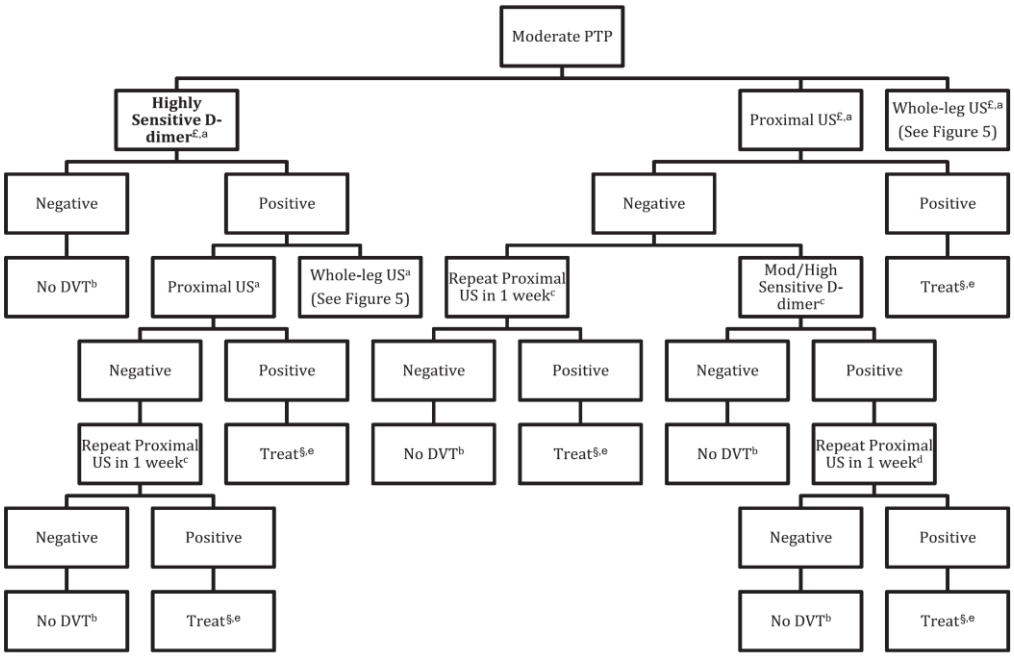


FIGURE 2. [Section 3.3] Recommendations for evaluation of suspected first lower extremity DVT: patients with moderate pretest probability (PTP) for DVT. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. Venography is not generally indicated in the figure, as it is not routinely used. §See Kearon et al.[11] £Beginning with highly sensitive D-dimer is suggested over beginning with US (Grade 2C). [a]Grade 1B vs no testing and vs venography. [b]Grade 1B vs further testing. [c]Grade 1C vs no further testing; Grade 2B vs venography. [d]Grade 1B vs no further testing; Grade 2B vs venography. [e]Grade 1B for treating DVT vs confirmatory venography. See Figure 1 legend for expansion of abbreviation.

If pre-test probability is high:

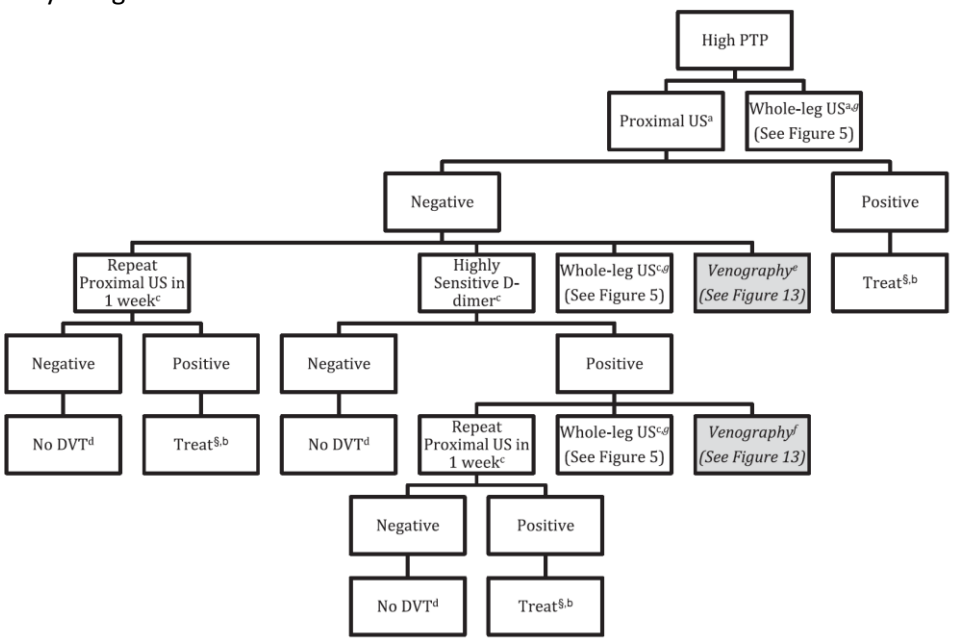


FIGURE 3. [Section 3.4] Recommendations for evaluation of suspected first lower extremity DVT: patients with high pretest probability (PTP) for DVT. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. Venography is not generally indicated in the figure, as it is not routinely used. [a]Grade 1B vs no testing and vs venography. [b]Grade 1B for treating DVT vs confirmatory venography. [c]Grade 1B vs no further testing; Grade 2B vs venography. [d]Grade 1B vs further testing. [e]Grade 2B for repeat proximal US, highly sensitive D-dimer or whole-leg US over venography. [f]Grade 2B for repeat proximal US over venography. [g]Grade 2B for no further testing over venography if whole-leg US is negative (see also Figure 5). See Figure 1 legend for expansion of abbreviation.

If no risk stratification is done:

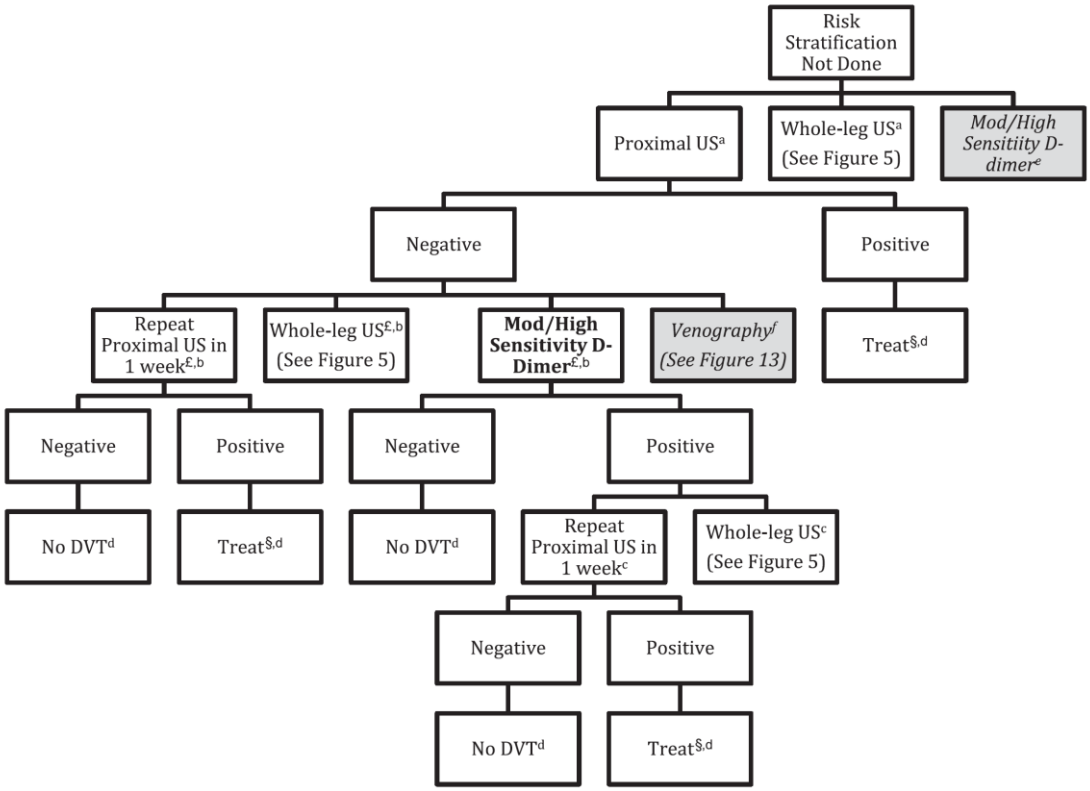


FIGURE 4. [Section 3.5] Recommendations for evaluation of suspected first lower extremity DVT: risk stratification not performed. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] £Use of D-dimer is suggested over use of repeat proximal US (Grade 2B) or whole-leg US (Grade 2C). [a]Grade 1B vs no testing and vs venography; Grade 2B vs D-dimer. [b]Grade 1B vs no further testing; Grade 2B vs venography. [c]Grade 1B vs no further testing. [d]Grade 1B vs venography. [e]Grade 2B for proximal US or whole-leg US over D-dimer. [f]Grade 2B for repeat proximal US, moderate or highly sensitive D-dimer, or whole-leg US over venography. [d]Grade 1B for treating DVT vs confirmatory venography. See Figure 1 legend for expansion of abbreviation.

In patient with suspected recurrent DVT: follow algorithm depending on results of initial diagnostic test.

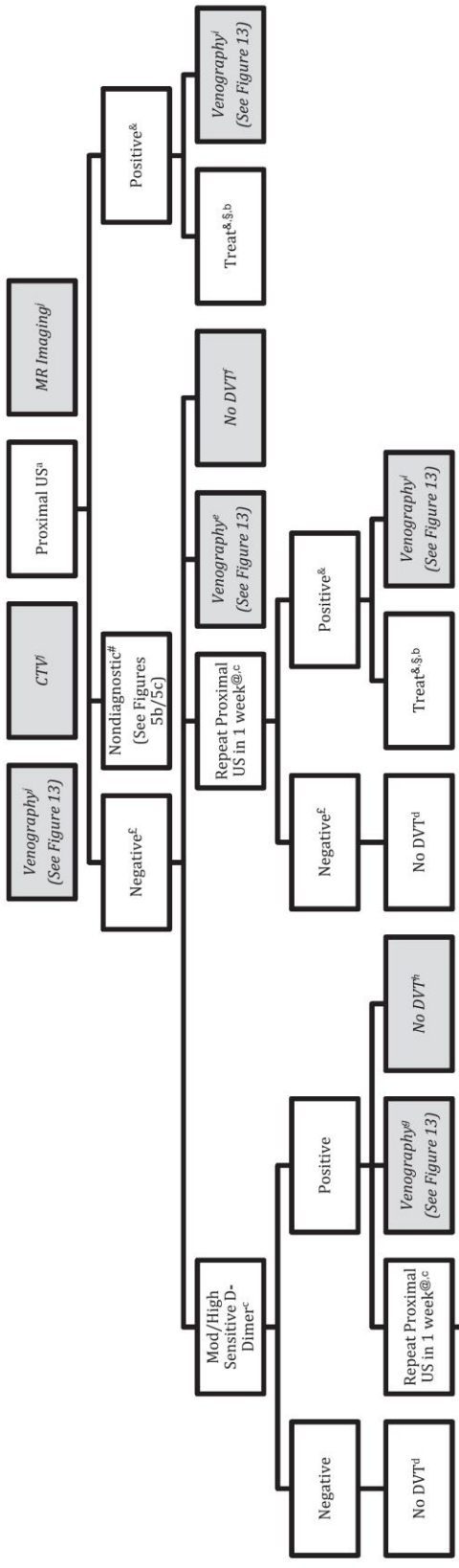


FIGURE 6. [Section 4.1] Recommendations for evaluation of suspected lower extremity recurrent DVT: proximal US as initial test. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] £"Negative" refers to a normal US or an area of prior noncompressibility with a stable or decreased residual diameter or an interval increase in residual diameter of <2 mm. #"Nondiagnostic" refers to a technically limited US, an area of prior noncompressibility with increase in residual venous diameter of <4 mm but ≥ 2 mm, or an area of prior noncompressibility without prior measurement of residual diameter for comparison. &"Positive" refers to a new noncompressible segment or an area of prior noncompressibility with an interval increase in residual diameter of ≥ 4 mm. @Consider additional serial proximal US. [a]Grade 1B vs venography, CTV, or MR venography. [b]Grade 1B for treating DVT vs venography if new noncompressible segment in the common femoral or popliteal vein; Grade 2B for treating DVT vs venography for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [c]Grade 2B vs no further testing and vs venography. [d]Grade 1B vs further testing with venography. [e]Grade 2B for at least one additional proximal US or moderate or highly sensitive D-dimer over venography. [f]Grade 2B for at least one additional proximal US over no further testing. [g]Grade 2B for at least one additional proximal US over venography. [h]Grade 2B for at least one additional proximal US over no further testing. [i]Grade 1B for treating DVT over venography for new noncompressible segment compared to previous CUS result; Grade 2B for treating DVT over venography for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [j]Grade 1B for proximal US (or highly sensitive D-dimer; see Figure 7) over venography, CTV, or MRI. CTV = CT scan venography; MR = magnetic resonance.

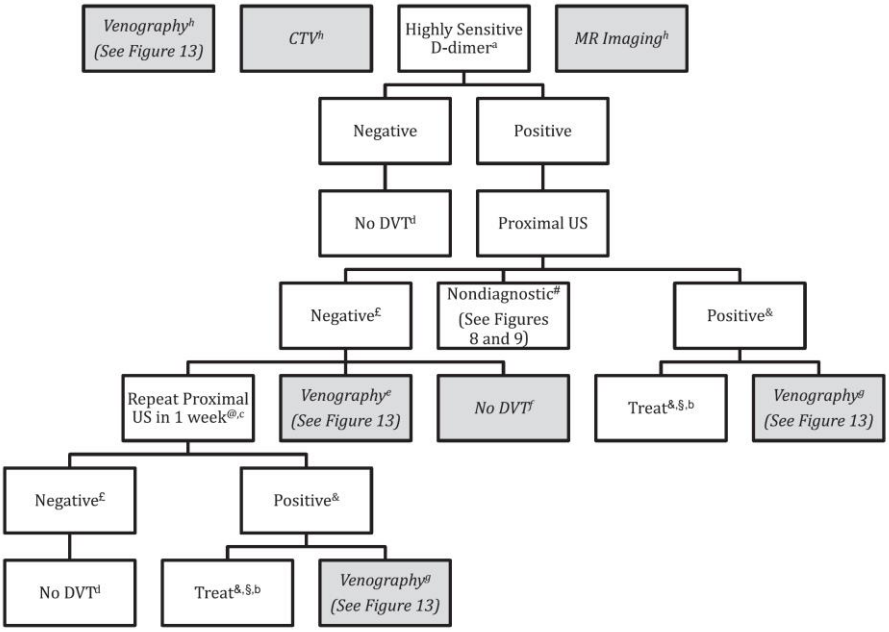


FIGURE 7. [Section 4.1] Recommendations for evaluation of suspected lower extremity recurrent DVT: highly sensitive D-dimer as initial test. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] £"Negative" refers to a normal US or an area of prior noncompressibility with a stable or decreased residual diameter or an interval increase in residual diameter of <2 mm. #"Nondiagnostic" refers to a technically limited US, an area of prior noncompressibility with increase in residual venous diameter of <4 mm but ≥ 2 mm, or an area of prior noncompressibility without prior measurement of residual diameter for comparison. &"Positive" refers to a new noncompressible segment or an area of prior noncompressibility with an interval increase in residual diameter of ≥ 4 mm. @Consider additional serial proximal US. [a]Grade 1B vs venography, CTV, or MR venography; preferred initial assay if prior US not available for comparison. [b]Grade 1B for treating DVT vs venography if new noncompressible segment in the common femoral or popliteal vein; Grade 2B for treating DVT vs venography for a $\geq$4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [c]Grade 2B vs no further testing and vs venography. [d]Grade 1B vs further testing with venography. [e]Grade 2B for at least one additional proximal US over venography. [f]Grade 2B for at least one additional proximal US over no further testing. [g]Grade 1B for treating DVT over venography if new noncompressible segment in the common femoral or popliteal vein; Grade 2B for treating DVT over venography for a $\geq$4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [h]Grade 1B for highly sensitive D-dimer (or proximal US; see Figure 6) over venography, CTV, or MRI. See Figure 1 and 6 legends for expansion of abbreviations.

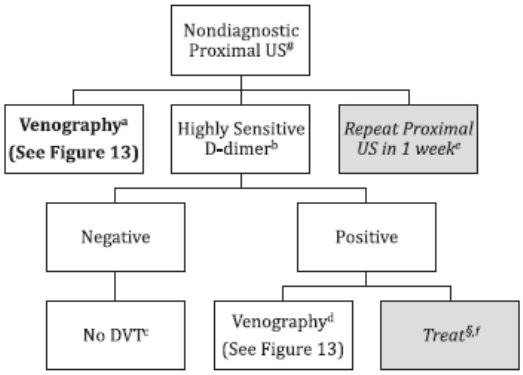


FIGURE 9. [Section 4.3] Recommendations for evaluation of suspected lower extremity recurrent DVT: evaluation following nondiagnostic proximal US and prior US result not available for comparison. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] Previous US with residual diameter measurements is not available for comparison. Current US is nondiagnostic (technically limited or only abnormality an area of prior noncompressibility). [a]Grade 1B vs repeat proximal US in 1 week. [b]Grade 2C vs repeat proximal US in 1 week. [c]Grade 2C vs further testing with venography. [d]Grade 2C vs treating for DVT. [e]Grade 2B for highly sensitive D-dimer (Grade 1B for venography) over repeat proximal US in 1 week. [f]Grade 2C for venography over treating for DVT. MRV = magnetic resonance venography. See Figure 1 legend for expansion of other abbreviation.

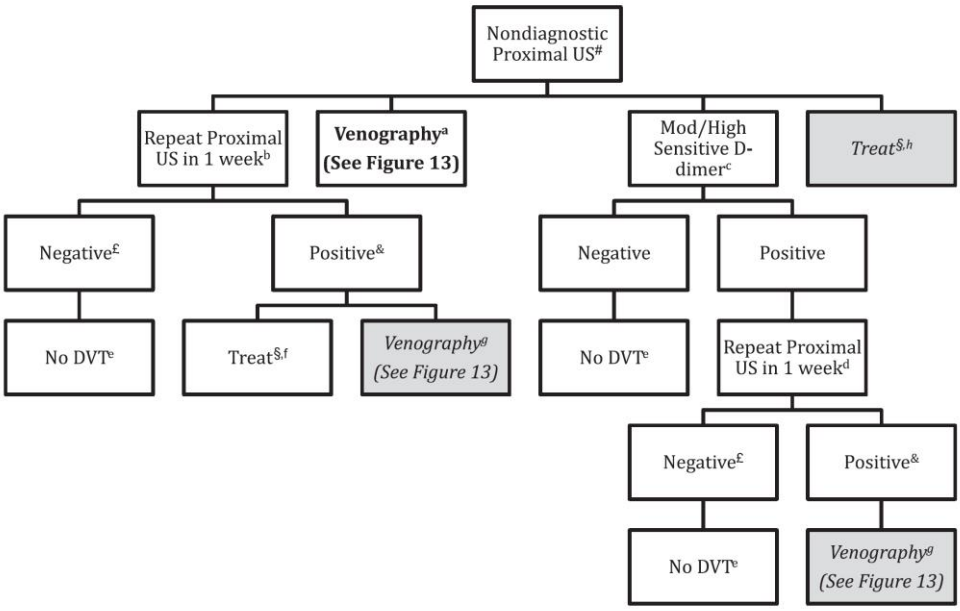


FIGURE 8. [Section 4.2] Recommendations for evaluation of suspected lower extremity recurrent DVT: evaluation following nondiagnostic proximal US and prior US result available for comparison. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] #Previous US with residual diameter measurements is available for comparison. Current US is nondiagnostic (technically limited or only abnormality an area of prior noncompressibility with increase in residual venous diameter of <4 mm but ≥ 2 mm). £"Negative" refers to a normal US or an area of prior noncompressibility with a stable or decreased residual diameter or an interval increase in residual diameter of <2 mm. &"Positive" refers to a new noncompressible segment or an area of prior noncompressibility with an interval increase in residual diameter of ≥ 4 mm. [a]Grade 1B vs treating for DVT and vs alternative test strategies. [b]Grade 2B vs treating for DVT and vs alternative test strategies. [c]Grade 2B vs treating for DVT and vs alternative test strategies. [d]Grade 2B vs no further testing and vs venography. [e]Grade 1B vs further testing with venography. [f]Grade 1B for treating DVT vs venography if new noncompressible segment in the common femoral or popliteal vein; Grade 2B for treating DVT vs venography for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [g]Grade 2B for treating DVT over venography if a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result (Grade 1B for treating DVT over venography if new noncompressible segment in the common femoral or popliteal vein). [h]Grade 2B for repeat proximal US in 1 week or moderate or highly sensitive D-dimer over treating for DVT (Grade 1B for venography over treating for DVT). See Figure 1 legend for expansion of abbreviation.

fig.5 and 13from ACCP 2012 Diagnosis guideline:

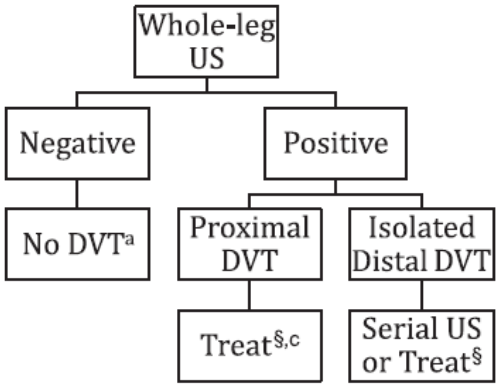


FIGURE 5. Use of whole-leg US (Referenced from Figures 1-4, 6). §See Kearon et al.[11] £If whole-leg US shows only isolated calf vein DVT, we suggest treating, rather than serial testing to rule out proximal extension only in patients with a high pretest probability or if high risk of extension or severe symptoms, see Kearon et al.[11] [a]Grade 1B vs repeat proximal US in 1 week, vs D-dimer testing and vs venography in patients with suspected first lower extremity DVT and a low, moderate, or unspecified pretest probability; Grade 2B vs venography and vs additional US in patients with suspected first lower extremity DVT and a high pretest probability. [b]Grade 2C vs treating DVT in patients with suspected first lower extremity DVT and a low, moderate, or unspecified pretest probability. [c]Grade 1B for treating DVT vs confirmatory venography. See Figure 1 legend for expansion of abbreviation.

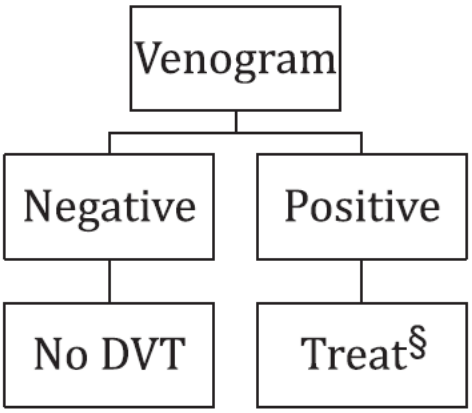


FIGURE 13. Use of venography (Referenced from Figures 1-12). §See Kearon et al.[11]

3.6 Summary of guidelines – guidelines on therapy

3.6.1 ACCP 2012 Therapy	**Grades of recommendation:** 1. strong recommendation; benefits clearly outweigh risk and burdens or vice versa 2. weak recommendation; benefits closely balanced with risks and burden
	Levels of evidence: 1. Strong recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence 2. Weak recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence
	Included populations, interventions, outcomes: - use of antithrombotic agents - use of devices or surgical techniques in the treatment of patients with DVT and pulmonary embolism (PE), also: patients with (1) postthrombotic syndrome (PTS), (2) chronic thromboembolic pulmonary hypertension (CTPH), (3) incidentally diagnosed (asymptomatic) DVT or PE, (4) acute upper-extremity DVT (UEDVT), (5) superfi cial vein thrombosis (SVT), (6) splanchnic vein thrombosis, and (7) hepatic vein thrombosis.
	Members of development group, target population: - cardiologists - health care providers, nurses, pharmacists, physicians, patients
	Recommendations: **DVT** - In patients with acute DVT of the leg treated with vitamin K antagonist (VKA) therapy, we recommend initial treatment with parenteral anticoagulation (low-molecular-weight heparin [LMWH], fondaparinux, IV unfractionated heparin [UFH], or subcutaneous [SC] UFH) over no such initial treatment (Grade 1B) . - In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C) . - In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C) . - In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C) In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C) . - In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension (see text), we suggest initial

	anticoagulation over serial imaging of the deep veins (Grade 2C) . - In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B) . - In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus - does not extend (Grade 1B) ; we suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C) ; we recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B) . - In patients with acute DVT of the leg, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed - initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the international normalized ratio (INR) is 2.0 or above for at least 24 h (Grade 1B) . - In patients with acute DVT of the leg, we suggest LMWH or fondaparinux over IV UFH (Grade 2C) and over SC UFH (Grade 2B for - LMWH; Grade 2C for fondaparinux) . - In patients with acute DVT of the leg treated with LMWH, we suggest once- over twice-daily administration (Grade 2C) . - In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B) . o In patients with acute proximal DVT of the leg, we suggest anti coagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C) . - In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (Grade 2C) . - In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over operative venous thrombectomy (Grade 2C) . - In patients with acute DVT of the leg who undergo thrombosis removal, we recommend the same intensity and duration of anticoagulant therapy as in comparable patients who do not undergo thrombosis removal (Grade 1B) . - In patients with acute DVT of the leg, we recommend against the use of an inferior vena cava (IVC) fi lter in addition to anticoagulants (Grade 1B) . - In patients with acute proximal DVT of the leg and contraindication to anticoagulation, we recommend the use of an IVC filter (Grade 1B) . - In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended - duration of therapy) over stopping anticoagulant therapy after about 1 week of initial therapy (Grade 1B) . - In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) , (ii) treatment of a longer time-limited period (eg, 6 or12 months) (Grade 1B) , or (iii) extended therapy (Grade 1B regardless of bleeding risk) . - In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) , (ii)

	treatment of a longer timelimited period (eg, 6 or 12 months) (Grade 1B) , and (iii) extended therapy if there is a high bleeding risk (Grade 1B) . We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B) . - In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C) and recommend treatment with anticoagulation for 3 months over treatment of a longer timelimited period (eg, 6 or 12 months) (Grade 1B) or extended therapy (Grade 1B regardless of bleeding risk) . - In patients with an unprovoked DVT of the leg (isolated distal [see remark] or proximal), we recommend treatment with anticoagulation - for at least 3 months over treatment of a shorter duration (Grade 1B) . After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefi t ratio of extended therapy. - In patients with a fi rst VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B) . - In patients with a fi rst VTE that is an unprovoked proximal DVT of the leg and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B) . - In patients with a fi rst VTE that is an unprovoked isolated distal DVT of the leg (see remark), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk (Grade 2B) and recommend 3 months of anticoagulant treatment in those with a high bleeding risk (Grade 1B) . - In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B), and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Grade 2B) . - In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of anticoagulant therapy over extended therapy (Grade 2B) . - In patients with DVT of the leg and active cancer, if the risk of bleeding is not high, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B) , and if there is a high bleeding risk, we suggest extended anticoagulant therapy (Grade 2B) . - *Remarks:* Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant - therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants (see section 2.3). - In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually). - In patients with DVT of the leg who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR , 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B) .

	- In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C) . For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy - (Grade 2C) . - In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (Grade 2B) . - In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy - (Grade 2B) . - *Remarks:* Choice of treatment in patients with and without cancer is sensitive to the individual patient's tolerance for daily injections, need for laboratory monitoring, and treatment costs. LMWH, rivaroxaban, and dabigatran are retained in patients with renal impairment, whereas this is not a concern with VKA. Treatment of VTE with dabigatran or rivaroxaban, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. When these guidelines were being prepared (October 2011), postmarketings studies of safety were not available. Given the paucity of currently available data and that new data are rapidly emerging, we give a weak recommendation in favor of VKA and LMWH therapy over dabigatran and rivaroxaban, and we have not made any recommendations in favor of one of the new agents overthe other. - In patients with DVT of the leg who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the first 3 months (Grade 2C) . - In patients who are incidentally found to have asymptomatic DVT of the leg, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic DVT (Grade 2B) . - In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B) . - *Remarks:* Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful. Patients who place a low value on preventing PTS or a high value on avoiding the inconvenience and discomfort of stockings are likely to decline stockings. - In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C) . - In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B) . - In patients with PTS of the leg, we suggest that venoactive medications (eg, rutosides, defi -brotide, and hidrosmin) not be used (Grade 2C) . **<u>Pulmonary embolism</u>** - In patients with acute PE, we recommend initial treatment with parenteral anticoagulation (LMWH, fondaparinux, IV UFH, or SC UFH) over no such initial treatment (Grade 1B) . - In patients with a high clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C) . - In patients with an intermediate clinical suspicion of acute PE, we suggest treatment with parenteral anticoagulants compared with no

	treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C) . - In patients with a low clinical suspicion of acute PE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C) - In patients with acute PE, we recommend early initiation of VKA (eg, same day as parenteral therapy is started) over delayed initiation, and continuation of parenteral anticoagulation for a minimum of 5 days and until the INR is 2.0 or above for at least 24 h (Grade 1B) . - In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux) and over SC UFH (Grade 2B for LMWH; Grade 2C for fondaparinux) . - In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C) . - In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B) .. - In patients with acute PE associated with hypotension (eg, systolic BP , 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C) . - In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1C) . - In selected patients with acute PE not associated with hypotension and with a low bleeding risk whose initial clinical presentation, or clinical course after starting anticoagulant therapy, suggests a high risk of developing hypotension, we suggest administration of thrombolytic therapy (Grade 2C) . - In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest catheterassisted thrombus removal over no such intervention (Grade 2C) . - In patients with acute PE associated with hypotension, we suggest surgical pulmonary embolectomy over no such intervention if they have (i) contraindications to thrombolysis, (ii) failed thrombolysis or catheter-assisted embolectomy, or (iii) shock that is likely to cause death before thrombolysis can take effect (eg, within hours), provided surgical expertise and resources are available (Grade 2C) . - In patients with acute PE who are treated with anticoagulants, we recommend against the use of an IVC fi lter (Grade 1B) . - In patients with acute PE and contraindication to anticoagulation, we recommend the use of an IVC fi lter (Grade 1B) . - In patients with acute PE and an IVC fi lter inserted as an alternative to anticoagulation, we suggest a conventional course of anticoagulant therapy if their risk of bleeding resolves (Grade 2B) . - In patients with PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) , (ii) treatment of a longer timelimited period (eg, 6 or 12

	months) (Grade 1B) , or (iii) extended therapy (Grade 1B regardless of bleeding risk) . - In patients with PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) , (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B) , and (iii) extended therapy if there is a high bleeding risk (Grade 1B) . We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B) . - In patients with an unprovoked PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B) . After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefi t ratio of extended therapy. - In patients with a fi rst VTE that is an unprovoked PE and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B) . - In patients with a fi rst VTE that is an unprovoked PE and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B) . - In patients with a second unprovoked VTE, we recommend extended anticoagulant therapy over 3 months of therapy in those who have a low bleeding risk (Grade 1B) , and we suggest extended anticoagulant therapy in those with a moderate bleeding risk (Grade 2B) . - In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of therapy over extended therapy (Grade 2B) . - In patients with PE and active cancer, if there is a low or moderate bleeding risk, we recommend extended anticoagulant therapy over 3 months of therapy (Grade 1B) , and if there is a high bleeding risk, we suggest extended anticoagulant therapy (Grade 2B) . - In patients with PE who are treated with VKA, we recommend a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5) over a lower (INR , 2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B) . - In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C) . For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C) . - In patients with PE and cancer, we suggest LMWH over VKA therapy (Grade 2B) . In patients with PE and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2C) . - In patients with PE who receive extended therapy, we suggest treatment with the same anticoagulant chosen for the fi rst 3 months (Grade 2C) . - In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B) .

3.7 Summary of guidelines - guidelines on prevention

3.7.1 ACCP 2012 Orthopedic prevention	**Grades of recommendation:** 3. strong recommendation; benefits clearly outweigh risk and burdens or vice versa 4. weak recommendation; benefits closely balanced with risks and burden
	Levels of evidence: 1. Strong recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence 2. Weak recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence
	Included populations, interventions, outcomes: - patients undergoing orthopedic surgery, including total hip arthroplasty, total knee arthroplasty and hip fracture surgery, below-knee injuries, arthroscopic procedures - non-pharmacologic prophylaxis (graduated compression stockings, intermittent pneumatic compression), heparin therapy, fondaparinux, dabigatran, apixaban, rivaroxaban, vitamin K antagonist, aspirin - fatal and symptomatic PE and symptomatic DVT, symptomatic bleeding events
	Members of development group, target population: - cardiologists - health care providers, nurses, pharmacists, physicians, patients
	Recommendations: *** Patients undergoing major orthopedic surgery** **total hip arthroplasty (THA), total knee arthroplasty (TKA), hip fracture surgery (HES)** *Thromboprophylaxis compared with no prophylaxis* In patients undergoing THA or TKA, the expert panel recommends use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose vitamin K antagonist (VKA), aspirin (all Grade 1B), or an intermittent pneumatic compression device (IPCD). (Grade 1C) Remarks: the expert panel recommends the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18h of daily compliance. One panel member believed strongly that aspirin alone should not be included as an option. In patients undergoing HFS, the expert panel recommends use of one of the following rather than no antithrombotic prophylaxis for a minimum of 10 to 14 days: LMWH, fondaparinux, LDUH, adjusted-dose VKA, aspirin (all Grade 1B), or an IPCD (Grade 1C). Remarks: the expert panel recommends the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a

	daily basis for inpatients and outpatients. Efforts should be made to achieve 18h of daily compliance. One panel member believed strongly that aspirin alone should not be included as an option. *Timing of commencement of anticoagulants* For patients undergoing major orthopedic surgery (THA, TKA, HFS) and receiving LMWH as thromboprophylaxis, the expert panel recommends starting either 12h or more preoperatively or 12h or more postoperatively rather than within 4h or less preoperatively or 4h or less postoperatively. (Grade 1B) *Choice of thromboprophylaxis* In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, the expert panel suggests the use of LMWH in preference to the other agents the panel has recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C). Remarks: if started preoperatively, the expert panel suggests administering LMWH ≥12h before surgery. Patients who place a high value on avoiding the inconvenience of daily injections with LMWH and a low value on the limitations of alternative agents are likely to choose an alternative agent. Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux, rivaroxaban, and VKA), possible decreased efficacy (LDUH, VKA, aspirin, and IPCD alone), and lack of long-term safety data (apixaban, dabigatran and rivaroxaban). Furthermore, patients who place a high value on avoiding bleeding complications and a low value on its inconvenience are likely to choose an IPCD over the drug options. In patients undergoing HFS, irrespective of the concomitant use of an IPCD or length of treatment, the expert panel suggests the use of LMWH in preference to the other agents the panel has recommended as alternatives: fondaparinux, LDUH (Grade 2B), adjusted-dose VKA, or aspirin (all Grade 2C). Remarks: for patients in whom surgery is likely to be delayed, the expert panel suggests that LMWH be initiated during the time between hospital admission and surgery but suggests administering LMWH at least 12h before surgery. Patients who place a high value on avoiding the inconvenience of daily injections with LMWH and a low value on the limitations of alternative agents are likely to choose an alternative agent. Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux), possible decreased efficacy (LDUH, VKA, aspirin, and IPCD alone), and lack of long-term safety data (apixaban, dabigatran and rivaroxaban). Furthermore, patients who place a high value on avoiding bleeding complications and a low value on its inconvenience are likely to choose an IPCD over the drug options. For patients undergoing major orthopedic surgery, the expert panel suggests extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days (Grade 2B). *Use of combination thromboprophylaxis* In patients undergoing major orthopedic surgery, the expert panel suggests using dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (Grade 2C). Remarks: the expert panel recommends the use of only portable, battery-

	powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18h of daily compliance. Patients who place a high value on avoiding the undesirable consequences associated with prophylaxis with both a pharmacologic agent and an IPCD are likely to decline use of dual prophylaxis. In patients undergoing major orthopedic surgery and increased risk of bleeding, the expert panel suggests using an IPCD or no prophylaxis rather than pharmacologic treatment (Grade 2C). Remarks: the expert panel recommends the use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Efforts should be made to achieve 18h of daily compliance. Patients who place a high value on avoiding the discomfort and inconvenience of IPCD and a low value on avoiding a small absolute increase in bleeding with pharmacologic agents when only one bleeding risk factor is present (in particular the continued use of antiplatelet agents) are likely to choose pharmacologic thromboprophylaxis over IPCD. *Other considerations* In patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD, the expert panel recommends using apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis (all Grade 1B). Screening for DVT before hospital discharge For asymptomatic patients following major orthopedic surgery, the expert panel recommends against Doppler (or duplex) ultrasound screening before hospital discharge (Grade 1B). *** Isolated lower-leg injuries distal to the knee** The expert panel suggests no prophylaxis rather than pharmacologic thromboprophylaxis in patients with isolated lower-leg injuries requiring leg immobilization (Grade 2C). *** Knee arthroscopy** For patients undergoing knee arthroscopy without a history of prior VTE, the expert panel suggests no thromboprophylaxis rather than prophylaxis (Grade 2B).

3.7.2	**ACCP 2012 Surgical prevention**	**Grades of recommendation:** 1. strong recommendation; benefits clearly outweigh risk and burdens or vice versa 2. weak recommendation; benefits closely balanced with risks and burden
		Levels of evidence: 1. Strong recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence 2. Weak recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence
		Included populations, interventions, outcomes: - non-orthopedic surgical patients at risk for VTE - non-pharmacologic prophylaxis (early mobilization, graduated compression stockings, intermittent pneumatic compression), heparin therapy, fondaparinux, aspirin - death from any cause, fatal PE, non-fatal symptomatic PE and DVT, fatal bleeding, bleeding requiring reoperation, major bleeding
		Members of development group, target population: - cardiologists - health care providers, nurses, pharmacists, physicians
		Recommendations: *** Risk stratification, rationale for prophylaxis and recommendations in general, abdominal-pelvic, bariatric, vascular and plastic and reconstructive surgery** For general and abdominal surgery patients at very low risk for VTE (<0.5%; Rogers score <7 Caprini score 0), the expert panel recommends that no specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis be used other than early ambulation. For general and abdominal surgery patients at low risk for VTE (~1.5%; Rogers score 7-10, Caprini score 1-2), the expert panel suggests mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC), over no prophylaxis (Grade 2C). For general and abdominal surgery patients at moderate risk for VTE (3.0%; Rogers score >10, Caprini score 3-4), the expert panel suggests LMWH (Grade 2B), low-dose unfractionated heparin (LDUH) (Grade 2B), or mechanical prophylaxis, preferably with (IPC), over no prophylaxis (Grade 2C). Remarks: 3 of the 7 authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group. For general and abdominal surgery patients at moderate risk for VTE (3.0%; Rogers score >10, Caprini score 3-4) who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, the expert panel suggests mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C). For general and abdominal-pelvic surgery patients at high risk for VTE (~6%; Caprini score ≥5) who are not at high risk for major bleeding complications, the expert panel recommends pharmacologic prophylaxis with LMWH (Grade 1B) or LDUH (Grade 1B) over no prophylaxis. The expert panel suggests that mechanical prophylaxis with elastic stockings or IPC should be added to

	pharmacologic prophylaxis (Grade 2C). For high-VTE risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, the expert panel recommends extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (Grade 1B). Remarks: patients who place a high value on minimizing out-of-pocket health-care costs might prefer limited-duration over extended-duration prophylaxis in settings where the cost of extended-duration prophylaxis is borne by the patient. For high-VTE risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, the expert panel suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C). For general and abdominal-pelvic surgery patients at high risk for VTE (~6%; Caprini score ≥5) in whom both LMWH and unfractionated heparin are contraindicated or unavailable and who are not at high risk for major bleeding complications, the expert panel suggests low-dose aspirin (Grade 2C), fondaparinux (Grade 2C), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prohylaxis. For general and abdominal-pelvic surgery patients, the expert panel suggests that an inferior vena cava (IVC) filter should not be used for primary VTE prevention (Grade 2C). For general and abdominal-pelvic surgery patients, the expert panel suggests that periodic surveillance with venous compression ultrasound should not be performed. (Grade 2C). *** Thoracic surgery** For thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding, the expert panel suggests LDUH (Grade 2B), LMWH (Grade 2B), or mechanical prophylaxis with optimally applied IPC (Grade 2C), over no prophylaxis. Remarks: 3 of the 7 authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group. For thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding, the expert panel suggests LDUH (Grade 1B) or LMWH (Grade 1B) over no prophylaxis. In addition, the expert panel suggests that mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis (Grade 2C). For thoracic surgery patients who are at high risk for major bleeding, the expert panel suggests use of mechanical prophylaxis, preferably with optimally applied IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated. (Grade 2C).

Risk scores from ACCP 2012 Surgical prevention

*One rigorously developed model used data from 183,069 patients in the Patient Safety in Surgery Study who underwent general, vascular, and thoracic procedures at one of 128 Veterans Administration medical centers or 14 private sector hospitals between 2002 and 2004. This model assigned points (the **Rogers** score) to variables that were found to be independent predictors of VTE*

risk, including type of operation, work relative value units, patient characteristics, and laboratory values. Using this model, the risk of symptomatic VTE varied from very low (0.1%) to low (ca. 0.5%) to moderate (ca. 1.5%) in both development and validation samples.
Unfortunately, this model is somewhat cumbersome to use and has not been externally validated. In addition, information was not provided about how many patients received prophylaxis. It is likely that at least some patients received mechanical prophylaxis, pharmacologic prophylaxis, or both, which may help to explain the relatively low observed risk of VTE.
*Another model (the **Caprini** score) estimates VTE risk by adding points for various VTE risk factors. In our adaptation of this model, VTE risk is categorized as being very low (0-1 point), low (2 points), moderate (3-4 points), or high (≥ 5 points). Although this model was not developed using rigorous statistical methods, and includes some variables that were later found not to be associated with VTE risk, 81 it is relatively easy to use and appears to discriminate reasonably well among patients at low, moderate, and high risk for VTE.*

Rogers score:

Risk Factor	Risk Score Points
Operation type other than endocrine:	
Respiratory and hernic	9
Thoracoabdominal aneurysm, embolectomy/ thrombectomy, venous reconstruction, and endovascular repair	7
Aneurysm	4
Mouth, palate	4
Stomach, intestines	4
Integument	3
Hernia	2
ASA physical status classification:	
3, 4, or 5	2
2	1
Female sex	1
Work RVU:	
> 17	3
10-17	2
Two points for each of these conditions:	2
Disseminated cancer	
Chemotherapy for malignancy within 30 d of operation	
Preoperative serum sodium > 145 mmol/L	
Transfusion > 4 units packed RBCs in 72 h before operation	
Ventilator dependant	
One point for each of the conditions:	1
Wound class (clean/contaminated)	
Preoperative hematocrit level ≤ 38%	
Preoperative bilirubin level > 1.0 mg/dL	
Dyspnea	
Albumin level ≤ 3.5 mg/dL	
Emergency	
Zero points for each of these conditions:	0

ASA physical status class 1	
Work RVU < 10	
Male sex	

ASA = American Society of Anesthesiologists; RVU = relative value unit

Caprini score:

1 Point	2 Points	3 Points	5 Points
Age 41-60 y	Age 61-74 y	Age ≥75 y	Stroke (<1 mo)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI >25 kg/m2	Major open surgery (>45 min)	Family history of VTE	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery (>45 min)	Factor V Leiden	Acute spinal cord injury (<1 mo)
Varicose veins	Malignancy	Prothrombin 20210A	
Pregnancy or postpartum	Confined to bed (>72h)	Lupus anticoagulant	
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement	Central venous access	Elevated serum homocysteine	
Sepsis (<1 mo)		Heparin-induced thrombocytopenia	
Serious lung disease, including pneumonia (<1 mo)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Acute myocardial infarction			
Congestive heart failure (< 1 mo)			
History of inflammatory bowel disease			
Medical patient at bed rest			

3.7.3	**ACCP 2012 Nonsurgical prevention**	**Grades of recommendation:** 1. strong recommendation; benefits clearly outweigh risk and burdens or vice versa 2. weak recommendation; benefits closely balanced with risks and burden
		Levels of evidence: 1. Strong recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence 2. Weak recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence
		Included populations, interventions, outcomes: - hospitalized medical, outpatients with cancer, the chronically immobilized, long-distance travelers, those with asymptomatic thrombophilia - non-pharmacologic prophylaxis (frequent ambulation, calf muscle exercise, sitting in aisle seat when traveling, graduated compression stockings, intermittent pneumatic compression), heparin therapy, fondaparinux, vitamin K antagonist, aspirin - symptomatic DVT, PE, death from PE and hemorrhagic deaths, major bleeding including intracranial and gastrointestinal bleeding, heparin-induced thrombocytopenia (HIT), mechanical thromboprophylaxis complications
		Members of development group, target population: - cardiologists - health care providers, nurses, pharmacists, physicians
		Recommendations**:** *** Hospitalised acutely ill medical patients** *Any anticoagulant vs none to prevent VTE* For acutely ill hospitalized medical patients at increased risk of thrombosis, the expert panel recommends anticoagulant thromboprophylaxis with LMWH, LUDH bid or tid, or fondaparinux (Grade 1B). Remarks: in choosing the specific anticoagulant drug to be used for pharmacoprophylaxis, choices should be based on patient preference, compliance and ease of administration, as well as on local factors affecting acquisition costs (e.g. prices of various pharmacological agents in individual hospital formularies). *LDUH vs LMWH to prevent VTE* For acutely ill hospitalized medical patients at low risk of thrombosis, the expert panel recommends against the use of pharmacologic thromboprophylaxis (Grade 1B). *Stockings to prevent VTE* For acutely ill hospitalized medical patients who are bleeding or at high risk for bleeding, the expert panel recommends against anticoagulant thromboprophylaxis (Grade 1B). *Intermittent pneumatic compression devices to prevent VTE* For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, the expert panel suggests the optimal use of mechanical thromboprophylaxis with graduated compression stockings (GCS) (Grade 2C) or intermittent pneumatic compression (IPC) (Grade 2C), rather than no mechanical thromboprophylaxis. When bleeding risk

	decreases, and if VTE risk persists, the expert panel suggests that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis (Grade 2B). Remarks: patients who are particularly averse to the potential for skin complications, cost and need for clinical monitoring of GCS and IPC use are likely to decline mechanical prophylaxis. *Extended-duration anticoagulant thromboprophylaxis to prevent VTE in hospitalized medical patients* In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, the expert panel suggests against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B). *** Patients with cancer in the outpatient setting** *Parenteral anticoagulants* In outpatients with cancer who have no additional risk factors for VTE, the expert panel suggests against routine prophylaxis with LMWH or LDUH (Grade 2B) and recommends against the prophylactic use of vitamin K antagonists (VKAs) (Grade 1B). Remarks: **additional risk factors** for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide and lenalidomide. In outpatients with solid tumors who have additional risk factors for VTE and who are at low risk of bleeding, the expert panel suggests prophylactic-dose LMWH or LDUH over no prophylaxis (Grade 2B). Remarks: additional risk factors for venous thrombosis in cancer outpatients include previous venous thrombosis, immobilization, hormonal therapy, angiogenesis inhibitors, thalidomide and lenalidomide. *Patients with cancer with indwelling central venous catheters (CVCs)* In outpatients with cancer and indwelling CVCs, the expert panel suggests against the routine prophylaxis with LMWH or LDUH (Grade 2B) and suggests against the prophylactic use of VKAs (Grade 2C). *** Chronically immobilized patients** In chronically immobilized persons residing at home or at a nursing home, the expert panel suggests against the routine use of thromboprophylaxis (Grade 2C). *** Long-distance travel** For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), the expert panel suggests frequent ambulation, calf muscle exercise, or sitting in an aisle seat if feasible (Grade 2C). For long-distance travelers at increased risk of VTE (including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age, limited mobility, severe obesity, or known thrombophilic disorder), the expert panel suggests use of properly fitted below-knee GCS providing 15 to 30 mmHg of pressure at the ankle during travel (Grade 2C). For all other long-distance travelers, the expert panel suggests against the use of GCS (Grade 2C). For long-distance travelers, the expert panel suggests against the use of aspirin

	or anticoagulants to prevent VTE (Grade 2C). *** Thromboprophylaxis to prevent VTE in asymptomatic persons with thrombophilia** In persons with asymptomatic thrombophilia (i.e. without a previous history of VTE), the expert panel recommends against the long-term daily use of mechanical or pharmacologic thromboprophylaxis to prevent VTE (Grade 1C).

3.7.4 ACP 2011	**Grades of recommendation:** 1. strong recommendation; benefits clearly outweigh risk and burdens or vice versa 2. weak recommendation; benefits closely balanced with risks and burden
	Levels of evidence: 1. Strong recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence 2. Weak recommendation A. high quality evidence B. moderate quality evidence C. low or very low quality evidence
	Included populations, interventions, outcomes: - hospitalized non-surgical patients (medical patients and patients with acute stroke) - subcutaneous low-dose heparin (LMWH, UFH), mechanical devices - total mortality up to 120 days after randomization, symptomatic DVT, all PEs, fatal PEs, all bleeding events, major bleeding events, effects on skin (for mechanical prophylaxis)
	Members of development group, target population: - physicians - internists, family physicians, other clinicians
	Recommendations: - ACP recommends assessment of the risk for thromboembolism and bleeding in medical patients prior to initiation of prophylaxis of VTE (Grade: strong recommendation, moderate quality evidence) - ACP recommends pharmacologic prophylaxis with heparin or a related drug for VTE in medical patients unless the assessed risk for bleeding outweighs the likely benefits (Grade: strong recommendation, moderate quality evidence) - ACP recommends against the use of mechanical prophylaxis with graduated compression stockings for prevention of VTE (Grade: strong recommendation, moderate quality evidence)

3.8 Conclusions from guidelines

See document de synthèse (Fr) and syntheserapport (Nl)

4 Evidence tables and conclusions: Treatment of venous thromboembolism

4.1 Initial treatment of venous thromboembolism

4.1.1 Anticoagulation versus placebo in the initial treatment

There are few studies comparing active treatment to placebo in patients with VTE. All available studies were discussed in the literature search of the previous consensus conference on VTE. None of these meet our current inclusion criteria (small numbers).

The chapter from the previous report is shown here as an illustration.

1.1.1. Meta-analyses and systematic reviews

There are no meta-analyses or systematic reviews found on this topic.

1.1.2. RCTs

There were three publications, all of sufficient quality, on RCTs that compared unfractionated heparin with a control group receiving no anticoagulation treatment (Barritt 1960(226), Nielsen 1994a en b(231,232)).

Table: RCT's on the effect of unfractionated heparin in acute treatment of deep-venous thrombosis (studies of insufficient quality are printed in italic)

Ref.	N	QS*	Treatments compared	Diagnosis	Time of FU	% FU	Recurrence VTE	Thrombus extension	Major bleeding	Mortality
Barritt 1960	*35*	*6.5*	***Heparin intravenous injection 10000 IU every 6h for six doses, without laboratory control + nicoumalone usually 16mg followed at 12h intervals by 8, 8, and 4mg*** *Vs. control group (no anticoagulant treatment)*	*Pulmonary embolism (clinical + radiography and electrocardiogram)*	*Not clear*	*100%*	Pulmonary embolism: *Treated: 0/16* *Untreated: 10/19* *p=0.0005* *SS*	NR	*Treated: 1 patient died from suppur. Pneumonia with haemorrh. From duodenal ulcer* *NT*	*<u>Death from PE:</u>* *Treated: 0/16* *Untreated: 5/19* *P=0.036* *SS*
Nielsen 1994 (b)	*90*	*8*	*See Nielsen 1994 (a)*	*See Nielsen 1994 (a)*	*3m 12m*	*3m: 66% 12m:?*	***Clinical evaluation:*** *Clinical signs of PE:* *AC: 2* *phen: 1* *NT* *Clinical signs of DVT :* *AC: 3* *phen: 9* *NT*	*<u>Thrombus regression at 3m (index of effectiveness)</u>* *Distal veins:* *AC vs. phen 4.4% (27.5% to –18.7%)* *NS* *Proximal veins :* *AC vs. Phen 10.9% (32% to –10.1%)* *NS*	***Major:*** *AC: 4* *Phen: 0* *NT* ***Minor:*** *AC: 2* *Phen: 0* *NT*	*12m:* *AC: 6 (1 from PE)* *Phen: 7 (0 from PE)* *NT*

Nielsen 1994 (a)	*87*	*9*	*AC treatment: Intravenous heparin bolus of 10000IU + infusion of 40000 IU/24h adjusted to APTT + phenprocoumon from d3 during 3m* *vs. phenylbutazone 3x200mg at day1 and 3x100mg on day 2-10* *All patients were actively mobilized from first day of admission wearing graduated compressing stockings*	*Symptomatic venographi-cally proven DVT*	*10d 60d 3m*	*10d: 92%* *60d: 69%* *3m: ?*	PE progression : *10d:* *AC 6/41 (15%)* *Phen 3/39 (8%)* *Diff=0.8% (95% CI from -19.9 to 21.5%)NS* *60d:* *AC 1/30 (3%)* *Phen 1/30 (3%)* *Diff=3.3% (95% CI from –21.8 to 28.5%)NS* ***Signs of DVT and PE progression at 3m:*** *AC: 19/? Phen: 19/? NT* ***Clinical signs of PE at 3m:*** *AC: 2/? Phen: 1/? NT*	*NR*	*NR*	*3m:* *AC: 1* *Phen: 0* *NT*

Legend:

n = number of patients; % FU = percentage of patients in follow-up;

NS= no statistically significant difference between treatments; SS= statistically significant difference between treatments; NR = not reported; NT = no statistical test

**: Quality score on 15*

VTE= venous thromboembolism; DVT= deep-venous thrombosis; PE= pulmonary embolism

Warf= warfarin; Phen= phenylbutazone; AC= anticoagulation

- *One RCT of 1960 compared treatment with intravenous heparin in combination with anticoagulation (n=16) to a control group (n=19) in patients with pulmonary embolism. (Barritt 1960) The RCT was of insufficient quality and found a significant difference between both groups for the recurrence of pulmonary embolism and for mortality resulting from pulmonary embolism.*
- *The two more recent publications presented the results of the same trial. (Nielsen 1994a, Nielsen 1994b). In 90 patients with symptomatic, venographically proven DVT, treatment with intravenous heparin in combination with phenprocoumon was compared to a control group of patients receiving phenylbutazone. The study could not show a significant difference between both treatments for the progression of pulmonary embolism based on a lung scan after 10 days and after 60 days. There was also no significant difference for thrombus regression at three months. No statistical test was reported for the other outcomes.*

1.2. Low-molecular weight heparin (LMWH)

1.2.1. LMWH versus placebo

1.2.1.1. Meta-analyses and systematic reviews

There are no meta-analyses or systematic reviews found on this topic

1.2.1.2. RCTs

There are no RCTs found on this topic.

4.1.2 Anticoagulation versus anticoagulation in the initial treatment

We could not include any studies that compare different active treatments in the initial treatment phase only. Existing trials compare LMWH vs UFH or vs fondaparinux, which was not a research question for this review.

A few trials compare treatments in both the initial and continuation phase of treatment. They are reported in the next chapter. Most trials compare different treatments in the continuation phase of treatment, after a (common) initial treatment for 5-14 days.

4.1.3 Duration of initial treatment

No trials were found.

4.2 Initial treatment and continued treatment to prevent recurrent venous thromboembolism

4.2.1 New anticoagulants versus standard treatment

4.2.1.1 Rivaroxaban versus enoxaparin followed by a vitamin K antagonist in acute symptomatic DVT

Study details	n/Population	Comparison	Outcomes		Methodological
EINSTEIN –DVT 2010(4) Acute DVT study Design: open-label, event-driven, noninferiority study RCT: OL, PG Setting: unclear Duration of follow-up: 3months (12%), 6 months (63%) or 12 months	n= 3449 Mean age: 56 Previous VTE(DVT/PE): (19.4% rivaroxaban) (19.2%standard therapy) Current malignancy: NR Recent surgery: NR Recent trauma: NR Immobilized: NR Pretreatment (LMWH, heparin, fondaparinux): 73% rivarox; 71% standard. Duration of pretreatment: • 1 day: 68.9% rivarox, 66.3% standard • 2 days: 3.9% rivarox, 3.9% standard) TTR (VKA): 57.7% and exceeding 3.0 only 16.2% of	Rivaroxaban 15mg 2x/d first 3 weeks, followed by 20mg/d. for the intended x months of treatment vs subcutaneous enoxaparin 1mg/kg body weight 2x/d and either warfarin or acenocoumarol, started within 48 hours after randomisation. INR target 2.0-3.0	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: unclear FOLLOW-UP: 99.3% in safety analysis 100% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: Yes Efficacy: ITT Safety: excluded patients who did not receive study medication Power and non-inferiority margin:
			Symptomatic , recurrent VTE (PO) (confirmed by with the use of diagnostic criteria for PE: CT scan, pulmonary angiogram, ventilation/perfusion scan; for DVT: compression ultrasound, venography)	Rivaroxaban: 36/1731 (2.1%) Enoxaparin-VKA: 51/1718 (3.0%) **HR: 0.68 (95 % CI 0.44 to 1.04); p<0.001 for noninferiority** SS (Hazard ratio stratified for intended treatment duration) "The results of the on-treatment and per-protocol analyses were similar to those of the intention-to-treat analysis (data not shown)"
			Net clinical benefit (VTE +major bleeding)	Rivaroxaban: 51/1731 (2.9%) Enoxaparin-VKA: 73/1718 (4.2%) **HR: 0.67 (95%CI 0.47 to 0.95); p=0.03** **SS in favour of rivaroxaban**
			Total deaths	Rivaroxaban: 38/1731(2.2%) Enoxaparin-VKA: 49/1718 (2.9%) HR: 0.67 (95% CI 0.44 to 1.02); p=0.06 NS
			Safety	

(25%) of treatment. (decided by the treating physician before randomization)	the time <u>Inclusion</u> acute, symptomatic, **objectively confirmed** proximal DVT, without symptomatic PE <u>Exclusion</u> received therapeutic doses of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for > 48 hours or received more than a single dose of a vitamin K antagonist before randomization; treated with thrombectomy, vena cava filter, or fibrinolytic agent for the current thrombosis; contraindication to enoxaparin, warfarin, or acenocoumarol. Another indication for a vitamin K antagonist; a creatinine clearance < 30 ml/min ; clinically significant liver disease or an ALT >3 x upper limit; bacterial endocarditis; active bleeding or a high risk of bleeding;		**Major or clinically relevant nonmajor bleeding** Major bleeding is defined as overt bleeding and: fall in hemoglobin of 2 g/dL or more, or leading to a transfusion of 2 or more units of packed red blood cells or whole blood, or occurring in a critical site or contributing to death Other clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention	Rivaroxaban: 139/1718 (8.1%) Enoxaparin-VKA: 138/1711 (8.1%) HR: 0.97 (95% CI 0.76 to 1.22); p=0.77 NS	"Assuming equal efficacy in the two study groups, a total of 88 events would provide a power of 90% to demonstrate that rivaroxaban is noninferior to standard therapy, with the use of a margin of 2.0 for the upper limit of the 95% confidence interval for the observed hazard ratio at a two-sided alpha level of 0.05. This margin corresponds to maintenance of at least 50% of the proven efficacy of standard therapy. On the basis of a 3% incidence of the primary efficacy outcome, we calculated that we would need a sample of approximately 3000 patients". Note:Basis of choice of margin unclear SELECTIVE REPORTING: no Other important methodological remarks • Unclear reporting of p-values for non-inferiority (or superiority) Sponsor: Bayer Schering Pharma and Ortho-McNeil
			Major bleeding	Rivaroxaban: 14/1718 (0.8%) Enoxaparin-VKA: 20/1711(1.2%) HR: 0.65 (95% CI 0.33 to 1.30); p=0.21 NS	
			Clinically relevant nonmajor bleeding	Rivaroxaban: 126/1718 (7.3%) Enoxaparin-VKA: 119/1711(7.0%)	
			Total deaths through end of intended treatment period	Rivaroxaban: 38/1718 (2.2%) Enoxaparin-VKA: 49 /1711(2.9%) HR: 0.67 (95% CI 0.44 to 1.02); p=0.06 NS	

	systolic BP> 180 mm Hg or diastolic BP> 110 mm Hg; childbearing potential without proper contraception, pregnancy, or breast-feeding; concomitantuse of strong cytochrome P-450 3A4 Inhibitors or inducers; a life expectancy of less than 3 months.				

4.2.1.2 Rivaroxaban versus enoxaparin followed by a vitamin K antagonist in symptomatic pulmonary embolism

Study details	n/Population	Comparison	Outcomes		Methodological
Einstein PE 2012(5) Design: noninferiority OL PG RCT Setting: Multicenter, 263 sites in 38 countries; 89% of patients hospitalized Duration of follow-up: 3, 6 or 12 months (decided by the treating physician before randomization; mean treatment duration 215 days)	n= 4832 Mean age: 58y Previous VTE(DVT/PE): 19% Current malignancy: 5% Recent surgery or trauma: 17% Immobilized: 16% Pretreatment (LMWH, heparin, fondaparinux): 92.5% rivarox; 92.1% standard. Duration of pretreatment: • 1 day: 57.4% rivarox, 58% standard • 2 days: 33.1% rivarox, 32.2% standard) TTR (VKA)= 62.7% of the time and exceeding 3.0 only 15.5% of the time <u>Inclusion</u> acute, symptomatic pulmonary embolism with objective	Rivaroxaban 2x15mg/d in first 3w, followed by 1x20mg/d (n=2419) Vs Enoxaparin 2x1.0mg per kg/d +vitamin K antagonist (warfarin or acenocoumarol) started within 48 hours after randomization (n=2413) Aspirin (dose of no more than 100 mg/d) and clopidogrel (dose of 75 mg/d) were	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: yes FOLLOW-UP: Lost-to follow-up: 0.4% Drop-out and Exclusions: 11.5% • Described: yes • Balanced across groups: yes ITT: Yes Power: adequate SELECTIVE REPORTING: low risk Other important methodological remarks : The authors state that "Since the study had an open design, there is a potential for a diagnostic-
			Symptomatic recurrent venous thromboembolism (VTE, PO): composite of fatal or nonfatal pulmonary embolism (PE) or deep-vein thrombosis (DVT) (the criteria for DVT were a calf trifurcation or more proximal vein that was not compressible on ultrasonography or an intraluminal filling defect on venography; criteria for pulmonary embolism were an intraluminal filling defect in subsegmental or more proximal pulmonary arteries on spiral computed tomography (CT) or pulmonary angiography, a high-probability finding on a ventilation–perfusion lung scan, or a nondiagnostic finding with documented deep venous thrombosis. Patients without chest symptoms in whom deep venous thrombosis wasdiagnosed were not routinely tested for pulmonary embolism)	No. of patients with VTE Rivaroxaban: 50/2419 (2.1%) Standard treatment: 44/2413 (1.8%) **HR= 1.12 (95% CI 0.75 to 1.68), SS, p=0.003 for noninferiority** (p=0.57 for superiority) The primary efficacy analysis was performed on an ITT basis with the use of a Cox proportional-hazards model stratified according to the intended duration of treatment, with adjustment for the presence or absence of cancer at baseline. The actual treatment duration was similar between both groups (93d for 3 month group, 182d for 6 month group, 355d for 12 month group). Results of per protocol analyses similar to ITT analysis, HR= 1.07 (95% CI, 0.70 to 1.63)(data not shown)." No. of patients with: Riv Enox Fatal PE 2 1 Death in which PE could not be ruled out 8 5 Nonfatal PE 22 19 Recurr DVT+ PE 0 2	

	confirmation, with or without symptomatic deep-vein thrombosis Exclusion therapeutic dose of LMWH, fondaparinux, or UFH for more than 48 hours; received more than a single dose of a vitamin K antagonist before randomization; thrombectomy performed; vena cava filter; fibrinolytic agent ; contraindication of enoxaparin, warfarin, or acenocoumarol; another indication for a VKA; creatinine clearance < 30 ml per minute; clinically significant liver disease or an ALT level > three times upper limit; bacterial endocarditis; active bleeding or a high risk of bleeding; systolic blood pressure> 180 mm Hg or diastolic blood pressure > 110 mm Hg; childbearing potential without proper contraception; pregnancy; breast-feeding; concomitant use of a strong inhibitor CYP3A4 or a CYP3A4 inducer; life expectancy < 3 months.	allowed; use of NSAID and antiplatelet agents was discouraged		Recurr DVT 18 17	suspicion bias. Indeed, the absolute number of patients with suspected recurrence was higher in the rivaroxaban group, and the proportions of patients with confirmed events were similar in the two groups (10.2% in the rivaroxaban group and 9.7% in the standard therapy group). This finding suggests that the open design may have caused a slight bias against rivaroxaban." Noninferiority margin of 2.0 for the upper limit of the 95% confidence interval for the observed hazard ratio, with a two-sided alpha level of 0.05 Sponsor: Bayer Health-Care and Janssen Pharmaceuticals
			Net clinical benefit (VTE + major bleeding)	Rivaroxaban: 83/2419 (3.4%) Enoxaparin: 96/2413 (4.0%) HR= 0.85 (95% CI 0.63 to 1.14), NS, p=0.28	
			Safety		
			Major[1] or clinically relevant nonmajor[2] bleeding (PO) [1] clinically overt and associated with a decrease in Hb level of 2.0 g per deciliter or more, if bleeding led to the transfusion of >=2 units of red cells, or if bleeding was intracranial or retroperitoneal, occurred in another critical site, or contributed to death [2] overt bleeding that did not meet criteria for major bleeding but associated with medical intervention, unscheduled contact with physician, interruption or discontinuation of study drug, or discomfort or impairment of activities of daily life	Rivaroxaban: 249/2412 (10.3%) Standard treatment: 274/2405 (11.4%) HR= 0.90 (95% CI 0.76 to 1.07), NS, p=0.23 The population for the safety analysis was defined as all patients who received at least one dose of a study drug.	
			Any major bleeding	Rivaroxaban: 26/2412 (1.1%) Standard treatment: 52/2405 (2.2%) **HR= 0.49 (95% CI 0.31 to 0.79, SS, p=0.003 in favour of rivaroxaban**	
			Clinically relevant nonmajor bleeding	Rivaroxaban: 228/2412 (9.5%) Standard treatment: 235/2405 (9.8%) NT	
			Death during intended treatment period	Rivaroxaban: 58/2412 (2.4%) Standard treatment: 50/2405 (2.1%) HR=1.13 (0.77 to 1.65), NS, p=0.53	

4.2.1.3 Summary and conclusions. Rivaroxaban versus enoxaparin followed by a vitamin K antagonist in patients with VTE

Rivaroxaban 15mg bid, then 20mg/d versus standard therapy with enoxaparin1mg/kg bid followed by adjusted dose VKA in patients with symptomatic DVT or PE			
Bibliography: Einstein DVT 2010(4), Einstein PE 2012(5)			
Outcomes	**N° of participants (studies) Follow up**	**Relative effect (95% CI)** ***Absolute effect***	**Quality of the evidence (GRADE)**
Mortality	8281 (2 studies) 3, 6 or 12m	Einstein 2010 (DVT patients) 2.2% vs 2.9% HR: 0.67 (95% CI 0.44 to 1.02) Einstein PE 2012 (PE patients) 2.4% vs 2.1% HR=1.13 (95%CI 0.77 to 1.65)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, noninferiority design Consistency: OK Directness: OK Imprecision: OK
Symptomatic recurrent VTE (PO)	8281 (2 studies) 3, 6 or 12m	Einstein 2010 (DVT patients) 2.1% vs 3.0% **HR: 0.68 (95 % CI 0.44 to 1.04); SS,** p<0.001 for noninferiority Einstein PE 2012 (PE patients) 2.1% vs 1.8% **HR= 1.12 (95% CI 0.75 to 1.68)** **SS,** p=0.003 for noninferiority	⊕⊕⊕⊖ **MODERATE** Study quality:-1 open label, unclear noninferiority reporting Consistency:OK Directness:OK Imprecision:OK
Major or clinically relevant nonmajor bleeding (PO)	8281 (2 studies) 3, 6 or 12m	Einstein 2010 (DVT patients) 8.1% vs 8.1% HR: 0.97 (95% CI 0.76 to 1.22) Einstein PE 2012 (PE patients) 10.3% vs 11.4% HR= 0.90 (95% CI 0.76 to 1.07)	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Consistency:OK Directness:OK Imprecision:OK
Any major bleeding	8281 (2 studies) 3, 6 or 12m	Einstein 2010 (DVT patients) 0.8% vs 1.2% HR: 0.65 (95% CI 0.33 to 1.30) Einstein PE 2012 (PE patients) 1.1% vs 2.2% **HR: 0.49 (95% CI 0.31 to 0.79)** **SS in favour of rivaroxaban**	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency:-1 Directness:OK Imprecision:OK

Two trials compare oral rivaroxaban to standard treatment with enoxaparin followed by adjusted dose vitamin K antagonist in the treatment of symptomatic VTE. One trial (Einstein DVT 2010) includes only patients with symptomatic DVT (excluding symptomatic PE), the other trial (Einstein PE 2012) includes patients with symptomatic PE (with or without DVT).
In the Einstein DVT trial, about 72% of patients had received 1 or 2 days of treatment with LMWH, heparin or fondaparinux prior to randomization. In the Einstein PE trial, about 92% of patients had

received 1 or 2 days of prerandomisation treatment. This means that we have insufficient data about the efficacy of rivaroxaban compared to enoxaparin in the first 24-48 hours of treatment.
Duration of treatment was 3, 6 or 12 months, decided by the treating physician before randomization.
Both trials had a non-inferiority design.

No significant difference in mortality is observed between both treatment regimens.
GRADE: MODERATE quality of evidence

Rivaroxaban is non-inferior to standard treatment with enoxaparin and VKA in preventing recurrent symptomatic VTE.
GRADE: MODERATE quality of evidence

No significant difference in total major or clinically relevant nonmajor bleeding is observed between both treatment groups.
GRADE: MODERATE quality of evidence

In patients with PE,there is significantly less major bleeding with rivaroxaban compared to standard treatment. In patients with DVT, this difference is not significant.
GRADE: LOW quality of evidence

4.2.1.4 Apixaban versus enoxaparin followed by a vitamin K antagonist in symptomatic VTE

Study details	n/Population	Comparison	Outcomes		Methodological
Agnelli 2013-AMPLIFY(6) Design: Non-inferiority DB PG RCT Setting: 358 centers - 28 countries Duration of follow-up: 6 months	n= 5395 Mean age: 57y Index event: (DVT 66%; PE 25%;DVT+PE 9%) Previous VTE:16% Current malignancy: 3% Recent surgery,recent trauma, immobilized: NR Pretreatment (LMWH, heparin, fondaparinux): 86.5% apix; 85.7% standard. Duration of pretreatment: • Up to 24h: 55.3% apix, 54.2% standard • Up to 48h: 30.4% apix, 30.5% standard) TTR (VKA): mean 61% <u>Inclusion</u> ≥ 18 years ; objectively confirmed, symptomatic proximal deep-vein thrombosis or pulmonary embolism (with or without	Apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months (n=2691) vs conventional therapy (subcutaneous enoxaparin 1mg/kg every 15 hours for at least 5 days, and warfarin begun concomitantly) for 6 months (n=2704)	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: 95 % in safety analysis 97 % in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: no (all efficacy analyses included data for patients in the intention-to-treat population for whom the outcome status at 6 months was documented. The effect of missing outcome data was evaluated with the use of a sensitivity analysis).
			Recurrent symptomatic VTE or death related to VTE (PO) DVT confirmed by compression ultrasound or venography. PE confirmed by CT scan or pulmonary angiogram or ventilation/perfusion lung scan	All patients (DVT+PE): Apixaban: 2.3% Enox+warf: 2.7% RR= 0.84 (0.60 to 1.18), **p-value for non-inferiority < 0.001** The difference in risk (apixaban minus conventional therapy) was −0.4 percentage points (95% CI, −1.3 to 0.4; **P<0.001 for noninferiority)** In patients with DVT at enrollment: Apixaban: 38/1698 (2.2%) Enox+warf: 47/1736 (2.7%) RR=0.83 (0.54 to 1.26) In patients with PE at enrollment: Apixaban: 21/900 (2.3%) Enox+warf: 23/886 (2.6%) RR=0.90 (0.50 to 1.61)
			Fatal PE	Apixaban: <0.1% Enox+warf: 0.1% NT
			Death for which PE could not be ruled out	Apixaban: 0.4% Enox+warf: 0.5% NT
			Nonfatal PE with or without DVT	Apixaban: 1.0% Enox+warf: 0.9% NT
			DVT only	Apixaban: 0.8%

	deep-vein thrombosis). Proximal deep-vein thrombosis was defined as thrombosis involving at least the popliteal vein or a more proximal vein. <u>Exclusion</u> active bleeding, high risk of bleeding, or other contra-indications to treatment with enoxaparin and warfarin; cancer and long-term treatment with LMWH planned; DVT or PE was provoked in the absence of a persistent risk factor for recurrence; <6 months of anticoagulant treatment planned; another indication for long-term anticoagulation therapy, dual antiplatelet therapy, treatment with aspirin > 165 mg daily, or treatment with potent inhibitors of cyt P-450 3A4; received more than two doses of a once-daily LMWH regimen, fondaparinux, or a vit K antagonist; >3 doses of a twice-daily LMWH regimen; > 36 hours of continuous intravenous heparin; hemoglobin level < 9 mg per deciliter, platelet count <100000 per mm2, serum creatinine level >2.5 mg per deciliter (220 µmol per liter), or a calculated creatinine clearance of less than 25 ml per min.			Enox+warf: 1.3% NT	Power: adequate SELECTIVE REPORTING: no Other important methodological remarks: -The criteria for noninferiority required that the upper limits of the 95% confidence intervals were below prespecified margins for both the relative risk (<1.80) and the risk difference (<3.5 percentage points) -If noninferiority was shown, testing for superiority was to be performed according to a prespecified hierarchy of outcomes Sponsor: Pfizer and Bristol-Myers Squibb
			VTE or death from cardiovascular cause	Apixaban: 2.3% Enox+warf: 2.9% RR=0.80 (0.57 to 1.11), NS, p=0.18	
			VTE or death from any cause	Apixaban: 3.2% Enox+warf: 3.9% RR=0.82 (0.61 to 1.08), NS, p=0.16	
			VTE, VTE-related death, or major bleeding	Apixaban: 2.8% Enox+warf: 4.5% **RR=0.62 (0.47 to 0.83), SS, p=0.001 in favour of apixaban**	
			Death during intended treatment period	Apixaban: 1.5% Enox+warf: 1.9% RR=0.79 (0.53 to 1.19) NS	
			Safety		
			Major bleeding (PO) (major if overt and associated with a decrease in the hemoglobin level of 2 g per dl or more, required the transfusion of 2 or more units of blood, occurred into a critical site, or contributed to death)	Apixaban: 0.6% Enox+warf: 1.8% **RR=0.31 (0.17 to 0.55), SS, p<0.001 in favour of apixaban**	
			Clinically relevant nonmajor bleeding (defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out activities of daily life)	Apixaban: 3.8% Enox+warf: 8.0% **RR=0.48 (0.38 to 0.60), SS in favour of apixaban**	

4.2.1.5 Summary and conclusions. Apixaban versus enoxaparin followed by a vitamin K antagonist in symptomatic VTE

Apixaban 10mg bid, followed by 5mg bid versus enoxaparin followed by warfarin (INR 2-3) for acute VTE			
Bibliography: Agnelli 2013-AMPLIFY(6)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	5395 (1 study) 6m	Apixaban: 1.5% Enox+warf: 1.9% RR=0.79 (0.53 to 1.19) NS	⊕⊕⊕⊕ **HIGH** Study quality:OK, but unclear allocation concealment and assessor blinding Consistency:NA Directness:OK Imprecision:OK
Recurrent symptomatic VTE or death related to VTE (PO)	5395 (1 study) 6m	2.3% vs 2.7% RR= 0.84 (0.60 to 1.18), **p-value for non-inferiority < 0.001**	⊕⊕⊕⊕ **HIGH** Study quality:OK, but unclear allocation concealment and assessor blinding Consistency:NA Directness:OK Imprecision:OK
Major bleeding (PO)	5395 (1 study) 6m	0.6% vs 1.8% **RR=0.31 (95%CI 0.17 to 0.55)** **SS in favour of apixaban**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 non-inferiority design, and unclear allocation concealment and assessor blinding Consistency:NA Directness:OK Imprecision:OK
Clinically relevant non-major bleeding	5395 (1 study) 6m	3.8% vs 8.0% **RR=0.48 (95%CI 0.38 to 0.60)** **SS in favour of apixaban**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Consistency:NA Directness:OK Imprecision:OK

In this trial, patients with acute VTE (DVT or PE) were randomized to treatment with apixaban (10mg twice daily for 7 days, followed by 5mg twice daily) or conventional treatment (enoxaparin 1mg/kg/12h for at least 5 days, and warfarin begun concomitantly – INR target 2-3).
About 86% of patients had received treatment with LMWH, heparin or fondaparinux prior to randomization (about 55% up to 24 h, about 30% up to 48 h). This means that we have insufficient data about the efficacy of apixaban compared to enoxaparin in the first 24-48 hours of treatment.
Duration of treatment and follow up was 6 months. This was a non-inferiority trial.

Mortality was not significantly different between treatment groups.
GRADE: HIGH quality of evidence

Apixaban was found to be non-inferior to conventional treatment for the composite endpoint of recurrent symptomatic VTE or death related to VTE.
GRADE: HIGH quality of evidence

Rates of major bleeding and clinically relevant nonmajor bleeding were significantly lower with apixaban compared to conventional treatment.
GRADE: MODERATE quality of evidence

4.2.2 Pharmacological treatment (+ compression stockings) versus no treatment (+ compression stockings)

4.2.2.1 Nadroparin+ graduated compression stockings versus graduated compression stockings in calf muscle vein thrombosis

Study details	n/Population	Comparison	Outcomes		Methodological
Schwarz 2010(7) Design: OL PG RCT Setting: vascular unit of University of Dresden Medical School Duration of follow-up: 3 months	n= 109 Mean age: 55y Previous VTE(DVT/PE): 21% Current malignancy:5% Recent trauma/ surgery: 34% Immobilized: 18% ICMVT in the gastrocnemial muscle veins 37%, MVT in the soleal muscle veins 63% <u>Inclusion</u> patients presenting with symptomatic (less than 14 days), sonographically proven acute isolated calf muscle vein thrombosis (ICMVT) in the gastrocnemial and/or soleal muscle veins, documented by venous compression ultrasound. <u>Exclusion</u> sonographical-proven DVT in the peroneal or tibial posterior veins and in the proximal	180 antiXa u/kg BW nadroparin once daily for about 10 days and compression therapy with graduated class-II-calf stockings for 3 months (n=55) vs. compression therapy with graduated class-II-calf stockings for 3 months (n=54)	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: unclear FOLLOW-UP: 98% in safety analysis 98% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: no Power: adequate SELECTIVE REPORTING: no Sponsor: Sanofi synthelabo, Berlin, Germany
			Sonographically proven progression of ICMVT into the deep veins and clinical PE as confirmed by objective testing (PO)	Nadro + compress: 2/54 (3.7%) Compress: 2/53 (3.8%) NS, p=0.99	
			Complete sonographically proven recanalization of the muscle vein	Nadro + compress: 36(66.6%) Compress: 32 (60.4%) p=0.23 NS	
			PE	Nadro + compress: 0 Compress: 0 NT	
			Safety		
			Major bleeding defined as a drop of hemoglobin of >2 mmol/2mg/dL, the need of transfusion of 2 U packed red cells, and joint, retroperitoneal, or cerebral hemorrhage	Nadro + compress: 0 Compress: 0 NT	
			Death	Nadro + compress: 0 Compress: 0 NT	

	venous segments, symptomatic PE, previous ICMVT and remaining thrombotic material, known heparin hypersensitivity, renal insufficiency and serum creatinine level above 180 µmol/L, malignant hypertension, active, clinically significant bleeding, cerebral hemorrhage, recent brain, spinal, ophthalmologic surgery, fibrinolysis within the last 24 hours, active peptic ulcer disease, acute bacterial endocarditis, a known familial bleeding disorder, all other indication for anticoagulant therapy, life expectancy <3 months, <8 years of age				

4.2.2.2 Summary and conclusion. Nadroparin+ graduated compression stockings versus graduated compression stockings in calf muscle vein thrombosis

There are very few studies that examine the treatment of distal vein thrombosis. Most treatment studies include only proximal deep vein thrombosis. Or fail to mention whether and how many patients with distal vein thrombosis were included.
Only 1 trial of distal vein thrombosis had a sufficient amount of patients to be included in our review. It consisted of patients with calf muscle vein thrombosis only.
The results are shown in the table.

Nadroparin 180u/kg once daily and compression therapy versus compression therapy in calf muscle vein thrombosis			
Bibliography: Schwarz 2010(7)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	109 (1 study) 3m	0 vs 0 NT	Not applicable
progression into deep veins	109 (1 study) 3m	3.7% vs 2.8% (distal veins) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 open label Consistency:NA Directness:? Imprecision: low event rates
PE	109 (1 study) 3m	0 vs 0 NT	Not applicable
Major bleeding	109 (1 study) 3m	0 vs 0 NT	Not applicable

In this trial 109 patients with isolated calf muscle vein thrombosis were randomized to either nadroparin + compression stockings or compression stockings only. Primary outcome was progression into the deep veins or PE.

No deaths, PE or major bleeding was observed in the trial
GRADE: not applicable

Progression to DVT (distal veins only) was seen in 2 patients in each group. The difference was not statistically significant.
GRADE: LOW quality of evidence

4.3 Continuation phase of treatment to prevent recurrent venous thromboembolism

4.3.1 Low molecular weight heparin versus vitamin K antagonist

Ref	Comparison	N/n	Outcomes	Result**
Nice 2012(8) Design: SR + MA Search date: aug 2011	LMWH vs VKA in the continuation phase of treatment	N= 16 n= 2953 (Beckman 2003, Cesarone 2003, Das 1996; Daskalopoulos 2005, Deitcher 2006, Gonzalez-Fajardo 1999, Hamann 1998, Hull 2006, Lee 2003, Lopaciuk 1999, Lopez-Beret 2001, Meyer 2002, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**All cause mortality – all patients**	LMWH:247/1499 (16.5%) VKA:239/1454 (16.4%) RR:0.99(95%CI 0.85 to 1.15) NS Absolute effect: 2 fewer per 1000 (95% CI 25 fewer to 25 more)
		N=11 n= 1872 (Cesarone 2003, Das 1996, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Hamann 1998, Hull 2006, Lopaciuk 1999, Lopez-Beret 2001, Pini 1994, Romera 2009, Veiga 2000)	**All cause mortality - subgroup: DVT**	LMWH:69/933 (7.4%) VKA:63/939 (6.7%) RR:1.1 (95%CI 0.79 to 1.51) NS Absolute effect: 7 more per 1000 (95% CI 14 fewer to 34 more)
		N=2 n=162 (Beckman 2003, Perez-de Llano 2010)	**All cause mortality - subgroup PE**	LMWH:4/92 (4.3%) VKA:0/70 (0.0%) RR: 3.28(95%CI 0.38 to28.33) NS Absolute effect: Not estimable
		N=3 n=919 (Deitcher 2006, Lee 2003, Meyer 2002)	**All cause mortality - subgroup: DVT or PE**	LMWH: 174/474 (36.7%) VKA: 176/445 (39.6%) RR: 0.94 (95%CI 0.79 to 1.11) NS Absolute effect: 24 fewer per 1000 (95% CI 83 fewer to 44 more)
		N=11 n=1538 (Beckman 2003, Das 1996; Daskalopoulos 2005,	**All cause mortality - subgroup: Non cancer**	LMWH: 42/776 (5.4%) VKA: 33/762 (4.3%) RR: 1.23 (95%CI 0.8 to 1.9)

		Gonzalez-Fajardo 1999, Hamann 1998, Lopaciuk 1999, Lopez-Beret 2001, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)		NS Absolute effect: 10 more per 1000 (95% CI 9 fewer to 39 more)
		N=7 n=1415 (Cesarone 2003, Deitcher 2006, Hull 2006, Lee 2003, Lopez-Beret 2001, Meyer 2002, Romera 2009)	**All cause mortality - subgroup: Cancer patients**	LMWH: 205/723 (28.4%) VKA: 206/692 (29.8%) RR: 0.95 (95%CI 0.81 to 1.11) NS Absolute effect: 15 fewer per 1000 (95% CI 57 fewer to 33 more)
		N= 5 n= 689 (Beckman 2003, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Perez-de-Llano 2010, Romera 2009)	**VTE related mortality**	LMWH: 4/354 (1.1%) VKA: 2/335 (0.6%) RR: 1.35 (95%CI 0.31 to 5.92) NS Absolute effect: 2 more per 1000 (95% CI 4 fewer to 29 more)
		N=3 n=527 (Daskalopoulos 2005, Gonzalez-Fajardo 1999, Romera 2009)	**VTE related mortality - subgroup: DVT**	LMWH: 2/262 (0.76%) VKA: 2/265 (0.75%) RR: 1.02 (95%CI 0.18 to 5.84) NS Absolute effect: 0 more per 1000 (95% CI 6 fewer to 37 more)
		N=2 n=162 (Beckman 2003, Perez-de-Llano 2010)	**VTE related mortality - subgroup: PE**	LMWH: 2/92 (2.2%) VKA: 0/70 (0.0%) RR: 2.56 (95%CI 0.13 to 50.95) NS Absolute effect: Not estimable
		N= 16 n= 2916 (Beckman 2003, Das 1996, Daskalopoulos 2005, Deitcher 2006, Gonzalez-Fajardo 1999, Gonzalez-Fajardo 2008, Hamann 1998, Hull 2006, Lee 2003, Lopaciuk 1999, Lopez-Beret 2001, Meyer 2002, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**Recurrent VTE rates - all**	**LMWH: 116/1482 (7.8%)** **VKA: 166/1434 (11.6%)** **RR: 0.68 (95%CI 0.54 to 0.85)** **SS in favour of LMWH** Absolute effect: 37 fewer per 1000 (95% CI 17 fewer to 53 fewer)
		N=11 n= 1845	**Recurrent VTE rates - all - subgroup: DVT**	**LMWH: 79/922 (8.6%)** **VKA: 107/923 (11.6%)**

		(Das 1996, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Gonzalez-Fajardo 2008, Hamann 1998, Hull 2006, Lopaciuk 1999, Lopez-Beret 2001, Pini 1994, Romera 2009, Veiga 2000)		**RR: 0.74 (95%CI 0.56 to 0.97)** **SS in favour of LMWH** Absolute effect: 30 fewer per 1000 (95% CI 3 fewer to 51 fewer)
		N=2 n=162 (Beckman 2003, Perez-de Llano 2010)	**Recurrent VTE rates - all - subgroup: PE**	LMWH: 4/92 (4.3%) VKA: 0/70 (0.0%) RR: 3.28 (95%CI 0.38 to 28.33) NS Absolute effect: Not estimable
		N=3 n=909 (Deitcher 2006, Lee 2003, Meyer 2002)	**Recurrent VTE rates - all - subgroup: DVT or PE**	**LMWH: 33/468 (7.1%)** **VKA: 59/441 (13.4%)** **RR: 0.53 (95%CI 0.35 to 0.79)** **SS in favour of LMWH** Absolute effect: 63 fewer per 1000 (95% CI 28 fewer to 87 fewer)
		N=12 n=1772 (Beckman 2003, Das 1996, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Gonzalez-Fajardo 2008, Hamann 1998, Lopaciuk 1999, Lopez-Beret 2001, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**Recurrent VTE rates - all - subgroup: Non cancer**	LMWH: 75/897 (8.4%) VKA: 87/875 (9.9%) RR: 0.85 (95%CI 0.63 to 1.13) NS Absolute effect: 15 fewer per 1000 (95% CI 37 fewer to 13 more)
		N=5 n=1144 (Deitcher 2006, Hull 2006, Lee 2003, Lopez-Beret 2001, Meyer 2002)	**Recurrent VTE rates - all - subgroup: Cancer patients**	**LMWH: 41/585 (7%)** **VKA: 79/559 (14.1%)** **RR: 0.5 (95%CI 0.35 to 0.71)** **SS in favour of LMWH** Absolute effect: 71 fewer per 1000 (95% CI 41 fewer to 92 fewer)
		N=15 n=2762 (Beckman 2003, Das 1996, Daskalopoulos 2005, Deitcher 2006, Gonzalez-Fajardo 1999, Hamann 1998, Hull 2006, Lee 2003, Lopaciuk 1999, Lopez-Beret 2001, Meyer 2002, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**Major bleeding - all patients**	LMWH: 47/1405 (3.3%) VKA: 56/1357 (4.1%) RR: 0.79 (95%CI 0.55 to 1.16) NS Absolute effect: 9 fewer per 1000 (95% CI 19 fewer to 7 more)

		N=11 n=1607 (Beckman 2003, Das 1996, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Hamann 1998, Lopaciuk 1999, Lopez-Beret 2001, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**Major bleeding - subgroup: Non cancer**	**LMWH: 10/812 (1.2%)** **VKA: 21/795 (2.6%)** **RR: 0.48 (95%CI 0.24 to 0.97)** **SS in favour of LMWH** Absolute effect: **14 fewer per 1000 (95% CI 1 fewer to 20 fewer)**
		N=5 n=1155 (Deitcher 2006, Hull 2006, Lee 2003, Lopez-Beret 2001, Meyer 2002)	**Major bleeding - subgroup: Cancer patients**	LMWH: 37/593 (6.2%) VKA: 35/562 (6.2%) RR: 1 (95%CI 0.64 to 1.58) NS Absolute effect: 0 fewer per 1000 (95% CI 22 fewer to 36 more)
		N=3 n=445 (Daskalopoulos 2005, Perez-de-Llano 2010, Romera 2009)	**Fatal bleeding**	LMWH:1/221 (0.45%) VKA: 1/224 (0.45%) RR: 1.04 (0.07 to 16.18) NS Absolute effect: 0 more per 1000 (95% CI 4 fewer to 68 more)
		N=1 n=102 (Perez-de-Llano 2010)	**Intracranial bleed/haemorrhage**	LMWH: 0/52 (0.0%) VKA: 0/50 (0.0%) RR: - Absolute effect: Not pooled
		N=1 n=165 (Gonzalez-Fajardo 2008)	**PTS**	LMWH: 34/85 (40%) VKA: 31/80 (38.8%) RR: 1.03 (0.71 to 1.51) NS Absolute effect: 12 more per 1000 (95% CI 112 fewer to 198 more)
		N=0 n=/	**Quality of life**	/

* Characteristics of included studies: see below

**For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Beckman 2003(9) Setting: Brigham and women hospital's Investigational Drug Service Study design: RCT, Parallel design, single institution treatment trial Duration of follow-up: 90 days total. Patients assessed at 2, 4, 8, 12 weeks	60	**Patient group:** Patients with objectively confirmed symptomatic PE **Inclusion criteria:** PE diagnosed by symptoms confirmed by objective methods: ▪ Symptoms included shortness of breath, lightheadedness, and/or chest discomfort ▪ Radiologic confirmation method: **either** o High probability ventilation/ perfusion lung scan or positive spiral chest CT with i.v. contrast or positive pulmonary angiography **or** o An intermediate ventilation/ perfusion scan in the presence of high clinical suspicion for PE.	90days	Enoxaparin (LMWH)1.5mg/kg (high dose) or 1.0mg/kg (moderate dose) (initial 14 days of 1.0mg) Vs 5 days continuous infusion of unfractionated heparin and concomitant warfarin for 90 days	**Recurrent VTE rates** confirmed by: see symptomatic PE and DVT) **Major bleeding**: defined as bleeding that caused a decrease in Hb level of >2g/dL, intracranial haemorrhage, cardiac tamponade, or haemorrhage that required major surgical intervention. **Symptomatic pulmonary embolism** confirmed by: spiral CT	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Open label study FOLLOW-UP: Drop outs: 7 Those treated with enoxaparin received echocardiogram for risk stratification of PE allowing for early discharge (within 48 hours for those with low risk), those in UFH arm did not receive echocardiogram. All high risk patients in enoxaparin arm and all patients in the UFH/OA arm were hospitalised for at least 120 hrs. ▪ 8% patients in the enoxaparin arm were undergoing chemotherapy whereas 0 in VKA group were undergoing chemotherapy. ITT: yes (Patients who did not completed study were analysed in the study using ITT analysis (according to randomised arm)

						Funding: Aventis and National Institute of Health (NIH)
Daskalopoulos 2005(10) **Country of study:** Greece **Setting:** Accident and Emergency Department of a district hospital. **Study design:** Open label RCT **Duration of follow-up:** Evaluated at 1.3, 6 and 12 months.	108	**Patient group:** Consecutive symptomatic adult patients with acute proximal lower limb DVT. Age (range): 58.6 (23-95) **Inclusion criteria:** ▪ Onset of symptoms less than one week. ▪ Thrombotic process had to objectively document by means of duplex ultrasound scan. **Exclusion criteria:** ▪ Segmental deep venous thrombosis restricted to infrapopliteal deep veins or calf muscles as determined by duplex ultrasonography; ▪ Symptomatic or clinically suspected PE, history of recently diagnosed DVT or PE; ▪ Patient already under anticoagulant therapy; ▪ Recently performed thrombolysis;	6 months	Tinzaparin sodium in a weight adjusted dose of 175 anti Xa IU/Kg vs Intravenous bolus of 5000IU UFH. Continuous intravenous UFH infusion for 5-7 days. Acenocoumarol commenced on third day. The dose of the drug was adjusted aiming at an INR 2-3. Patients encouraged to ambulate wearing elastic support stockings. UFH treatment discontinued as soon as the INR value reached 2 or more.	Recurrent DVT rates (documented by duplex ultrasound scan) Incidence of PE confirmed at post mortem. Major bleeding overt and associated with a drop in the haemoglobin level of 2g/dlor more, if it required transfusion of two blood units or more, if it was intracranial, intraspinal, intraocular, pericardial, retroperitoneal or associated with death or the treatment had to permanently discontinued. Minor bleeding: hemorrhagic event not considered major	ALLOCATION CONC: unclear RANDO: not stated BLINDING : Participants: no Personnel no Assessors yes FOLLOW-UP: 6 consent withdrawal before initiation of assigned treatment. ITT: no **Funding:** Leo Pharmaceutical, University of Athens.

GonzalezFajardo 1999(11) and 2008(12) **Country of study:** Spain **Setting: NR** **Study design:** RCT **Duration of follow-up:** 3, 6 and 12 months and yearly thereafter for 5 years.	165	**Patient group:** Consecutive patients with symptomatic, unilateral, first episode DVT confirmed by venography. Age (mean): 57.4 (14.4) **Inclusion criteria:** Symptomatic, unilateral and first episode DVT confirmed by venography **Exclusion criteria:** ▪ Clinically suspected pulmonary embolism ▪ Two or more previously documented episodes of DVT or pulmonary embolism, Instructed and motivated to wear graduate compression stockings daily during diurnal activities for at least 2 years.	3 months	LMWH – enoxaparin 40mg once daily, started on 8th day [Initial therapy: Enoxaparin 40 mg twice daily for 7 days] vs. Coumarin (not specified which drug in the class was used) INR, 2-3	**Recurrent VTE rates:** confirmed by: see symptomatic DVT and PE. This does not include the recurrent VTE events in those patients that died during follow up, or those lost to follow up. **Post thrombotic syndrome**: classified according to validated Villalta scale **Symptomatic pulmonary embolism:** confirmed by perfusion lung scan, chest radiography, angio-CT **Symptomatic DVT:** confirmed by new clinical signs of DVT, if signs could be confirmed independently by ultrasound scanning at vascular laboratory, phlebography or non-compressibility ofpreviously normal venous segment	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants unclear Personnel unclear Assessors yes FOLLOW-UP: **Drop outs:** 65 at 5 years After 2nd year of follow up 37 patients lost: Group 1: 12 Group 2: 25 (p=0.08) Significant differences in baseline characteristics between groups regarding risk factor for DVT (Cancer p=0.041 and thrombophilia p=0.032) ITT: no Recurrent VTE rates, post thrombotic syndrome, symptomatic PE and symptomatic DVT analysis only includes those patients who did not die and were not lost to follow up.
Van der heijden 2002 *van der Heijden JF, Hutten*	1137	**Patient group:** Symptomatic VTE, all 7 studies included	3 months (2 studies),	**LMWH** Enoxaparin (n=3	**Recurrent VTE rates** definition of	ALLOCATION CONC: Unclear RANDO: Unclear (4 studies)

BA, Buller HR, Prins MH. Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism. Cochrane database of systematic reviews. 2002(1):CD002001. **Study design:** Cochrane systematic review including 7 RCTS (Hamann 1998(13), Das 1996(14), Gonzalez-Fajardo 1999(11), Lopaciuk 1999(15), Lopez-Beret 2001(16), Pini 1994(17), Veiga 2000(18)) **Duration of follow-up:** 3, 6, and/or 9 months		only patients with DVT **Inclusion:** - Symptomatic VTE ▪Long term treatment of with LMWH or Vit K antagonists **Exclusion:** ▪ Accepted objective tests were not used to confirm diagnosis of deep vein thrombosis (venography, ultrasound, or any sequence of tests that results in a high positive predictive forlue for the diagnosis of symptomatic DVT) or the diagnosis of PE (high probability ventilation perfusion scan or pulmonary angiography)	3-9months (2 studies), 3 or 6 months (3 studies)	studies), Tinzaparin (n=1), dalterparin (n=1), nadroparin (n=1). vs **Vitamin K antagonist (VKA)** 5/7 studies defined that the INR was titrated to between 2 and 3	-Recurrent symptomatic DVT: includes an extension of an intraluminal filling defect on a venogram, -New intraluminal filling defect, -Extension of non-visualization of proximal veins in the presence of a sudden cut-off defect on a venogram seen on at least 2 projections. -Abnormal results of compression US in an area where compression had been normal, or a substantial increase in the diameter of the thrombus during full compression at the popliteal or femoral vein -A change in the results of impedance plethysmography from normal to abnormal, accompanied by a change from negative to positive result on a D-dimer test **Recurrent symptomatic PE**: A -New intraluminal filling defect, an extension of an existing defect, or the sudden cut-off of vessels more than 2.5 mm in diameter on a PA. -Intraluminal filling defect or sudden cut-off of vessels more than 2.5 mm in diameter on PA ▪ Defect of at least 75% of a segment on the perfusion scan with normal ventilation ▪ Where the VQ scan non-diagnostic & no PA, satisfaction of the above criteria for deep venous thrombosis was acceptable.	BLINDING : Participants:no Personnel: no Assessors: yes(All studies were not blinded. Outcome assessors blinded in 3 studies) ITT: unclear All analyses were according to the ITT analysis. When the individual studies did not use ITT, the analyses of this review were on the basis of the data provided by the individual study. **Methodology of review:** **Only include studies if:** ▪ Initial treatment consisted of UFH or LMWH lasting 5- 10 days ▪ Randomised study

					-Autopsy **Major bleeding:** Clinically overt and associated with a fall in hemoglobin level of≥ 2 g/dl ; clinically overt and leading to a transfusion of ≥2 units of packed cells; intracranial; retroperitoneal; leading directly to death; leading to interruption of antithrombotic treatment or (re)operation	
Akl 2008 *Akl EA. Anticoagulation for the long term treatment of venous thromboembolism in patients with cancer. Cochrane database of systematic reviews. 2008((Issue 2)):CD006650.* **Setting:** Outpatients **Study design:** Cochrane systematic review including 6 randomised controlled trials (RCTs) (Cesarone 2003(19), Deitcher 2006(20); Hull 2006(21); Lee 2003(22); Lopez Beret 2001(16); Meyer 2002(23))	1661	Patients with cancer and symptomatic objectively confirmed VTE. **Inclusion:** Patients could be of any age group, with either solid or hematological cancer at any stage of their cancer and respectively of the type of cancer therapy. DVT should have been diagnosed using one of the following objective diagnostic tests: venography, 125I-fibrinogen-uptake test, impedance plethysmography or Doppler ultrasound. Pulmonary embolism should have been diagnosed using one of the following objective diagnostic tests: pulmonary perfusion/ventilation scans, computed tomography or	3-6 months	**LMWH**: Enoxaparin (n=3 studies), Tinzaparin (n=1), dalterparin (n=1), nadroparin (n=1). vs **Vitamin K antagonist (VKA)**		ALLOCATION CONC: Adequate(3)/unclear(3) RANDO: not stated BLINDING : Participants: no/personnel: no/assessors:unclear FOLLOW-UP: ? % in safety analysis 89-100 % in efficacy analysis ITT: Unclear **Funding:** Deitcher 2006 funding from Aventis Pharmaceutical. Hull 2006 funded by Canadian Institute for Health Research, industry grant, Leo Pharmaceutical, Pharmion Pharmaceutical and Dupont Pharmaceutical. Lee 2003 funding from Pharmacia. Meyer 2002

		pulmonary angiography.				funding from Aventis, Assistance Publique, Hospitaux de Paris. 2 remaining studies did not report funding.
Perez-de-Llano 2010(24) **Country of study:** Spain **Setting:** Initial inpatient then outpatient. 4 hospital centres **Study design:** Randomized multicentre, open-label trial **Duration of follow-up:** Follow up at 1,3 and 6 months	102 **Age (mean):** 72.2 (41.2% over 75)	Consecutive patients with symptomatic acute PE (April 2005-December 2008). Diagnosis of PE objectively confirmed. Majority of patients from a rural area. **Inclusion criteria:** Consecutive patients with symptomatic acute PE. **Exclusion criteria:** ▪ need for indefinite anticoagulation and poor life expectancy (including advanced malignancy)	6 months.	LMWH: Tinzaparin 175 IU/kg once daily Route: subcutaneous **vs** VKA: Acenocoumarol adjusted to target INR 2.0-3.0. Given within 48 hours (range 1-8days) of 1st dose of tinzaparin. Route: oral <u>Initial therapy</u> Tinzaparin stopped when INR>2 on two consecutive days. Median duration of tinzaparin 7 days. Initial dose N/R **For all patients:** Initial treatment with tinzaparin s/c 175anti-Xa	**VTE related mortality=** Haemodynamic shock from initial massive PE Patient satisfaction (not validated) **Recurrent VTE rates:** Symptomatic only. Jugular vein thrombosis day 25. Confirmed by compression US or helical CT as appropriate **Major bleeding**: Clinically overt and associated with decrease Hb level ≥2g/dl, or required transfusion of at least 2 units, or retroperitoneal or intracranial bleed **Minor bleeding:** Epistaxis, gingivitis, haematuria, metrorrhagia, rectorrhagia	ALLOCATION CONC:Unclear RANDO: Unclear BLINDING : No Participants/personnel/assessors Inadequate FOLLOW-UP: **Drop outs: 8** ITT:unclear **Funding:** LEO Pharma (manufacturer of tinzaparin)

				IU/kg once daily		
Romera 2009(25) **Country of study:** Spain **Setting:** 2 centres. Vascular surgery department then outpatient **Study design:** Randomised, open-label	241	**Patient group:** Consecutive symptomatic proximal DVT or the lower limbs confirmed by duplex ultrasound. January 2002 to January 2005 **Inclusion criteria:** - Over 18 years old - First episode, onset of symptoms less than 2 weeks **Exclusion criteria:** ▪ PE requiring thrombolytic therapy, surgical thrombectomy or vena cava interruption, ▪ Hb <7g/dl, severe renal failure necessitating dialysis, ▪ Pregnancy, history of HIT, surgery within previous 14 days, lumbar puncture within previous 24 hours, receiving anti-coagulant or anti-platlet drugs for other conditions unable to discontinue medication during treatment interval. Those who had received heparin, LMWH or oral-anticoagulant therapy for >2days. Distal DVT.	12 months Duplex scan at 6 and 12 months Treatment for 6 months	LMWH Tinzaparin (Innohep) Dose, and frequency: 175 IU anti-Xa/kg once daily Route: subcutaneous injection vs VKA Acenocoumarol Start time: Day 1 Dose, and frequency: 3mg (initial dose) adjusted to give INR 2-3. Tinzaparin given until INR≥2 on two consecutive days Route: oral	**Recurrent VTE rates at 6 months** Symptomatic, USS, hi prob lung scan, abnormal perfusion scan with documented new DVT, or spiral CT **Recurrent VTE rates at 12 months (inc at 6 months)** Confirmed as above **Major bleeding** overt and associated with ≥2g/dl fall in Hb, resulted in transfusion of 2 or more units of blood, retroperitoneal, into a major joint or intracranial **Symptomatic pulmonary embolism at 6 months** (confirmed by: see above) **Symptomatic DVT at 6 months**(confirmed by: see above) **Symptomatic DVT at 12 months (exc at 6 months)** (confirmed by: see above)	ALLOCATION CONC: Adequate RANDO: unclear BLINDING : open-label Participants:no personnel:no assessors: unclear FOLLOW-UP: Drop outs: 2(died from cancer) ITT:yes **For all patients:** Tinzaparin (innohep, LEO PHarma A/S) subcutaneously 175IU anti-Xa per kg once daily. All patients told to come to hospital immediately if signs or symptoms suggestive of recurrent VTE and given ultrasound. Outpatient at 1,6,12 months for clinical examination and ultrasound Post randomisation cancer subgroup analysis **Funding:** LEO Pharma) , provided funding and performed statistical analysis

4.3.2 Summary and conclusions. Low molecular weight heparin versus vitamin K antagonist

Long term LMWH versus VKA for patients with VTE			
Bibliography: meta-analysis Nice 2012(8) included these RCTs: Beckman 2003(9); Daskalopoulos 2005(10); Gonzalez-Fajardo 2008(12), Hamann 1998(13), Das 1996(14), Gonzalez-Fajardo 1999(11), Lopaciuk 1999(15), Lopez-Beret 2001(16), Pini 1994(17), Veiga 2000(18), Cesarone 2003(19), Deitcher 2006(20); Hull 2006(21); Lee 2003(22); Lopez Beret 2001(16); Meyer 2002(23), Perez-de-Llano 2010(24), Romera 2009(25)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
All-cause mortality	2953 (16 studies) 3m-6m	16.5% vs 16.4% RR: 0.99 (95%CI 0.85 to 1.15)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment, open label Consistency: OK Directness: OK Imprecision: OK
All-cause mortality – subgroup DVT	1872 (11 studies) 3m-6m	7.4% vs 6.7% RR: 1.1 (95%CI 0.79 to 1.51)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI
All-cause mortality – subgroup PE	162 (2 studies) 3m-6m	4.3% vs 0% RR: 3.28 (95%CI 0.38 to 28.33)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI
Recurrent VTE	2916 (16 studies) 3m-6m	7.8% vs 11.6% **RR: 0.68 (95%CI 0.54 to 0.85)** **SS in favour of LMWH** Absolute effect: 37 fewer per 1000 (95% CI 17 fewer to 53 fewer)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: OK Directness: OK Imprecision: OK
Recurrent VTE – subgroup DVT	1845 (11 studies) 3m-6m	8.6% vs 11.6% **RR: 0.74 (95%CI 0.56 to 0.97)** **SS in favour of LMWH** Absolute effect: 30 fewer per 1000 (95% CI 3 fewer to 51 fewer)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI
Recurrent VTE – Subgroup PE	162 (2 studies) 3m-6m	4.3% vs 0% RR: 3.28 (95%CI 0.38 to 28.33)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI
Major bleeding	2762 (15 studies) m-6m	3.3% vs 4.1% RR: 0.79 (95%CI 0.55 to 1.16)	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

A systematic review and meta-analysis that was conducted for the 2012 NICE guideline on venous thromboembolic disease compares low molecular weight heparin (LMWH) to vitamin K antagonists (VKA) for the continuation phase of the treatment of venous thromboembolism. 16 RCTs of patients with either acute DVT (excluding PE),acute PE or acute VTE (both DVT or PE) were included.

No significant difference in mortality was observed between treatment with LMWH and treatment with VKA for all studies.
GRADE: MODERATE quality of evidence

There is also no significant difference in mortality when only RCTs of patients with DVT are considered (exclusion of patients with PE).
Nor is there a significant difference in mortality in 2 studies that include only patients with PE.
GRADE: LOW quality of evidence

For all studies, there is significantly less recurrence of VTE with LMWH compared to VKA (RR: 0.68; 95%CI 0.54 to 0.85).
GRADE: MODERATE quality of evidence

For studies that include only patients with DVT (excluding patients with PE), there is significantly less recurrence of VTE with LMWH compared to VKA (RR: 0.74; 95%CI 0.56 to 0.97).
GRADE: LOW quality of evidence

There is no significant difference in recurrence rates of VTE in 2 trials that include only patients with PE.
GRADE: LOW quality of evidence

No significant difference in major bleeding is observed when comparing LMWH to VKA in all studies.
GRADE: LOW quality of evidence

4.3.3 Summary and conclusions. Low molecular weight heparin versus vitamin K antagonist in cancer patients

Long term LMWH versus VKA for cancer patients with VTE			
Bibliography: meta-analysis Nice 2012(8) included these RCTs: Romera 2009(25), Cesarone 2003(19), Deitcher 2006(20); Hull 2006(21); Lee 2003(22); Lopez Beret 2001(16); Meyer 2002(23)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
All-cause mortality	1415 (7 studies) 3m-12m	28.4% vs 29.8% RR: 0.95 (95%CI 0.81 to 1.11) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment, open label Consistency: OK Directness: OK Imprecision: OK
Recurrent VTE	1144 (5 studies) 3m-6m	7% vs 14.1% **RR: 0.5 (95%CI 0.35 to 0.71)** **SS in favour of LMWH**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: OK Directness: OK Imprecision: OK
Major bleeding	1155 (5 studies) 3m-6m	6.2% vs 6.2% RR: 1 (95%CI 0.64 to 1.58) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

A systematic review and meta-analysis that was conducted for the 2012 NICE guideline on venous thromboembolic disease compares low molecular weight heparin (LMWH) to vitamin K antagonists (VKA) for the continuation phase of the treatment of venous thromboembolism in cancer patients. 7 RCTs of cancer patients with VTE were included.

No significant difference in mortality was observed between treatment with LMWH and treatment with VKA.
GRADE: MODERATE quality of evidence

For all studies, there is significantly less recurrence of VTE with LMWH compared to VKA RR: 0.5 (95%CI 0.35 to 0.71).
GRADE: MODERATE quality of evidence

No significant difference in major bleeding is observed when comparing LMWH to VKA in all studies.
GRADE: LOW quality of evidence

4.3.4 Dabigatran versus vitamin K antagonist after 10d initial treatment

Ref	Comparison	N/n	Outcomes	Result
Fox 2012(26) Design: SR + MA Search date: April 2012	Dabigatran vs Vitamin K antagonist	N= 2 n= 5107 Schulman 2011 Schulman 2009	**Recurrent VTE**	RR: 1.09 (95%CI, 0.76 to 1.57) NS
			Major bleeding (= clinically overt and associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need fortransfusion of 2 or more units of red cells, involved in a critical site, or was fatal)	RR: 0.76 (95%CI, 0.49 to 1.18) NS
			All cause mortality	RR: 1.00 (95%CI, 0.67 to 1.50) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Schulman 2011 RE-COVER II(27) Design:RCT; DB Non-inferiority	n = 2568	Similar design as RECOVER I Results from abstract	6 months	Initial LMWH 5 days Dabigatran (150mg /twice a day) vs Warfarin (dose adjusted to achieve INR of 2.0 to 3.0)	see RE-COVER I	ALLOCATION CONC: unclear RANDO: unclear BLINDING : unclear FOLLOW-UP: unclear ITT: unclear
Schulman 2009 RE-COVER I(28)	see under					

Study details	n/Population	Comparison	Outcomes		Methodological
Schulman 2009-RE-COVER I(28) Design: RCT - DB Double dummy Non inferiority trial Setting: 228 clinical centers in 29 countries Duration of follow-up: 6 months	n= 2564 Mean age: 55y Index event: DVT 69% PE 21% DVT+PE 10% Previous VTE : 25% Current malignancy: 61% Recent surgery:NR Recent trauma: NR Immobilized:NR TTR (VKA): 60% (66% during the last month) <u>Inclusion</u> Patients 18 years of age or older who had acute, symptomatic, objectively verified proximal deep-vein thrombosis of the legs orpulmonary embolism Before randomization, the diagnosis of venous thromboembolism was established with the use of compression ultrasonography or	Dabigatran (2x150 mg /d)+ warfarin-like placebo versus warfarin + dabigatran-like placebo (dose-adjusted to achieve an INR of 2.0 to 3.0) initially given parenteral anticoagulation therapy for a median of 9 days (interquartile range, 8 to 11)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 84.4% in safety analysis 88.8 % in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: No modified intention-to-treat for efficacy (since patients who did not receive any study drug were excluded from all analyses, as was prespecified in the protocol) Per protocol-analysis for safety (on the basis of the patient's actual treatment with the study drug) Power: adequate SELECTIVE REPORTING:unclear
			Venous thromboembolism (6-month incidence of recurrent symptomatic, objectively confirmed) and related deaths (PO) confirmed by compression ultrasonography or venography of leg veins and ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries.	<u>modified intention-to-treat</u> Dabigatran: 30/1274 (2.4%) Warfarin: 27/1265 (2.1%) HR: 1.10 (CI 0.65 to 1.84) **P<0.001 for the prespecified noninferioritymargin** ARD=0.4% (95%CI −0.8 to 1.5) **P<0.001 for the prespecified noninferiority margin**
			Symptomatic deep-vein thrombosis	No. of subjects Dabigatran: 16/1274 (1.3%) Warfarin: 18/1265 (1.4%) HR: 0.87 (CI 0.44 to 1.71) NS
			Symptomatic nonfatal pulmonary embolism	No. of subjects Dabigatran: 13/1274 (1%) Warfarin: 7/1265 (0.6%) HR: 1.85(CI 0.74 to 4.64) NS
			Death related to venous thromboembolism	No. of subjects Dabigatran: 1/1274 (0.1%) Warfarin:3/1265 (0.2%) HR: 0.33(CI 0.03 to 3.15) NS
			All deaths	No. of subjects Dabigatran:21/1274 (1.6%) Warfarin:21/1265 (1.7%) HR: 0.98(CI 0.53 to 1.79) NS
			Safety	

	venography of leg veins and ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries. <u>Exclusion</u> duration of symptoms longerthan 14 days, pulmonary embolism with hemodynamic instability or requiring thrombolytic therapy,another indication for warfarin therapy, recent unstable cardiovascular disease, a high risk of bleeding, liver disease with an aminotransferase level that was two times the local upper limit, an estimated creatinine clearanceof < 30 ml per minute, a life expectancy of less than 6 months, a contraindication to heparin or to radiographic contrast material, pregnancy or risk of becoming pregnant, or a requirement for long-term antiplatelet therapy (≤100 mg of acetylsalicylic acid daily was acceptable).		**Major bleeding event** Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal	No. of subjects Dabigatran: 20/1274 (1.6%) Warfarin: 24/1265 (1.9%) HR: 0.82(CI 0.45 to 1.48) NS	Non-inferiority margin: '90% power to exclude a hazard ratio of 2.75 and an absolute increase in risk of 3.6 percentage points for the primary outcome with dabigatran, at a one-sided alpha level of 0.025. These noninferiority margins were estimated to correspond to preservation of 57% (for assessment of hazard ratio) and 75% (for assessment of difference in risk) of the lower boundary of the 95% confidence interval for the efficacy of warfarin as compared with no anticoagulation, as assessed in four studies that compared discontinuing warfarin therapy at 4 to 6 weeks with continuing it for 3 to 6 months' Note: this is quite a large margin for noninferiority Sponsor: Boehringer Ingelheim
			Major or clinically relevant nonmajor bleeding event Less severe bleeding episodes were classified as minor and were subcategorized as clinically relevant bleeding or nuisance bleeding.	No. of subjects Dabigatran: 71/1273 (5.6%) Warfarin:111/1265 (8.8%) HR: 0.63(CI 0.47 to 0.84) p=0.002 **SS in favor of dabigatran**	
			Any bleeding event	No. of subjects Dabigatran:205/1273 (16.1%) Warfarin:277/1265 (21.9%) HR: 0.71(CI 0.59 to 0.85) **SS in favor of dabigatran**	
			Acute coronary events	Dabigatran:205/1273 (16.1%) Warfarin:277/1265 (21.9%) p=0.73 NS	
			Other adverse events No. of subjects/total treatment period	Any event : Dabigatran:5/1273 (0.4%) Warfarin:3/1266 (0.2%) P= 0.51 NS Serious event: Dabigatran:165/1273 (13.0%) Warfarin:150/1266 (11.8%) P= 0.43 NS	

				Event leading to discontinuation of study drug Dabigatran:115/1273 (9.0%) Warfarin:86/1266 (6.8%) P= 0.05 NS Events with an incidence of at least 3% NS except **Dyspepsia:** **Dabigatran:39/1273 (3.1%)** **Warfarin:9/1266 (0.7%)** **SS P<0.001** Abnormal liver-function tests NS	

4.3.5 Summary and conclusions. Dabigatran versus vitamin K antagonist after 10d initial treatment

Dabigatran 150mg bid versus warfarin (target INR 2.0 to 3.0) for VTE, after initial parenteral anticoagulation for 5-9 days			
Bibliography: meta-analysis Fox 2012(26) included these RCTs: Schulman 2011 RE-COVER II(27), Schulman 2009 RE-COVER I(28)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	5107 (2 studies) 6m	Fox 2012 RR: 1.00 (95%CI, 0.67 to 1.50) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 >10% drop-out, no ITT, non-inferiority trials Consistency:OK Directness:OK Imprecision:OK
Recurrent VTE	5107 (2 studies) 6m	Fox 2012 RR: 1.09 (95%CI, 0.76 to 1.57) NS Schulman 2009 only **2.4% vs 2.1%** **HR: 1.10 (CI 0.65 to 1.84)** **p<0.001 for noninferiority**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Consistency:OK Directness:OK Imprecision:OK
Major bleeding	5107 (2 studies) 6m	Fox 2012 RR: 0.76 (95%CI, 0.49 to 1.18) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Consistency:OK Directness:OK Imprecision:OK
Major or clinically relevant nonmajor bleeding	2564 (1 study) 6m	Schulman 2009 only **5.6% vs 8.8%** **HR: 0.63(95%CI 0.47 to 0.84)** **SS in favor of dabigatran**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 non-inferiority trial, >10% exclusion, no ITT Consistency:OK Directness:OK Imprecision:OK
Any bleeding event	2564 (1 study) 6m	Schulman 2009 only **16.1% vs 21.9%** **HR: 0.71(95%CI 0.59 to 0.85**) **SS in favor of dabigatran**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Consistency:OK Directness:OK Imprecision:OK

Two trials (Schulman 2009 and Schulman 2011) compared dabigatran 150 mg twice daily to warfarin treatment (INR target 2-3), after initial parenteral anticoagulation for 5-9 days in patients with acute VTE. One of these trials (Schulman 2011) is not yet published, but a meta-analysis of both trials (Fox 2012) was performed with the unpublished data.
Both trials were non-inferiority trials.

There is no significant difference in mortality between dabigatran treatment and warfarin treatment.
GRADE: MODERATE quality of evidence

Rates of recurrent VTE were not significantly different between both treatments. Dabigatran is found to be non-inferior to warfarin in the prevention of recurrent VTE. Pre-specified margins for non-inferiority were set rather high.
GRADE: MODERATE quality of evidence

There is no significant difference in major bleeding events between both treatments.
GRADE: MODERATE quality of evidence

Treatment with dabigatran resulted in lower rates of all bleeding events and lower rates of the composite of major and clinically relevant nonmajor bleeding events, compared to warfarin.
GRADE: MODERATE quality of evidence

4.3.6 Dabigatran versus vitamin K antagonist after 10d initial treatment in cancer patients

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: Schulman 2009 RE-COVER I(28) Subgroup analysis of 1 RCT, as reported in Cochrane review Akl 2011(29) Design:RCT DB Double-dummy Phase III non-inferiority Setting: Multicentered International	n = 2564 (total population) n=112 for the subgroup cancer patients Mean age 60.5 TTR (VKA): 60% in target range <u>Inclusion</u> Patients with acute and symptomatic DVT and PE <u>Exclusion</u> - duration of symptoms > 14 days, PE with hemodynamic instability or requiring thrombolytic therapy, another indication for warfarin, recent unstable CV disease, high risk of bleeding, liver disease, estimated creatinine	Initial parenteral anticoagulation for a median of 9 days, then Dabigatran (150mg /twice a day) + placebo 'warfarin' (mock-inr scheme) vs Warfarin (dose adjusted to achieve INR of 2.0 to 3.0) + placebo 'dabigatran'	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 84.8 % in safety analysis 88.8 % in efficacy analysis Described: yes ITT: no Modified ITT for efficacy: patients who did not receive any study drug were excluded from all analyses Per protocol-analysis for safety (on the basis of the patient's actual treatment with the study drug)
			Mortality	Dabigatran: 6/64 (9.4%) Warfarin: 6/57 (10.5%) RR= 0.89 (95% CI 0.30 to 2.61) NS	
			Recurrent venous thromboembolism *[Symptomatic VTE, diagnosed with the use of compression ultrasonography or venography of leg veins and ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries]*	Dabigatran: 2/64 (3.1%) Warfarin: 3/57 (5.3%) RR= 0.59 (95% CI 0.10 to 3.43) NS	
			Safety		
			Major bleeding	Dabigatran: 5/64 (7.8%) Warfarin: 3/57 (5.3%) 1.48 (95% CI 0.37 to 5.94) NS	

(29 countries) Duration of follow-up: 6 months	clearance < 30 ml per minute, life expectancy < 6 months,contraindication to heparin or to radiographic contrast material, - requirement for long-term antiplatelet therapy (≤100 mg of ASA daily acceptable)		Thrombocytopenia	Dabigatran: 3/64 (7.8%) Warfarin: 0/57 (5.3%) 6.25 (95% CI 0.33 to 118.38) NS	Power: adequate Sponsor: Boehringer Ingelheim

Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong, S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism.

4.3.7 Summary and conclusions. Dabigatran versus vitamin K antagonist after 10d initial treatment in cancer patients

Dabigatran 150mg bid versus warfarin (INR 2-3), after initial parenteral anticoagulation (5-9 days) for the long-term treatment (6 mo) of VTE in patients with cancer			
Bibliography: 1 RCT Schulman 2009 RE-COVER I(28), reported in systematic review: Akl 2011(29)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	112 (1 study)	9.4% vs 10.5% RR= 0.89 (95% CI 0.30 to 2.61) NS	⊕⊕⊖⊖ **LOW** Study quality:-1: non-inferiority trial, >10% exclusion, no ITT Consistency:NA Directness:OK Imprecision:-1: wide CI
Recurrent venous thromboembolism	112 (1 study)	3.1% vs 5.3% RR= 0.59 (95% CI 0.10 to 3.43) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 non-inferiority trial, >10% exclusion, no ITT Consistency:NA Directness: OK Imprecision:-1: wide CI
Major bleeding	112 (1 study)	7.8% vs 5.3% RR= 0.59 (95% CI 0.10 to 3.43) NS	⊕⊕⊖⊖ **LOW** Study quality:-1: no-inferiority trial, >10% exclusion, no ITT Consistency:NA Directness:OK Imprecision:-1: wide CI

A Cochrane review did a subgroup analysis of patients with cancer who were included in one RCT comparing dabigatran (2*150mg) versus warfarin (INR 2.0-3.0) in the treatment of symptomatic DVT and PE. Both groups received initial parenteral anticoagulation for a median of 9 days.
This noninferiority trial included 2564 patients, 4% of this population (subgroup) was diagnosed with cancer. This subgroup was prespecified.

The difference in mortality rates between dabigatran and warfarin is not statistically significant.
GRADE: LOW quality of evidence

The difference in recurrent venous thromboembolism rates between dabigatran and warfarin is not statistically significant.
GRADE: LOW quality of evidence

The difference in major bleeding rates between dabigatran and warfarin is not statistically significant.
GRADE: LOW quality of evidence

4.3.8 Dabigatran versus vitamin K antagonist after at least 3 months of continued anticoagulant treatment

Study details	n/Population	Comparison	Outcomes		Methodological
Schulman 2013-RE-MEDY(30) Design: DB PG noninferiority and superiority RCT Setting: Patients from 265 sites in 33 countries Duration of follow-up: 36m	n= 2866 Mean age: 55y Index event: DVT 65%; PE 32%; DVT + PE 12% Current malignancy: 4% Recent surgery: NR Recent trauma: NR Immobilized: 7% TTR (VKA)= median of 65.3% of the time <u>Inclusion</u> at least 18 years; objectively confirmed, symptomatic, proximal deep-vein thrombosis or pulmonary embolism that had already been treated with an approved anticoagulant or received dabigatran in one of two previous clinical trials of short-term treatment of venous thromboembolism (RE-COVER3 and RE-COVER	Dabigatran 2x150mg/d (n=1435) + placebo (sham INR) vs Warfarin (target INR 2 to 3) + placebo (n=1431) for 6-36 months (≠protocol: initial duration 18months) Randomization was stratified according to the presence or absence of active cancer and according to the index	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: unclear Personnel: unclear Assessors: yes FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 6.5% • Described: yes • Balanced across groups: yes ITT: No, modified (exclusion of patients who did not receive any dose of the study drug) Power: adequate SELECTIVE REPORTING: no *"The sample size was determined on the basis of an expected rate of the primary efficacy outcome of 2.0% in both groups with a power of 85% to exclude a hazard ratio of 2.85*
			Recurrent or fatal VTE (PO) (clinically suspected recurrent DVT had to be objectively verified using pre-specified imaging studies)	Dabigatran: 26/1430 (1.8%) Warfarin: 18/1426 (1.3%) HR= 1.44 (95% CI 0.78 to 2.64), NS p for noninferiority=0.01	
			Symptomatic DVT	Dabigatran: 17/1430 (1.2%) Warfarin: 13/1426 (0.9%) HR= 1.32 (95% CI 0.64 to 2.71), NS, p=0.46	
			Symptomatic nonfatal PE	Dabigatran: 10/1430 (0.7%) Warfarin: 5/1426 (0.4%) HR= 2.04 (95% CI 0.70 to 5.98), NS, p=0.19	
			Death related to VTE	Dabigatran: 1/1430 (0.1%) Warfarin: 1/1426 (0.1%) HR= 1.01 (95% CI 0.06 to 16.2), NS, p=0.99	
			All deaths	Dabigatran: 17/1430 (1.2%) Warfarin: 19/1426 (1.3%) HR= 0.90 (95% CI 0.47 to 1.72), NS, p=0.74	
			Safety		
			Major bleeding (defined as clinically overt and associated with a fall of the hemoglobin level of 20 g/L or required transfusion of at least 2	Dabigatran: 13/1430 (0.9%) Warfarin: 25/1426 (1.8%) HR= 0.52 (95% CI 0.27 to 1.02), NS, p=0.06	

	II4 studies). Considered to be at increased risk for recurrent venous thromboembolism on the basis of the site investigator's assessment . DVT confirmed by venous compression ultrasonography (CUS)or venography. PE confirmed by ventilation-perfusion (VQ), or lung scan, or pulmonary angiography, or spiral (helical) CT. In case of death, autopsy is an additional way to confirm VTE. <u>Exclusion:</u> Symptomatic DVT or PE at screening; primary PE with suspected origin other that leg limbs; actual or anticipated use of vena cava filter; interruption of anticoagulant therapy for 2 or more weeks during the 3-6 months of treatment for the prior VTE; patients who in the investigator's opinion should not be treated with warfarin; allergy to warfarin or dabigatran; excessive risk of bleeding; known anaemia ; need of	diagnosis (DVT or PE) <u>The required duration of initial treatment before trial enrollment was 3 to 12 months</u> (≠ protocol: duration of treatment 3 to 6 months)	units of red cells or, involved a critical organ or was fatal)		*(the noninferiority margin for the hazard ratio) and an absolute increase in the risk of recurrent venous thromboembolism of 2.8 percentage points at 18 months (the noninferiority margin for the risk difference), at a one-sided alpha level of 0.025. To meet these specifications, we estimated that we would need to enroll 2000 patients"* Other important methodological remarks: -the prespecified noninferiority margin for the hazard ratio of 2.85 for the PO is large, since it allows an increase in risk by a factor of nearly 3 to be accepted as noninferior -The upper limit of the 95% CI for the hazard ratio of the PO (2.64) was close to the predefined noninferiority margin (2.85), and the CI gives boundaries for the event rate with dabigatran as low as 1.0% and as high as 3.4%. Sponsor: Boehringer Ingelheim
			Clinically relevant non-major bleeding (At least one of the following criteria had to be fulfilled: spontaneous skin hematoma of at least 25 cm; spontaneous nose bleed > 5 minutes duration ; macroscopic hematuria, lasting more than 24 hours ; spontaneous rectal bleeding (more than spotting on toilet paper); gingival bleeding for more than 5 minutes; bleeding leading to hospitalization and/or requiring surgical treatment; Bleeding leading to a transfusion of less than 2 units of whole blood or red cells; any other bleeding considered clinically relevant by the investigator)	NR	
			Major or clinically relevant bleeding event	Dabigatran: 80/1430 (5.6%) Warfarin: 145/1426 (10.2%) **HR= 0.54 (95% CI 0.41 to 0.71), SS, p<0.001 in favour of dabigatran**	
			Any bleeding event	Dabigatran: 277/1430 (19.4%) Warfarin: 373/1426 (26.2%) **HR= 0.71 (95% CI 0.61 to 0.83), SS, p<0.001 in favour of dabigatran**	

	anticoagulant treatment ; recent unstable cardiovascular disease; elevated AST or ALT > 2x ULN; liver disease expected to have any potential impact on survival; developed transaminase elevations upon exposure to ximelagatran; severe renal impairment; pregnant, nursing or of childbearing potential who refuse to use a medically acceptable form of contraception		**Adverse event**	Dabigatran: 1029/1430 (72.0%) Warfarin: 1010/1426 (70.8%) p=0.53	
			Adverse event leading to discontinuation of study drug	Dabigatran: 145/1430 (10.1%) Warfarin: 126/1426 (8.8%) p=0.26	
			Serious adverse event	Dabigatran: 227/1430 (15.9%) Warfarin: 224/1426 (15.7%) p= 0.97	
			Acute coronary syndrome:	<u>During treatment</u> Dabigatran: 13/1.430 (0.9%) Warfarin: 3/1.426 (0.2%) **p= 0.02 in favour of warfarin** <u>Within 30d after treatment</u> Dabigatran: 1/1430 (0.1%) Warfarin: 3/1426 (0.2%) p-value NR	

4.3.9 Summary and conclusions. Dabigatran versus vitamin K antagonist after at least 3 months of continued anticoagulant treatment

Dabigatran 150mg bid versus warfarin (INR 2-3) after >3m long term treatment, for the prevention of recurrent VTE			
Bibliography: Schulman 2013-RE-MEDY(30)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	2866 (1 study) 36m	1.2% vs 1.3% HR= 0.90 (95%CI 0.47 to 1.72) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 non-inferiority, protocol alterations Consistency:NA Directness:OK Imprecision:-1 low event rates
Recurrent or fatal VTE (PO)	2866 (1 study) 36m	**1.8% vs 1.3%** **HR= 1.44 (95 CI 0.78 to 2.64)** **p for noninferiority=0.01**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 non-inferiority poor reporting. Wide margin? Consistency:NA Directness:OK Imprecision:see study quality
Symptomatic DVT	2866 (1 study) 36m	1.2% vs 0.9% HR= 1.32 (95%CI 0.64 to 2.71) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency:NA Directness:OK Imprecision:-1
Symptomatic nonfatal PE	2866 (1 study) 36m	0.7% vs 0.4% HR= 2.04 (95%CI 0.70 to 5.98) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency:NA Directness:OK Imprecision:-1
Major bleeding	2866 (1 study) 36m	0.9% vs 1.8% HR= 0.52 (95%CI 0.27 to 1.02) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency:NA Directness:OK Imprecision:-1
Major or clinically relevant bleeding event	2866 (1 study) 36m	5.6% vs 10.2% **HR= 0.54 (95%CI 0.41 to 0.71)** **SS in favour of dabigatran**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Consistency:NA Directness:OK Imprecision:OK
Acute coronary syndrome	2866 (1 study) 36m	0.9% vs 0.2% **p= 0.02 in favour of warfarin**	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency:NA Directness:OK Imprecision:-1 low event rates

This trial recruited patients with a previous VTE-event, who had received long-term anticoagulant treatment for 3-12 months. These patients were randomized to receive either dabigatran 150mg bid or warfarin (INR target 2-3) for a maximum of 36 months. This was a non-inferiority trial.

There was no significant difference in mortality between the dabigatran group and the warfarin group.
GRADE: LOW quality of evidence

Dabigatran was found to be non-inferior to warfarin in preventing recurrent of fatal VTE. The trial quality and choice of non-inferiority margin however is somewhat debatable.
GRADE: MODERATE quality of evidence

There was no significant difference in symptomatic DVT or symptomatic nonfatal PE between both treatment arms.
GRADE: LOW quality of evidence

There was no significant difference in major bleeding between both treatments.
GRADE: LOW quality of evidence

There was significantly less major or clinically relevant bleeding with dabigatran compared to warfarin.
GRADE: MODERATE quality of evidence

There were significantly more cases of acute coronary syndrome with dabigatran than with warfarin treatment
GRADE: LOW quality of evidence

4.4 Duration of continuation phase of treatment

4.4.1 6 months of continued treatment versus 3 months of continued treatment

Ref	Comparison	N/n	Outcomes	Result*
Nice 2012(8) Design: SR + MA Search date: aug 2011	6 months vs 3 months oral anticoagulation	N= 2 n= 789 (Campbell 2007, Schulman 1985)	**VTE Recurrence**	6 months: 28/400 (7%) 3 months: 32/389 (8.2%) RR: 0.85 (95% CI 0.52 to 1.39) NS Absolute effect: 12 fewer per 1000 (95% CI from 39 fewer to 32 more)
		N= 1 n= 749 (Campbell 2007)	**Major bleeding**	6 months: 8/380 (2.1%) 3 months: 0/369 (0%) RR: 16.51 (95% CI0.96 to 285) NS Absolute effect: -
		N= 2 n= 789 (Campbell 2007, Schulman 1985)	**All cause mortality**	6 months: 21/400 (5.3%) 3 months: 17/389 (4.4%) RR: 1.2 (95% CI 0.64 to 2.24) NS Absolute effect: 9 more per 1000 (95% CI from 16 fewer to 54 more)
		N=2 n=789 (Campbell 2007, Schulman 1985)	**VTE related mortality**	6 months: 3/400 (0.8%) 3 months: 3/389 (0.8%) RR: 1.02 (95 % CI 0.22 to 4.8) NS Absolute effect: 0 more per 1000 (95% CI from 6 fewer to 29 more)
		N=2 n=789 (Campbell 2007, Schulman 1985)	**Fatal bleeding**	6 months: 2/400 (0.5%) 3 months: 0/389 (0%) RR: 4.86 (95% CI0.23 to 100.8) NS Absolute effect: -
		N=1 n=749	**Intracranial bleeding**	6 months: 1/380 (0.3%) 3 months: 0/369 (0%)

		(Campbell 2007)		RR: 2.91 (95% CI 0.12 to 71.29) NS Absolute effect: -
		N=0	**PTS**	-
		N=0	**Quality of life**	-

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Campbell 2007(31) **Country of study:** UK **Setting:** Multicentre, 46 hospitals. Inpatient and outpatient **Study design:** RCT.	**n:** 810 randomised (749 received allocated intervention) **Age (mean):** 58.7±15.4	**Patient group:** Suspected or proven DVT and/or PE without persistent risk factors. September 1999 – December 2002. **Inclusion criteria:** - Age ≥18 - Suspected or proven DVT and/or PE **Exclusion criteria:** -Requirement for thrombolysis or pulmonary embolectomy -DVT or PE in preceding 3 years	**Duration of follow-up:** 1 year (at 3, 6 and 12 months) post randomisation	6 months Vs 3 months anticoagulation with heparin for five days accompanied and followed by warfarin, with a target international normalised ratio of 2.0-3.5. **For all patients:** Target INR 2.0 – 3.5 Warfarin started on day 1	**Major bleeding:** description: transfusion needed, Fall in Hb ≥20 g/l, intracranial or retroperitoneal, serious enough for anticoagulation to be discontinued) **Intracranial bleeding:** description: died of unspecified cerebrovascular event at home during treatment	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : No (open design) List who was masked to interventions: no masking FOLLOW-UP: Post-randomisation exclusions: 61 **Drop outs:** 43 (inc 33 deaths) ITT: no **NOTE:** ***Encouraged*** confirmation with US, radioisotope, venography or angiography "but patients managed without the aid of such tests were accepted for the trial". Patients who met exclusion criteria after randomisation were removed from analysis before there was any knowledge of the outcome of the study Power calculation: 2400 patients to have 80% power to detect difference, significant at 5% level, between recurrence rates of 6% and 9% > **insufficient power to show results** **Funding:** Phamacia Upjohn (part of Pfizer) supplied dalteparin "GSK (manufacturer for LMWH)"
Schulman 1985(32)	60	Patient group: 1st or 2nd event of	Clinical follow-up: 15-27	**1st episode of idiopathic DVT or**	Venous occlusion plethysmography at	ALLOCATION CONC: adequate RANDO: Unclear

Country of study: Sweden **Setting:** Outpatients at specialist thrombosis unit **Study design:** RCT.		DVT Inclusion criteria: - 1st or 2nd event of DVT For group 1 and 2 **almost half idiopathic**	months.	**DVT caused by permanent risk factor:** 6 months vs 3 months **2nd episode of DVT:** 12 months vs 6 months **For all patients:** -iv UFH with warfarin started on day 1 Target INR **2.5 – 4.8** Given information on symptoms of VTE and bleeding and instructed to report to ER if any symptoms occurred. - Thrombolytic therapy with streptokinase if not contraindicated.	diagnosis, on stopping OA and then every 3 months for 1 year. **All cause mortality** (every patient who died was autopsied) **VTE related mortality** (confirmed at autopsy) PE whilst on treatment in patient with uterine cancer **VTE related mortality** PE – confirmed at autopsy, 11 months post treatment (subgroup outcome) **Recurrent VTE rates:** confirmed by venography, perfusion lung scan **Major bleeding:** description: needing transfusion, hospitalisation, leading to chronic or fatal sequelae **Fatal bleeding:** description: GI bleed (subgroup outcome) **Minor bleeding:** description: bleeding not classified as major	BLINDING : No (open study with no one blinded) FOLLOW-UP: **Drop outs:** 7/60 (11.7%) – all deaths ITT: No Small patient numbers -iv UFH with warfarin started on day 1 Target INR 2.5 – 4.8 > High upper range of target INR Given information on symptoms of VTE and bleeding and instructed to report to ER if any symptoms occurred. **Funding:** The Karolinska Institute

4.4.2 Summary and conclusions. 6 months of continued treatment versus 3 months of continued treatment

6 months versus 3 months of anticoagulation for VTE			
Bibliography: meta-analysis Nice 2012(8) included these RCTs: Campbell 2007(31), Schulman 1985(32)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
All cause mortality	789 (2 studies) 1-2y	5.3% vs 4.4% RR: 1.2 (95% CI 0.64 to 2.24) NS	⨁⨁⨀⨀ **LOW** Study quality:-1 unclear allocation concealment or randomization, open label, 10% drop out Consistency:OK Directness:OK Imprecision:-1 wide CI; power?
VTE recurrence	789 (2 studies) 1-2y	7% vs 8.2% RR: 0.85 (95% CI 0.52 to 1.39) NS	⨁⨁⨁⨀ **MODERATE** Study quality:-1 Consistency:OK Directness:OK Imprecision:OK
Major bleeding	789 (2 studies) 1-2y	2.1% vs 0% RR: 16.51 (95% CI0.96 to 285) NS	⨁⨀⨀⨀ **VERY LOW** Study quality:-1 Consistency:OK Directness:OK Imprecision:-2

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

NICE 2012 conducted a meta-analysis of 2 studies comparing 6 months of treatment to 3 months of treatment to prevent recurrence of VTE.

There was no significant difference in mortality rates between both groups.
GRADE: LOW quality of evidence

There was no significant difference in recurrence rates of VTE.
GRADE: MODERATE quality of evidence

There was no significant difference in major bleeding. Due to the low event rates, there is insufficient power to draw any strong conclusions.
GRADE: VERY LOW quality of evidence

4.4.3 Longer versus shorter duration of continued treatment

Ref	Comparison	N/n	Outcomes	Result**
Nice 2012(8) Design: SR-MA Search date: dec 2011	Longer vs shorter duration of oral anticoagulation	N= 8 n= 1889 (Agnelli 2003, Agnelli 2001, Campbell 2007, Eischer 2009, Farraj 2004, Kearon 1999, Schulman 1997, Schulman 1985)	**VTE Recurrence**	**Longer duration: 74/953 (7.8%)** **Shorter duration: 121/936 (12.9%)** **RR: 0.57 (95% CI 0.34 to 0.97)** **SS in favour of Longer duration** **Absolute effect: 56 fewer per 1000 (95% CI from 4 fewer to 85 fewer)**
		N= 2 n= 789 (Campbell 2007, Schulman 1985)	**VTE Recurrence – subgroup: 1st episode**	Longer duration: 28/400 (7%) Shorter duration: 32/389 (8.2%) RR: 0.85 (95% CI 0.52 to 1.39) NS Absolute effect: 12 fewer per 1000 (95% CI from 39 fewer to 32 more)
		N= 5 n= 853 (Agnelli 2003, Agnelli 2001, Eischer 2009, Farraj 2004, Kearon 1999)	**VTE Recurrence – subgroup: 1st episode unprovoked**	Longer duration: 42/427 (9.8%) Shorter duration: 65/426 (15.3%) RR: 0.63 (95% CI 0.32 to 1.24) NS Absolute effect: 56 fewer per 1000 (95% CI from 104 fewer to 37 more)
		N= 2 n= 247 (Schulman 1997, Schulman 1985)	**VTE Recurrence – subgroup: 2nd episode**	Longer duration: 4/126 (3.2%) Shorter duration: 24/121 (19.8%) RR: 0.25 (95% CI 0.04 to 1.75) NS Absolute effect: 149 fewer per 1000 95% CI (from 190 fewer to 149 more)
		N=7 n=1829 (Agnelli 2003, Agnelli 2001, Campbell 2007, Eischer 2009, Farraj 2004, Kearon 1999, Schulman 1997)	**Major bleeding**	**Longer duration: 31/923 (3.4%)** **Shorter duration: 8/906 (0.9%)** **RR: RR 2.83 (95% CI 1.34 to 5.97)** **SS in favour of shorter duration** Absolute effect: 16 more per 1000 (95% CI from 3 more to 44 more)

		N=7 n=1855 (Agnelli 2003, Agnelli 2001, Campbell 2007, Farraj 2004, Kearon 1999, Schulman 1997, Schulman 1985)	**All cause mortality**	Longer duration: 52/936 (5.6%) Shorter duration: 51/919 (5.5%) RR: 0.99 (95% CI 0.68 to 1.45) NS Absolute effect: 1 fewer per 1000 (95% CI from 18 fewer to 25 more)
		N=7 n=1765 (Agnelli 2003, Agnelli 2001, Campbell 2007, Farraj 2004, Kearon 1999, Schulman 1997, Schulman 1985)	**VTE related mortality**	Longer duration: 5/846 (0.6%) Shorter duration: 6/919 (0.7%) RR: 0.96 (95% CI 0.32 to 2.84) NS Absolute effect: 0 fewer per 1000 (95% CI from 4 fewer to 12 more)
		N=7 n=1829 (Agnelli 2003, Agnelli 2001, Campbell 2007, Eischer 2009, Farraj 2004, Kearon 1999, Schulman 1997)	**Fatal bleeding**	Longer duration: 4/923 (0.4%) Shorter duration: 3/906 (0.3%) RR: 1.31 (95% CI 0.23 to 7.33) NS Absolute effect:1 more per 1000 (95% CI from 3 fewer to 21 more)
		N=7 n=1829 (Agnelli 2003, Agnelli 2001, Campbell 2007, Eischer 2009, Farraj 2004, Kearon 1999, Schulman 1997)	**Intracranial bleeding**	Longer duration: 2/923 (0.2%) Shorter duration: 3/906 (0.3%) RR: 0.7 (95% CI 0.14 to 3.6) NS Absolute effect:1 fewer per 1000 (95% CI from 3 fewer to 9 more)
		N=0	**PTS**	-
		N=0	**Quality of life**	-

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Agnelli 2003(33) WODIT-PE Trial **Country of study:** Italy **Setting:** Outpatients attending anticoagulant clinics at 19 hospitals **Study design:** RCT – multicentre, open trial.	326	**Patient group:** 1st episode of PE confirmed by pulmonary angiography or spiral CT or high probability lung scan or intermediate lung scan with objectively diagnosed DVT Age: 62y. **Inclusion criteria:** - Patients who had 3 months of oral anticoagulation ***without VTE recurrence or bleeding*** - Age 15-85 years - Informed consent - Group 1a: Patients with temporary risk factors (recent trauma, surgery or childbirth, immobilisation >7 days, OCP, pregnancy) - Group 1b: Patients with idiopathic PE (no cancer, thrombophilia or transient risk factor) NOTE: systematic screening for occult cancer or thrombophilia was not performed prior to enrolment **Exclusion criteria:** ▪ PE with permanent risk factors (known cancer or known thrombophilia) ▪ Prolonged anticoagulant therapy required for reasons	**Duration of follow-up:** 2 years after discontinuation of treatment Follow up at 3, 6 and 12 months post randomisation and then every 6 months until completion of study	Group 1: 6 months – 1 year Vs. Group 2: 3 months **For all patients:** 3 months of warfarin or acenocoumarol prior to enrolling. Target INR 2.0-3.0	**VTE related mortality:** defined as by: sudden unexplained death **Recurrent VTE rates:** confirmed by new filling defect on pulmonary angiography or spiral CT, new high probability perfusion defect on VQ scan, sudden unexplained death, new non-compressible proximal vein on USS, new/extension of intraluminal filling defect on venography, increase of ≥4mm in diameter of proximal vein thrombus on USS **Major bleeding:** description:clinically overt and assoc with decrease in Hb ≥20g/L, transfusion of ≥2 units, retroperitoneal, intracranial, warranted permanent discontinuation of the study drug, required rehospitalisation **Composite VTE:** description: recurrent PE and proximal DVT **Minor bleeding:** description:none given just	ALLOCATION CONC: NR in NICE 2012 RANDO: Adequate (Randomisation performed centrally in permuted blocks of six) BLINDING : No (open design) FOLLOW-UP: **Drop outs:** 13/326 (4.0%) ITT:yes **Overall rate of VTE recurrence <7.5%** **An unequivocal reduction in rate of recurrent VTE in Group 1** **Risk of recurrence in Group 1 <25% that in Group 2** **Rate of major bleeding >5% in Group 1** **Interim analysis showed <25% risk for recurrent VTE therefore stopped**

		other than VTE			"Total Bleeding Events" minus "Major Bleeding "	
Agnelli 2001(34) WODIT Trial **Country of study:** Italy **Setting:** Outpatients attending anticoagulant clinics at 10 study centres **Study design:** RCT – multicentre, open trial.	267	Patient group: 1st episode idiopathic proximal DVT confirmed by compression ultrasonography or venography Age:67y. Inclusion criteria: - Patients who had 3 months of oral anticoagulation without VTE recurrence or bleeding - Age 15-85 years - Informed consent NOTE: Systematic screening for occult cancer or thrombophilia was not performed prior to enrolment	2 years after discontinuation of treatment Follow up at 3, 6 and 12 months post randomisation and then every 6 months until completion of study	Group 1: 1 year Vs Group 2: 3 months **For all patients:** 3 months of warfarin (97%) or acenocoumarol prior to enrolling. Target INR 2.0-3.0 Approx 20% in each group received LMWH before OA, rest received UFH	**VTE related mortality:** defined as by: autopsy if PE could not be excluded as cause of death **Recurrent VTE rates:** confirmed by PA or spiral CT, high probability VQ scan, intermediate lung scan with objectively diagnosed recurrent DVT, compression USS, new/extension of intraluminal filling defect on venography **Major bleeding:** description: clinically overt and associated with decrease in Hb ≥2g/dL, transfusion of ≥2 units, retroperitoneal, intracranial, warranted permanent discontinuation of the study drug **Fatal bleeding:** description: 1 intracranial 1 month after discontinuation of OA, 1 GI bleed 12 months after.	ALLOCATION CONC:NR in NICE 2012 RANDO: adequate BLINDING : No (open design) FOLLOW-UP: Drop out: 11.2% group 1, 5.3% group 2 ITT & per protocol analysis Limitations: - ?insufficient power to show results - Stopped early - Different lengths of follow up in control and intervention = bias in favour of shorter duration Average time to VTE recurrence: Group 1: 16.0 months Group 2: 11.2 months
Campbell 2007(31) **Country of study:** UK	**n:** 810	**Patient group:** Suspected or proven DVT and/or PE without persistent risk factors. **Inclusion criteria:** - Age ≥18	**Duration of follow-up:** 1 year (at 3, 6 and 12 months) post randomisation	6 months vs 3 months	**Major bleeding:** description: transfusion needed, Fall in Hb ≥20 g/l, intracranial or retroperitoneal, serious	ALLOCATION CONC: NR in NICE 2012 RANDO:Adequate BLINDING : No (open design)

Setting: Multicentre, 46 hospitals. Inpatient and outpatient **Study design:** RCT.		- Suspected or proven DVT and/or PE **Exclusion criteria:** -Requirement for thrombolysis or pulmonary embolectomy -DVT or PE in preceding 3 years		**For all patients:** Target INR 2.0 – 3.5 Warfarin started on day 1	enough for anticoagulation to be discontinued) **Intracranial bleeding:** description: died of unspecified cerebrovascular event at home during treatment	FOLLOW-UP: **Drop outs:** 43 (inc 33 deaths) ITT: no **NOTE:** ***Encouraged*** confirmation with US, radioisotope, venography or angiography "but patients managed without the aid of such tests were accepted for the trial". Patients who met exclusion criteria after randomisation were removed from analysis before there was any knowledge of the outcome of the study Power calculation: 2400 patients to have 80% power to detect difference, significant at 5% level, between recurrence rates of 6% and 9% > insufficient power to show results **Funding:** Phamacia Upjohn (part of Pfizer) supplied dalteparin "GSK (manufacturer for LMWH)"
Eischer 2009(35) AUREC-FVIII Investigators **Country of study:** Austria, Sweden **Setting:**	34	Patients with 1st spontaneous VTE and high factor VIII (objectively confirmed by venography or colour coded duplex US, VQ scan or spiral CT) **Inclusion criteria:**	**Duration of follow-up:** 2+ years (mean 37 months) (at 1 month and then every 6 months)	Group 1: 30 months Vs. Group 2: 6 months	**Recurrent VTE rates** (confirmed by venography or colour coded duplex US, VQ scan or spiral CT). Recurrent DVT defined as other leg, different vein in same leg or extension of ≥5cm above original thrombus	ALLOCATION CONC: NR in NICE 2012 RANDO: NR in NICE BLINDING : No (open label) ***"central adjudication committee assessed outcomes"*** FOLLOW-UP:

Outpatient, 13 centres **Study design:** RCT, open label.		• First spontaneous VTE • Factor VIII >230 IU/dl • >18 years old • Written informed consent **Exclusion criteria:** - Prolonged immobility - E.a. (not VTE-related)		**For all patients:** Randomised after 6 months of VKA therapy to continue or discontinue therapy Target INR 2.0-3.0 Patients who stopped received thromboprophylaxis for high risk situations including surgery, trauma, immobilisation >3 days, long distance flights. Given written information on symptoms of VTE and bleeding and instructed to report any symptoms.	**Major bleeding**: death, hospitalisation, chronic sequelae, transfusion with blood, plasma or coagulation factors	**Drop outs:** 4/34 (11.8%) ITT: yes Power calculation: 40 patients in each arm for 90% power and 0.05 to show risk of recurrence and major haemorrhage 6% in Group 1 Prolonged follow up of longer duration groups leading to bias towards shorter durations **Funding:** Kamillo-Eisner-Stiftung, Hergiswil, Switzerland
Farraj 2004(36) **Country of study:** Jordan **Setting:** Outpatient from tertiary care centre **Study design:** RCT	64	1st episode idiopathic VTE. Consecutive patients being followed by Internal Medicine team A. Symptomatic proximal DVT objectively proven by Doppler US or PE proven by spiral CT **Age (mean):** 42±15 **Inclusion criteria:** ▪ Patients with 1st episode	**Duration of follow-up:** 12 months after stopping anticoagulation (seen every 4 months). All patients asked to report immediately any symptoms suggestive of PE	Group 1: 24 months Vs Group 2: 6 months **For all patients:** INR 2.0 – 3.0 Initial treatment	**Recurrent VTE rates (all & after stopping treatment):** confirmed by Doppler US +D-dimer ±spiral CT **Major bleeding**: clinically overt, fall in Hb≥2g/dL, transfusion ≥2 units, intracranial or retroperitoneal	ALLOCATION CONC: NR in NICE 2012 RANDO: Adequate BLINDING : open design, unclear blinding FOLLOW-UP: Drop outs: 0 ITT:yes

		idiopathic VTE **Exclusion criteria:** - Known thrombophilia - E.a. (not VTE-related)	or DVT in 24 month period	with iv UFH or sc LMWH for 5 days. Warfarin started on first day of therapy. INR monitored monthly once INR stable in treatment range for 2 consecutive weeks.		**Funding:** None disclosed
Kearon 1999(37) **Country of study:** Canada and US **Setting:** Multicentre outpatient with visits to clinic **Study design:** RCT DB PG	172	1st ***idiopathic*** episode of VTE (objectively confirmed, symptomatic proximal DVT or PE). **Age (mean):** 59±16 **Inclusion criteria:** - **Completed 3 months OA** after initial course of LMWH or UFH - Patients with previous VTE due to transient risk factor included if this episode idiopathic - Written informed consent	**Duration of follow-up:** Mean duration 10 months (12months for group 1[warfarin] and 9 months for group 2 [placebo]). Follow up was discontinued after diagnosis of recurrent VTE	**Group 1** Warfarin for 24 months INR 2.0-3.0 vs **Group 2** Placebo for 24 months Sham INR 2.0-3.0 **For all patients:** All patients had 3 months of OA prior to randomistaion Initial dose of study drug prescribed according to INR on day of randomisation Baseline VQ scan,	**VTE related mortality:** defined as confirmed PE **Recurrent VTE rates:** confirmed by VQ scan, compression ultrasonography, venography, or pulmonary angiography **Major bleeding:** clinically overt and fall in Hb ≥2g/dl , need for ≥2 units transfusion, retroperitoneal, intracranial **Symptomatic pulmonary embolism:** confirmed by: VQ scan ± compression ultrasonography, bilateral venography, or pulmonary angiography **Symptomatic DVT:** confirmed by: compression ultrasonography or venography	ALLOCATION CONC: NR in NICE 2012 RANDO: Adequate BLINDING : Participants: adequate/personnel: adequate/assessors: yes FOLLOW-UP: **Drop outs:** 27/172 (15.7%) ITT:no **Funding:** Dupont Pharma, Medical Research Council of Canada, Heart and Stroke Foundation of Canada and Ministry of Health of Ontario Limitations: *"Stopped early (due to effectiveness of intervention)and stopped follow up at this time"*

				bilateral compression ultrasonography and if possible bilateral impendence plethysmography at randomisation		
Schulman 1997(38) DURAC II trial **Country of study:** Sweden **Setting:** Multicentre (16 centres) **Study design:** RCT, open label.	227	2nd episode of VTE (objectively confirmed by venography, pulmonary angiography or combination of CXR and VQ scan) **Inclusion criteria:** - Age ≥15 years - 2nd episode of VTE - Oral informed consent **Exclusion criteria:** - Unconfirmed DVT/PE	**Duration of follow-up:** 4 years post randomisation (1.5, 3, 6, 9, 12, 24, 36, 48)	**Group 1** Indefinite (mean 42.7 months during follow up) Vs **Group 2** 6 months (mean 7.7 months) **For all patients:** Target INR 2.0-2.85 Patients with DVT were given graduated compression stocking to wear during the day for at least one year LMWH or UFH at physician's discretion Thrombolytic therapy could be	**VTE related mortality**: Mesenteric vein thrombosis confirmed at laparotomy and one suspected sudden death at 27 months **Recurrent VTE rates** (confirmed by venography, pulmonary angiography or combination of CXR and VQ scan). Recurrent DVT defined as other leg, different vein in same leg or extension of ≥5cm above original thrombus **Major bleeding**: death, required hospitalisation, treatment with blood products or vitamin K **Intracranial bleeding**: cerebral haemorrhage, subarachnoid	ALLOCATION CONC: NR in NICE 2012 RANDO: Adequate BLINDING : participants and personnel: no, assessors: yes FOLLOW-UP: **Drop outs:** (16-22%) received different (shorter) duration of treatment from schedule ITT:yes **Funding:** Swedish Heart Lung Foundation, Swedish Society of Medicine, the Karolinska Institute, Skandia, Trygg-Hansa, Triolab, and Stago

				given at start of study.		
Schulman 1985(32) **Country of study:** Sweden **Setting:** Outpatients at specialist thrombosis unit **Study design:** RCT, open label	60	Patient group: 1st or 2nd event of DVT Inclusion criteria: - 1st or 2nd event of DVT For group 1 and 2 **almost half idiopathic**	Clinical follow-up: 15-27 months. Venous occlusion plethysmography at diagnosis, on stopping OA and then every 3 months for 1 year.	**1st episode of idiopathic DVT or DVT caused by permanent risk factor:** 6 months vs 3 months **2nd episode of DVT:** 12 months vs 6 months **For all patients:** - Thrombolytic therapy with streptokinase if not contraindicated. Target INR 2.5 – 4.8 > High upper range of target INR	**All cause mortality** (every patient who died was autopsied) **VTE related mortality** (confirmed at autopsy) PE whilst on treatment in patient with uterine cancer **VTE related mortality** PE – confirmed at autopsy, 11 months post treatment (subgroup outcome) **Recurrent VTE rates:** confirmed by venography, perfusion lung scan **Major bleeding:** description: needing transfusion, hospitalisation, leading to chronic or fatal sequelae **Fatal bleeding:** description: GI bleed (subgroup outcome) **Minor bleeding:** description: bleeding not classified as major	ALLOCATION CONC: adequate RANDO: Unclear BLINDING : No (open study with no one blinded) FOLLOW-UP: **Drop outs:** 7/60 (11.7%) – all deaths ITT: No Small patient numbers **Funding:** The Karolinska Institute

4.4.4 Summary and conclusions. Longer versus shorter duration of continued treatment

Longer (6-42m) versus shorter (3-6m) duration of oral anticoagulation for VTE			
Bibliography: meta-analysis Nice 2012(8) included these RCTs: Agnelli 2003(33)WODIT-PE Trial, Agnelli 2001(34)WODIT Trial, Campbell 2007(31), Eischer 2009(35)AUREC-FVIII, Farraj 2004(36), Kearon 1999(37), Schulman 1997(38)DURAC II trial, Schulman 1985(32)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
All cause mortality	1855 (7 studies) 10m-4y treatment: 6-42m vs 3-6m	5.6% vs 5.5% RR: 0.99 (95% CI 0.68 to 1.45) NS	⊕⊕⊕⊖ **MODERATE** Study quality:open label, but OK Consistency:OK Directness:-1 very different durations Imprecision: OK
VTE Recurrence	1889 (8 studies) 10m-4y treatment: 6-42m vs 3-6m	7.8% vs 12.9% **RR: 0.57 (95% CI 0.34 to 0.97)** **SS in favour of longer duration** Absolute effect: 56 fewer per 1000 (95% CI from 4 fewer to 85 fewer)	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:OK Directness:-1 Imprecision:OK
VTE Recurrence – subgroup: 1st episode	789 (2 studies) 1-1.5y treatment: 6m vs 3m	7% vs 8.2% RR: 0.85 (95% CI 0.52 to 1.39) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 allocation concealment, rando, 10% drop out Consistency:OK Directness:OK Imprecision:OK
VTE Recurrence – subgroup: 2nd episode	247 (2 studies) 2-4y treatment: 12-42,7m vs 6m	3.2% vs 19.8% RR: 0.25 (95% CI 0.04 to 1.75) NS	⊕⊕⊖⊖ **LOW** Study quality:OK Consistency:OK Directness:-1 Imprecision:-1
Major bleeding	1829 (7 studies) treatment: 6-42m vs 3-6m	**3.4% vs 0.9%** **RR 2.83 (95% CI 1.34 to 5.97)** **SS in favour of shorter duration** Absolute effect: 16 more per 1000 (95% CI from 3 more to 44 more)	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency:OK Directness:-1 Imprecision:OK

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

NICE 2012 performed a meta-analysis of all RCTs comparing longer duration treatment to shorter duration treatment in the prevention of recurrent VTE. There was a wide range of treatment durations: long term treatment ranged from 6 months to 42 months, shorter duration ranged from 3 months to 6 months. The populations enrolled had a potentially different recurrence risk: some studies consisted of only unprovoked VTE, some studies included only a first ever VTE, other studies included only second episodes of VTE. It is difficult to draw any firm conclusions from this meta-analysis.

No significant difference in mortality rates was seen when comparing longer duration treatment to shorter duration treatment.
GRADE: MODERATE quality of evidence

There was a lower rate of VTE recurrence with longer treatment compared to shorter treatment.
GRADE: MODERATE quality of evidence

No significant difference in recurrence of VTE was seen in populations with a first episode VTE. Neither was there a significant difference in recurrence rates in populations with a second episode of VTE.
GRADE: MODERATE to LOW quality of evidence

There was significantly more major bleeding with longer duration treatment compared to shorter duration treatment.
GRADE: MODERATE quality of evidence

4.4.5 Dabigatran versus placebo after at least 6 months of anticoagulant treatment

Study details	n/Population	Comparison	Outcomes		Methodological
Schulman 2013-RE-SONATE(30) Design: DB PG superiority RCT Setting: Patients from 147 sites in 21 countries Duration of follow-up: 6 months (= treatment) extended up to 12 months after completion of the study treatment(≠protocol)	n= 1353 Mean age: 56y Index event: DVT 65%; PE 27%; DVT + PE 6% Recent surgery: NR Recent trauma: NR Immobilized: 6% <u>Inclusion</u> at least 18 years; objectively confirmed, symptomatic, proximal deep-vein thrombosis or pulmonary embolism that had already been treated with an approved anticoagulant or received dabigatran in one of two previous clinical trials of short-term treatment of venous thromboembolism (RE-COVER3 and RE-COVER II4 studies). DVT confirmed by venous compression ultrasonography (CUS) or venography.	Dabigatran 2x150mg/d (n=685) vs. placebo (n=668) Randomization was stratified according to study center for 6 months The required duration of initial treatment before trial enrollment was 6 to 18 months	Efficacy (during 6m of treatment)		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: unclear Personnel: unclear Assessors: yes FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 2.6% • Described: yes • Balanced across groups: yes ITT: no, modified (exclusion of patients who did not receive any dose of the study drug) Power: adequate? (1800 patients were needed according to sample size calculation)
			Recurrent or fatal VTE or unexplained death (**PO**) (clinically suspected recurrent DVT had to be objectively verified using pre-specified imaging studies)	Dabigatran: 3/681 (0.4%) Placebo: 37/662 (5.6%) **HR= 0.08 (95% CI 0.02 to 0.25),SS, p<0.001 in favour of dabigatran**	
			Symptomatic DVT	Dabigatran: 2/681 (0.3%) Placebo: 22/662 (3.3%) P value NR	
			Symptomatic nonfatal PE	Dabigatran: 1/681 (0.1%) Placebo: 14/662 (2.1%) P value NR	
			Unexplained death	Dabigatran: 0/681 (0%) Placebo: 2/662 (0.3%) P value NR	
				"no cases of objectively verified fatal PE or any other deaths"	
			Safety		
			Major bleeding (defined as clinically overt and associated with a fall of the hemoglobin level of 20 g/L or required transfusion of at least 2 units of red cells or, involved a critical organ or was fatal)	Dabigatran: 2/684 (0.3%) Placebo: 0/659 (0%) HR= not estimable	

	PE confirmed by ventilation-perfusion (VQ), or lung scan, or pulmonary angiography, or spiral (helical) CT. In case of death, autopsy is an additional way to confirm VTE. <u>Exclusion:</u> < 18 y; indication for vitamin K antagonist other than DVT and/or PE; patients in whom anticoagulant treatment for their index PE or DVT should be continued; active liver disease or liver disease decreasing survival or ALT >3 x ULN; creatinine clearance <30 ml/min; acute bacterial endocarditis; active bleeding or high risk for bleeding; uncontrolled hypertension; intake of another experimental drug < 30 days ; life expectancy <6 months; childbearing potential without proper contraceptive measures, pregnancy or breast feeding; known hypersensivity to dabigatran or any other component of the investigational product; active cancer		**Clinically relevant non-major bleeding** (At least one of the following criteria had to be fulfilled: spontaneous skin hematoma of at least 25 cm; spontaneous nose bleed > 5 minutes duration ; macroscopic hematuria, lasting more than 24 hours ; spontaneous rectal bleeding (more than spotting on toilet paper); gingival bleeding for more than 5 minutes; bleeding leading to hospitalization and/or requiring surgical treatment; bleeding leading to a transfusion of less than 2 units of whole blood or red cells; any other bleeding considered clinically relevant by the investigator)	NR	SELECTIVE REPORTING: no Sponsor: Boehringer Ingelheim
			Major or clinically relevant bleeding event	Dabigatran: 36/684 (5.3%) Placebo: 12/659 (1.8%) **HR= 2.92 (95% CI 1.52 to 5.60), SS, p=0.001 in favour of placebo**	
			Any bleeding event	Dabigatran: 72/684 (10.5%) Placebo: 39/659 (5.9%) **HR= 1.82 (95% CI 1.23 to 2.68), SS, p=0.003 in favour of placebo**	
			Acute coronary syndrome	Dabigatran: 1/684 (0.1%) Placebo: 1/659 (0.2%) NT	

4.4.6 Summary and conclusions. Dabigatran versus placebo after at least 6 months of anticoagulant treatment

Dabigatran 150mg bid versus placebo after long term treatment, for the prevention of recurrent VTE			
Bibliography: Schulman 2013-RE-SONATE(30)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Recurrent or fatal VTE or unexplained death (PO)	1353 (1study) 6m	0.4% vs 5.6% **HR= 0.08 (95%CI 0.02 to 0.25) SS in favour of dabigatran**	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:NA Directness:OK Imprecision:OK
Symptomatic DVT	1353 (1study) 6m	0.3% vs 3.3% No statistical test	Not applicable
Symptomatic nonfatal PE	1353 (1study) 6m	0.1% vs 2.1% No statistical test	Not applicable
Major bleeding	1353 (1study) 6m	0.3% vs 0% HR= not estimable	⊕⊕⊖⊖ **LOW** Study quality:OK Consistency:NA Directness:OK Imprecision: -2 no event in placebo group
Major or clinically relevant bleeding event	1353 (1study) 6m	5.3% vs 1.8% **HR= 2.92 (95%CI 1.52 to 5.60) SS in favour of placebo**	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:NA Directness:OK Imprecision:OK
Acute coronary syndrome	1353 (1study) 6m	0.1% vs 0.2% NT	Not applicable

This trial recruited patients with a previous VTE-event, who had received long-term anticoagulant treatment for 6 to 18 months. They were randomized to receive either dabigatran 150mg bid or placebo, for an additional 6 months.

Mortality was not reported as a separate endpoint.

The rate of recurrent VTE (fatal or non-fatal) or unexplained death (as a composite endpoint) was significantly higher in the placebo group. Most of the events were VTE-events.
GRADE: HIGH quality of evidence

The rates of major bleeding were very low in both groups (0 event in the placebo group).
GRADE: LOW quality of evidence

Major bleeding or clinically relevant non-major bleeding (as a composite endpoint) was observed more frequently in the dabigatran group. This difference was statistically significant.
GRADE: HIGH quality of evidence

4.4.7 Apixaban versus placebo after at least 6 months of anticoagulant treatment

Study details	n/Population	Comparison	Outcomes		Methodological
Agnelli 2013-AMPLIFY-EXT(39) Design: DB PG RCT Setting: ambulatory, multicenter, at 328 sites in 28 countries Duration of follow-up: 12m	n= 2486 Mean age: 57y Initial diagnosis: DVT: 65% PE: 35% Previous VTE: 13% Current malignancy: 2% Immobilized: 3% <u>Inclusion</u> 18 years or older; objectively confirmed, symptomatic deep-vein thrombosis (DVT)* or pulmonary embolism (PE)** with or without deep-vein thrombosis); <u>treated for 6 to 12 months with standard anticoagulant therapy or completed treatment with apixaban or enoxaparin and warfarin</u>; no symptomatic recurrence during prior anticoagulant therapy; clinical equipoise about the continuation or	Apixaban 2x2.5 mg/d vs. Apixaban 2x5 mg/d vs. placebo stratified by disease (symptomatic proximal DVT or symptomatic PE) after treatment 6-12m with anticoagulant treatment duration: 12m	Efficacy		RANDO: adequate ALLOCATION CONC: adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 99.6% in safety analysis 99.8% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: Yes Power: adequate Other important methodological remarks: -Low risk of reporting bias - only 15% of the patients in this study were older than 75 years of age and few had a body weight
			Recurrent VTE or death from any cause (PO) Recurrent VTE included fatal and nonfatal pulmonary embolism and deep-vein thrombosis	Apixaban 2.5 mg: 32/840 (3.8%) Apixaban 5 mg: 34/813 (4.2%) Placebo: 96/829 (11.6%) Apix 2.5 vs pla: **RR=0.33 (95% CI 0.22 to 0.48), SS** Apix 5 vs pla: **RR=0.36 (95% CI 0.25 to 0.53), SS** Apix 2.5 vs apix 5: NA	
			Recurrent VTE or VTE-related death	Apixaban 2.5 mg: 14/840 (1.7%) Apixaban 5 mg: 14/813 (1.7%) Placebo: 73/829 (8.8%) Apix 2.5 vs pla: **RR= 0.19 (95% CI 0.11 to 0.33), SS** Apix 5 vs pla: **RR= 0.20(95% CI 0.11 to 0.34), SS** Apix 2.5 vs apix 5: RR= 0.97 (95% CI 0.46 to 2.02), NS	
			Non–VTE-related cardiovascular death, myocardial infarction, or stroke	Apixaban 2.5mg: 4/840 (0.5%) Apixaban 5mg: 5/813 (0.6%) Placebo: 11/829 (1.3%) Apix 2.5 vs pla: RR= 0.36 (95% CI 0.11 to 1.12), NS Apix 5 vs pla: RR=0.47 (95% CI 0.16 to 1.33), NS	

	cessation of anticoagulant therapy. *<u>Symptoms of DVT</u>: For a NEW DVT: abnormal CUS, including grey-scale or color-coded Doppler, or an intraluminal filling defect on venography. For a RECURRENT DVT: abnormal CUS where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression, or an extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography. **<u>Symptoms of PE with one of the following findings</u>: • A new intraluminal filling defect in (sub)segmental or more-proximal branches on spiral computed tomography (CT) of the chest. • A new intraluminal filling defect, or an extension of an existing defect, or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram. • A new perfusion defect of at least 75% of a segment, with a local normal ventilation result	During the course of the trial, dual antiplatelet therapy, aspirin at a dose higher than 165 mg daily, and potent inhibitors of cytochrome P-450 3A4 and P-glycoprotein were prohibited		Apix 2.5 vs apix 5: RR=0.77 (95% CI 0.21 to 2.88), NS	below 60 kg or moderate or severe renal impairment. Consequently, more data are needed to better determine the benefit-to-risk profile of apixaban with respect to bleeding in such patients. Sponsor: Bristol-Myers Squibb and Pfizer
			Recurrent VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease–related death	Apixaban 2.5mg: 18/840 (2.1%) Apixaban 5mg: 19/813 (2.3%) Placebo: 83/829 (10.0%) Apix 2.5 vs pla: **RR= 0.21 (95% CI 0.13 to 0.35), SS** Apix 5 vs pla: **RR= 0.23 (95% CI 0.14 to 0.38), SS** Apix 2.5 vs apix 5: RR= 0.92 (95% CI 0.48 to 1.74), NS	
			Safety		
			Major bleeding (PO) defined as acute clinically overt bleeding accompanied by one or more of the following: o A decrease in hemoglobin of 2 g/dl or more o A transfusion of 2 or more units of packed red blood cells o Bleeding that occurs in at least one critical site o bleeding that is fatal	Apixaban 2.5 mg: 2/840 (0.2%) Apixaban 5 mg: 1/813 (0.1%) Placebo: 4/829 (0.5%) Apix 2.5 vs pla: RR= 0.49 (95% CI 0.09 to 2.64), NS Apix 5 vs pla: RR=0.25 (95% CI 0.03 to 2.24), NS Apix 2.5 vs apix 5: RR= 1.93 (95% CI 0.18 to 21.25), NS	
			Clinically relevant non-major bleeding defined as acute clinically overt bleeding that consists of: • any bleeding compromising hemodynamics • any bleeding leading to hospitalization	Apixaban 2.5 mg: 25/840 (3.0%) Apixaban 5 mg: 34/813 (4.2%) Placebo: 19/829 (2.3%) Apix 2.5 vs pla: RR= 1.29 (95% CI 0.72 to 2.33), NS Apix 5 vs pla:	

	(high probability) on ventilation/perfusion lung scintigraphy (VQ scan). • Inconclusive spiral CT, pulmonary angiography, or VQ scan evidence of a new or recurrent PE, with demonstration of a new or recurrent deep vein thrombosis (DVT) in the lower extremities by compression ultrasound (CUS) or venography. <u>Exclusion</u> contraindication to continued anticoagulant therapy; requiring ongoing anticoagulant therapy, dual antiplatelet therapy, or aspirin at a dose> 165 mg daily; hemoglobin level <9 mg/dl; platelet count < 100000/mm^3; serum creatinine level > 2.5 mg/dl (221 µmol/l); calculated creatinine clearance < 25 ml/min, alanine aminotransferase or aspartate aminotransferase level > 2 times upper limit of normal range; total bilirubin level > 1.5 times the upper limit of the		• subcutaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause • intramuscular hematoma documented by ultrasonography • epistaxis that lasted for more than 5 minutes, was repetitive, or led to an Intervention • gingival bleeding occurring spontaneously • hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation of the urogenital tract • macroscopic gastrointestinal hemorrhage • hemoptysis, if more than a few speckles in the sputum and not occurring within the context of PE, or o any other bleeding type considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life.	RR= 1.82 (95% CI 1.05 to 3.18), NS Apix 2.5 vs apix 5: RR= 0.71 (95% CI 0.43 to 1.18), NS	
			Major or clinically relevant non-major bleeding	Apixaban 2.5 mg: 27/840 (3.2%) Apixaban 5 mg: 35/813 (4.3%) Placebo: 22/829 (2.7%) Apix 2.5 vs pla: RR=1.20 (95% CI 0.69 to 2.10), NS Apix 5 vs pla: RR= 1.62 (95% CI 0.96 to 2.73), NS Apix 2.5 vs apix 5: RR= 0.74 (95% CI	

	normal range			0.46 to 1.22), NS	
			VTE, VTE-related death, myocardial infarction, stroke, cardiovascular disease-related death, or major bleeding (a reduction of this composite outcome was considered to represent the net clinical benefit)	Apixaban 2.5 mg: 20/840 (2.4%) Apixaban 5 mg: 20/813 (2.5%) Placebo: 86/829 (10.4%) Apix 2.5 vs pla: **RR= 0.23 (95% CI 0.14 to 0.37), SS** Apix 5 vs pla: **RR= 0.24 (95% CI 0.15 to 0.38), SS** Apix 2.5 vs apix 5: RR=0.97 (95% CI 0.52 to 1.79), NS	

4.4.8 Summary and conclusions. Apixaban versus placebo after at least 6 months of anticoagulant treatment

Apixaban 2.5mg bid or 5mg bid versus placebo after long term treatment (6-12m) for VTE, for the prevention of recurrent VTE			
Bibliography: Agnelli 2013-AMPLIFY-EXT(39)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Recurrent VTE or death from any cause (PO)	2486 (1 study) 12m	Apix 2.5 vs apix 5 vs pla 3.8% vs 4.2% vs 11.6% Apix 2.5 vs pla: **RR=0.33 (95% CI 0.22 to 0.48)** **SS in favour of apixaban 2.5** Apix 5 vs pla: **RR=0.36 (95% CI 0.25 to 0.53)** **SS in favour of apixaban 5**	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:NA Directness:OK Imprecision:OK
Recurrent VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease–related death	2486 (1 study) 12m	2.1% vs 2.3% vs 10.0% Apix 2.5 vs pla: **RR= 0.21 (95%CI 0.13 to 0.35)** **SS in favour of apixaban 2.5** Apix 5 vs pla: **RR= 0.23 (95%CI 0.14 to 0.38)** **SS in favour of apixaban 5**	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:NA Directness:OK Imprecision:OK
Major bleeding	2486 (1 study) 12m	0.2% vs 0.1% vs 0.5% Apix 2.5 vs pla: RR= 0.49 (95%CI 0.09 to 2.64) NS Apix 5 vs pla: RR=0.25 (95%CI 0.03 to 2.24) NS	⊕⊕⊖⊖ **LOW** Study quality:OK Consistency:NA Directness:OK Imprecision:-2 very wide CI; low event rates
Clinically relevant non-major bleeding	2486 (1 study) 12m	3.0% vs 4.2% vs 2.3% Apix 2.5 vs pla: RR= 1.29 (95% CI 0.72 to 2.33) NS Apix 5 vs pla: **RR= 1.82 (95%CI 1.05 to 3.18)** **SS (more bleeding with apixaban 5 mg)**	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:NA Directness:OK Imprecision:-1 wide CI

This trial recruited patients that had experienced a recent VTE (65% DVT, 35% PE) and had been treated for 6-12 months with standard anticoagulant treatment or apixaban. The patients were randomized to either apixaban 2.5mg bid, 5mg bid or placebo, for an additional 12 months.
An average of 13% of these patients had already experienced a previous VTE event.

Mortality was not reported as a separate outcome.

The rate of recurrent VTE or death from any cause (as a composite endpoint) was significantly lower in the apixaban treatment groups compared to placebo.
GRADE: HIGH quality of evidence

The rate of either recurrent VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease–related death (as a composite outcome) was significantly lower in the apixaban treatment groups compared to placebo.
GRADE: HIGH quality of evidence

The rate of major bleeding was low. There was no significant difference in major bleeding between the apixaban treatment groups and placebo, but precision for this outcome is weak.
GRADE: LOW quality of evidence

There was no significant difference in clinically relevant non-major bleeding when comparing apixaban 2.5 mg bid to placebo. There was however a significant difference for this outcome when comparing apixaban 5mg bid to placebo.
GRADE: MODERATE quality of evidence

4.4.9 Rivaroxaban versus placebo after at least 6 months of anticoagulant treatment

Study details	n/Population	Comparison	Outcomes		Methodological
EINSTEIN-extension 2010 (4) Continued treatment study Design: double-blind, randomized, event-driven superiority study RCT: DB, PG Setting: unclear Duration of follow-up: treatment duration of 6 or 12 months	n= 1197 Mean age:58 Patients had been treated for 6 to 12 months with acenocoumarol or warfarin or rivaroxaban Previous VTE(DVT/PE): 108 (17.9%) (rivaroxaban) 84 (14.1%) (placebo) <u>Inclusion</u> **objectively** confirmed, symptomatic DVT or pulmonary embolism and had been treated for 6 to 12 months with acenocoumarol or warfarin (in the EINSTEIN studies or from routine care) or rivaroxaban (in the EINSTEIN studies) and if there was equipoise with respect to the need for continued anticoagulation. <u>Exclusion</u>	Rivaroxaban 20 mg 1x/d vs placebo	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: >99% Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT:Yes, for efficacy Safety analysis: all patients that received study drug were analysed Power: adequate SELECTIVE REPORTING: no Sponsor: Bayer Schering Pharma and Ortho- McNeil
			Symptomatic recurrent VTE (PO) (confirmed by with the use of diagnostic criteria for PE: CT scan, pulmonary angiogram, ventilation/perfusion scan; for DVT: compression ultrasound, venography)	**Rivaroxaban: 8/602 (1.3%)** **placebo:42/594 (7.1%)** **HR: 0.18 (95% CI 0.09-0.39 p<0.001)** **SS in favour of rivaroxaban**	
			Safety		
			First major or clinically relevant nonmajor bleeding Major bleeding is defined as overt bleeding and: fall in hemoglobin of 2 g/dL or more, or leading to a transfusion of 2 or more units of packed red blood cells or whole blood, or occurring in a critical site or contributing to death Other clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention	**Rivaroxaban: 36/598(6.0%)** **Placebo: 7/590 (1.2%)** **HR: 5.19 (95% CI 2.3 to 11.7); p<0.001** **SS in favour of placebo**	
			Major bleeding	Rivaroxaban: 4/598 (0.7%)	

	Another indication for a vitamin K antagonist; a creatinine clearance < 30 ml /min; clinically significant liver disease or an ALT >3x; bacterial endocarditis; active bleeding or a high risk of bleeding; systolic BP> 180 mm Hg ordiastolic BP> 110 mm Hg; childbearing potential without proper contraception, pregnancy, or breast-feeding; concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers, ; a life expectancy of less than 3 months.			Placebo: 0 (0%) HR: NA; p=0.11	
			Clinically relevant nonmajor bleeding	Rivaroxaban: 32/598(5.4%) Placebo: 7 /590 (1.2%)	
			All-cause mortality	Rivaroxaban: 1/598(0.2%) Placebo: 2/590 (0.3%)	
			Vascular events (acute coronary syndrome, ischemic stroke, transient ischemic attack, or systemic embolism)	Rivaroxaban: 3 /598 (0.5%) Placebo: 4 /598(0.7%)	

4.4.10 Summary and conclusions. Rivaroxaban versus placebo after at least 6 months of anticoagulant treatment

Rivaroxaban 20mg/d versus placebo for VTE, in patients who had completed 6-12 m of treatment			
Bibliography: EINSTEIN-extension 2010(4)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1197 (1 study) 6m-12m	0.2% vs 0.3% No statistical test	**NOT APPLICABLE**
Symptomatic recurrent VTE (PO)	1197 (1 study) 6m-12m	1.3% vs 7.1% **HR: 0.18 (95% CI 0.09 to 0.39)** **SS in favour of rivaroxaban**	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:NA Directness:OK Imprecision:OK
Major or clinically relevant nonmajor bleeding (PO)	1197 (1 study) 6m-12m	6.0% vs 1.2% **HR: 5.19 (95% CI 2.3 to 11.7)** **SS in favour of placebo**	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:NA Directness:OK Imprecision:OK
Major bleeding	1197 (1 study) 6m-12m	0.7% vs 0% NS	⊕⊕⊖⊖ **LOW** Study quality:OK Consistency:NA Directness:OK Imprecision:-2 low event rates

This trial includes patients that had been treated for 6 to 12 months with a VKA or with rivaroxaban for a VTE episode (DVT or PE). For 14.1% to 17.9% of these patients, this was not the first VTE event. They were randomized to receive either rivaroxaban 20mg daily or a matching placebo. Treatment duration in the trial was 6 or 12 months.

Mortality rates were very low in both groups. No statistical test was done.
GRADE: NOT APPLICABLE

There was significantly fewer recurrent symptomatic VTE in patients treated with rivaroxaban compared to patients treated with placebo (HR: 0.18; 95% CI 0.09 to 0.39).
GRADE: HIGH quality of evidence

There was significantly more major or clinically relevant nonmajor bleeding in rivaroxaban-treated patients (HR: 5.19 95% CI 2.3 to 11.7).
GRADE: HIGH quality of evidence

Rates of major bleeding were very low. The difference between rivaroxaban and placebo was not significant.
GRADE: LOW quality of evidence

Lower rates of VTE with rivaroxaban are accompanied by almost equally higher rates of bleeding. The clinical benefit needs to be questioned.

4.4.11 Low dose aspirin versus placebo after continued treatment with anticoagulant

Study details	n/Population	Comparison	Outcomes		Methodological
Brighton 2012-ASPIRE(40) Design: DB PG RCT Setting: 56 sites in five countries Duration of follow-up: Median 37.2 months	n= 822 Mean age: 55y Index event: (proximal DVT 57%; PE 28%; DVT+PE 14%) Previous VTE(DVT/PE): 5% Current malignancy: 2% Recent surgery: NR Recent trauma: NR Immobilized: NR 73% of the patients had received anticoagulation therapy for at least 6 months before randomization <u>Inclusion</u> at least 18 years of age; have had a first unprovoked episode of objectively diagnosed symptomatic DVT involving	Aspirin 100mg/d (n=411) vs. placebo (n=411) after initial anticoagulation of 6w-12m (heparin, followed by VKA) stratification according to center and duration of initial oral anticoagulation therapy (≤26 weeks or >26 weeks) duration of	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: unclear Personnel: unclear Assessors: yes FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 30% • Described: yes • Balanced across groups: yes ITT: Yes (Data from patients who withdrew consent or who were lost to follow-up were censored at the time of the last follow-up assessment. All patients who stopped using the study drug continued to be followed and were included in the intention-to-treat analysis). Power: adequate? (at least 1800 patients were needed
			Recurrence of VTE (composite of objectively confirmed symptomatic DVT or PE, nonfatal PE or fatal PE) (**PO**)	<u>Unadjusted</u>: Aspirin: 57/411 (14%) Placebo: 73/411 (18%) 4.8% per year vs 6.5% per year HR= 0.74 (95% CI 0.52 to 1.05) NS, p=0.09 "The event rate for venous thromboembolism in the first year was 10.6% with placebo, as compared with 4.9% with aspirin." <u>Adjusted for baseline characteristics</u>: HR= 0.72 (95% BI 0.51 to 1.01), NS, p=0.06	
			Major vascular events (Composite of symptomatic VTE, myocardial infarction, stroke, or cardiovascular death)	<u>Unadjusted</u>: Aspirin: 62/411 (15.1%) Placebo: 88/411 (21.4%) 5.2% per year vs 8.0% per year **HR= 0.66 (95% CI 0.48 to 0.92), SS, p=0.01 in favour of aspirin**	
			Net clinical benefit: Composite of symptomatic VTE, myocardial infarction, stroke, all cause mortality and major	<u>Unadjusted</u>: Aspirin: 71/411 (17.3%) Placebo: 99/411 (24.1%) 6.0% per year vs 9.0% per year **HR= 0.67 (95% CI 0.49 to 0.91), SS in favour of aspirin**	

	the popliteal vein or more proximal leg veins or an acute PE. VTE was considered to be unprovoked if it occurred in the absence of the following transient risk factors during the preceding 2 months: confinement to bed for more than 1 week, major surgery, trauma requiring a cast, pregnancy or the puerperium, and the use of the oral contraceptive pill or hormone-replacement therapy. All patients were required to have completed initial anticoagulation therapy with heparin followed by warfarin (or an effective alternative anticoagulant). The duration of the initial anticoagulation therapy had to be between 6 weeks and 24 months; however, it was recommended that a target INR of 2 to 3 be maintained with warfarin	treatment 2 to 4 years	**bleeding**	<u>Adjusted for baseline characteristics</u>: **HR= 0.64 (95% CI 0.47 to 0.87), SS in favour of aspirin**	according to sample size calculation) SELECTIVE REPORTING: no Sponsor: supported by National Health and Medical Research Council (Australia), Health Research Council (New Zealand), Australasian Society of Thrombosis and Hemostasis, National Heart Foundation of Australia, and Bayer HealthCare. Aspirin and matching placebo were provided without charge by Bayer Health-Care Pharmaceuticals; the company played no other role in the study and was not involved in the collection or analysis of the data or in the preparation of the manuscript.
			Fatal VTE	One in each group	
			Safety		
			Major[1] or clinically relevant non-major[2] bleeding (**PO**) [1]defined as clinically overt bleeding associated with a decrease in haemoglobin of at least 20g/L, or requiring transfusion of 2 or more units of blood, or involving a critical site, or disabling, or requiring surgical intervention, or contributing to death [2]defined as all bleeding episodes not meeting the definition of major bleeding, but which leads to the discontinuation of study medication for more than 14 days	Aspirin: 14/411 (3.4%) Placebo: 8/411 (1.9%) 1.1% per year vs 0.6% per year HR= 1.73 (95% CI 0.72 to 4.11), NS, p=0.22	
			Major bleeding	Aspirin: 8/411 (1.9%) Placebo: 6/411 (1.5%) NT	
			Clinically relevant non-major bleeding	Aspirin: 6/411 (1.5%) Placebo: 2/411 (0.5%) NT	
			Death any cause	Aspirin (n=411) Placebo (n=411)	

	therapy for 6 to 12 months (VTE documented by ultrasound) <u>Exclusion</u> first unprovoked episode of VTE had occurred more than 2 years before enrollment; indication or contraindication for the use of aspirin, other antiplatelet therapy, or a NSAID; indication for continuing oral anticoagulation therapy; other medical problems that would interfere with participation in the trial or limit life expectancy			16 **PE** **MI** **Other CV cause** **Cancer** **Bleeding** **Other non-CV cause**	18 1 2 5 4 2 4	NT NT NT NT NT NT NT	
			AE leading to hospitalization	Aspirin: 102/411 (24.8%) Placebo: 117/411 (28.5%) NT			
			Discontinuation	<u>Total:</u> Aspirin: 117/411 (28.5%) Placebo: 121/411 (32.1%) HR= 0.79 (95% CI 0.62 to 1.01), NS, p=0.06 <u>Indication for thromboprophylaxis</u>: Aspirin: 21/411 (5.1%) Placebo: 32/411 (7.8%) NT <u>Gastro-intestinal AE or bleeding</u>: Aspirin: 14/411 (3.4%) Placebo: 2/411 (0.5%) NT		

Study details	n/Population	Comparison	Outcomes		Methodological
Becattini 2012-WARFASA(41)	n= 403	ASA 100mg/d	Efficacy*		RANDO: unclear
	Mean age: 62y		**Recurrence of VTE: DVT + non-fatal PE + fatal PE (PO)** (confirmed by compression US, CT or lung scan)	**ASA: 28/205 (13.7%)** **Placebo: 43/197 (21.8%)** **(6.6% vs 11.2% per year)** **HR=0.58 (95%CI: 0.36 to 0.93)** **P= 0.02, SS in favour of ASA**	ALLOCATION CONC: unclear
	Index event:	Vs			BLINDING :
Design:	ASA group: 59.5% DVT + 40.5% PE	Placebo			Participants: yes
	Placebo group: 65.9% DVT +				Personnel: yes
RCT (DB) (PG)	34.1% PE	duration of treatment:	**Recurrent PE**	ASA: 11/205 (5.4%) Placebo: 14 /197 (7.1%) HR=0.70 (95%CI: 0.32 to 1.54) P= 0.37, NS	Assessors: yes
	Current malignancy: no	2y			FOLLOW-UP:
	Recent surgery: no				Lost-to follow-up: 1.7%
Setting:	Recent trauma: no	after initial	**Recurrent DVT**	**ASA: 16 /205 (7.8%)** **Placebo: 28 /197 (14.2%)** **HR=0.51 (95%CI: 0.27 to 0.94)** **P= 0.03, SS in favour of ASA**	Drop-out and Exclusions: 16%
multicenter	Immobilized: no	treatment			• Described: yes
	(unprovoked: no risk factors)	with VKA			• Balanced across groups: yes
		for 6-18m			
	Inclusion		Safety*		
Duration of follow-up: 2y	Age >18y; Prior treatment with VKA for 6-18m; First-ever **objectively confirmed*** symptomatic proximal DVT, PE or both *DVT confirmed on compression ultrasonography PE confirmed on CT or lung scan		**Major bleeding or clinically relevant non-major bleeding** An overt bleeding event was defined as major if it was fatal, occurred in a critical location (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular [leading to a compartment syndrome]), or was associated with a decrease in the hemoglobin level of at least 2.0 g per deciliter or required a transfusion of 2 or more	ASA: 4 /205 (2.0%) Placebo: 4 /197 (2.0%) HR=0.98 (95%CI: 0.24 to 3.96) P= 0.97, NS	ITT: no ('modified ITT': all patients who received at least one dose of study drug) Power: adequate SELECTIVE REPORTING: no Other important methodological remarks: The end of the study was event-driven; in about 5% of the patients the duration of
	Exclusion The main exclusion criteria were known cancer; known major thrombophilia; an indication for long-term anticoagulant therapy other than venous				

	thromboembolism (as atrial fibrillation or prosthetic heart valve); previous symptomatic complications of atherosclerosis requiring treatment with aspirin or other anti-platelet agents; active bleeding or high risk for bleeding or a bleeding episode which occurred during the 6-18 months of anticoagulation; known allergy or intolerance to aspirin; life expectancy shorter than six months; anticipated non-adherence to study medications; pregnancy or breast-feeding; participation in another experimental pharmacotherapeutic program within 30 days before randomization. Women with venous thromboembolism associated with the use of estro - progestin therapy were excluded from the study.		units of whole blood or red cells. Clinically relevant, nonmajor bleeding, defined as any overt bleeding that required a medical intervention and did not meet any of the criteria for major bleeding.		the treatment was shorter than the intended 2 years. Patients were reexamined every 3m in the first year and every 6m thereafter. They were instructed to report if they had symptoms suggestive of recurrent VTE or bleeding complications. In cases of suspected recurrence, objective testing was required. Sponsor: Bayer HealthCare
			Death	ASA: 6 /205 (2.9%) Placebo: 5 /197 2.5%) (1.4% per year vs 1.3% per year) HR=1.04 (95%CI: 0.32 to 3.42) P= 0.95, NS	
			Recurrent VTE or arterial event (nonfatal myocardial infarction, unstable angina, stroke, transient ischemic attack, acute ischemia of the lower limbs)	ASA: 36 /205 (17.6%) Placebo: 48 /197 (24.4%) HR=0.67 (95%CI: 0.43 to 1.03) P= 0.06, NS	

* Table in original article specifies number of events, but text clearly states: number of patients with an event. After careful analysis of the numbers, we conclude that these numbers reflect the number of patients with an event;

4.4.12 Summary and conclusions. Low dose aspirin versus placebo after continued treatment with anticoagulant

Aspirin 100mg/d versus placebo after long-term treatment with vitamin K antagonists, for the prevention of recurrent VTE			
Bibliography: Becattini 2012-WARFASA(41), Brighton 2012-ASPIRE(40)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1225 (2 studies) 2-4y	Becattini 2012 1.4% per year vs 1.3% per year HR=1.04 (95%CI: 0.32 to 3.42) NS Brighton 2012 3.9% vs 4.4% (rate over median 37.2m) NT	⊕⊕⊖⊖ **LOW** Study quality:-1 secondary endpoints Consistency:OK Directness:OK Imprecision:-1, wide CI, low event rates
Recurrent VTE (symptomatic DVT or PE, nonfatal or fatal PE)	1225 (2 studies) 2-4y	Becattini 2012 6.6% vs 11.2% per year **HR=0.58 (95%CI: 0.36 to 0.93)** **SS in favour of aspirin** Brighton 2012 4.8% per year vs 6.5% per year HR= 0.74 (95% BI 0.52 to 1.05) NS, p=0.09	⊕⊕⊖⊖ **LOW** Study quality:-1 moderate drop-out Consistency:OK Directness:-1 difference in baseline recurrence rate: different risk populations Imprecision:OK
Major bleeding or clinically relevant nonmajor bleeding	1225 (2 studies) 2-4y	Becattini 2012 2.0% vs 2.0% (rate over 2y) HR=0.98 (95%CI: 0.24 to 3.96) NS Brighton 2012 1.1% per year vs 0.6% per year HR= 1.73 (95% CI 0.72 to 4.11) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency:OK Directness:OK Imprecision:-1 low event rates
Recurrent VTE or arterial event (nonfatal myocardial infarction, unstable angina, stroke, transient ischemic attack, acute ischemia of the lower limbs)	403 (1 study) 2y	Becattini 2012 17.6% vs 24.4% (rate over 2y) HR=0.98 (95%CI: 0.24 to 3.96) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 moderate drop-out Consistency:OK Directness:OK Imprecision:-1 wide CI
Major vascular event (symptomatic VTE, myocardial infarction, stroke, or cardiovascular death)	822 (1 study) median 37.2m	Brighton 2012 5.2% per year vs 8.0% per year **HR= 0.66 (95% CI 0.48 to 0.92)** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 moderate drop-out Consistency:OK Directness:OK Imprecision:OK

Two RCTs recruited patients with a previous first-ever VTE, who had received long-term treatment with a vitamin K antagonist (for 6 weeks to 18months; 86.5% of patients received VKA >6months). The patients were randomized to either aspirin 100mg or to placebo, for 2 to 4 years.

There was no observed difference in mortality rates between both groups.
GRADE: LOW quality of evidence

A lower rate of recurrent VTE was observed with aspirin treatment. This difference was statistically significant in only 1 trial (Becattini 2012). However, recurrence risk was different in both studies. Placebo-treated patients in the Becattini trial had a recurrence rate of 11.2%, whereas this was only 4.8% in the Brighton trial. Populations in these studies are clinically heterogenous.
GRADE: LOW quality of evidence

There was no statistically significant difference in the rate of major or clinically relevant nonmajor bleeding between aspirin and placebo treatment.
GRADE: LOW quality of evidence

There was no significant difference in the rate of the composite endpoint 'recurrent VTE or arterial events' in the Becattini trial. This endpoint did not include mortality.
There was a statistically significant difference in favour of aspirin, for the composite endpoint that included recurrent VTE, myocardial infarction, stroke, or cardiovascular death in the Brighton trial.
GRADE: MODERATE to LOW quality of evidence

4.5 Ambulatory treatment versus in-hospital treatment of VTE

4.5.1 Home treatment versus in-hospital treatment for deep vein thrombosis

Ref	Comparison	N/n	Outcomes	Result
Othieno 2007(42) Design: SR+MA Search date: November 2007	Home treatment (LMWH) vs Hospital treatment (LMWH or UFH)	N= 6 n= 1708 Boccalon 2000, Chong 2005, Daskalopoulos 2005, Koopman 1996, Levine 1996, Ramacciotti 2004	**Recurrent VTE**	**RR: 0.61 (95%CI, 0.42 to 0.90)** **SS in favour of home treatment**
			Major bleeding	RR: 0.67 (95%CI, 0.33 to 1.36) NS
			Minor bleeding	RR: 1.29 (95%CI, 0.94 to 1.78) NS
			Mortality	RR: 0.72 (95%CI, 0.45 to 1.15) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Boccalon 2000(43) Design RCT OL PG Setting: Home or hospital, France	n = 201	Mean age: 63.8 (range 18 to 85 years) <u>Inclusion criteria:</u> Confirmed diagnosis (by ultrasonography or venography) of proximal DVT not more than 30 days before enrolment <u>Exclusion criteria:</u> Thrombus in the inferior vena cava, a floating thrombus, history of DVT within the previous 6 months, DVT with symptomatic PE, a clinical condition requiring hospitalisation, contraindication to anticoagulant treatment, pregnancy, heparin treatment within the 48 hours preceding inclusion, home or hospital treatment were impossible for any reason, participant lived too far away from the trial centre, written consent was not given	6 months	Home treatment – LMWH vs Inpatient treatment - LMWH <u>Treatment for both groups:</u> Subcutaneous injection of LMWH (dalteparin sodium, enoxaparin sodium or nadroparin calcium as chosen by the attending physician) at the recommended dose followed by anticoagulant for 6 months <u>Anticoagulants</u>: Oral vitamin K antagonist or fluindione, 20 mg/day for the first 3 days, followed by regimen to maintain INR between 2.0 and 3.0 for up to 6 months Participants were also given <u>compression stockings</u> and were	Primary: Recurrent VTE, PE, major bleeding. Secondary: Death, minor bleeding, economic analysis.	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Unclear Remarks on blinding method: No blinding possible in this study FOLLOW-UP: Lost-to follow-up: 19% Drop-out and Exclusions: 4% Described: Yes Balanced across groups: unclear ITT: no

				encouraged to return to physical activity according to a schedule approved by the general practitioner and nurse Mean hospital stay was 9.6 days for the hospital-treated group and one day for the home-treated group		
Chong 2005(44) Design RCT OL PG Setting: Home or hospital Australia, New Zealand, Poland, South Africa	n = 298	Mean age: Not mentioned (Age > 18 years) <u>Inclusion criteria:</u> diagnosis of symptomatic lower extremity DVT (proximal or distal) confirmed by either contrast venography and/or ultrasonography, be suitable for treatment in an outpatient setting, be prepared to self administer daily subcutaneous injections, life expectancy > 6 months <u>Exclusion criteria:</u> 1) received therapeutic doses of heparin for more than 24 hours before randomisation; 2) clinically overt signs or symptoms of PE or evidence of PE on lung scanning or	24 weeks	<u>Home treatment - LMWH</u> (once daily subcutaneous injection of enoxaparin 1.5mg/kg for a minimum of 5 days plus 10 mg of warfarin for 3 months with dose adjusted to achieve and maintain the International Normalised Ratio (INR) above 2 and within range accepted by the investigator) Vs <u>Hospital treatment - UFH</u> (5000 IU bolus of unfractionated heparin (UFH) for a minimum of 5 days plus 10 mg warfarin started on day 1 of the	Primary: efficacy endpoint- incidence of symptomatic recurrent DVT safety endpoint- incidence of adverse effect,major or minor bleeding during the first 14 days Secondary: incidence of PE, recurrent VTE	ALLOCATION CONC: Yes RANDO: unclear BLINDING : No Remarks on blinding method: No blinding possible in this study FOLLOW-UP: drop-outs described in original article ITT: unclear (yes by Cochrane authors) Seventy-seven percent of participants in the home arm (LMWH group) of the Chong trial were admitted to hospital

		pulmonary angiography; 3) impending venous gangrene; 4) previous heparin -induced thrombocytopenia or another hypersensitivity reaction to heparin; 5) a platelet count < 50 x 10/9 per liter; treatment with fibrinolytics or oral anticoagulants within the previous 5 days, or with other investigational therapeutic agents within the previous 4 weeks; 6) pregnancy or lactation; 7) any clinical significant medical condition other than DVT that would prevent the patient from being discharged from hospital		treatment for 3 months) Did not report duration of hospital stay.		(Chong 2005). Twelve percent were released on the day of admission, 34% were kept for one day and 31% were kept for two or more nights
Daskalopoulos 2005(10) Design RCT OL PG Prospective Setting: Outpatient or hospital Greece	n = 102	Mean age: 58.6 years (Age > 18 years) <u>Inclusion criteria:</u> acute proximal DVT confirmed by colour duplex UScan not more than 1 week onset <u>Exclusion criteria:</u> Segmental deep venous thrombosis restricted to infrapopliteal deep veins or calfmuscles as determined by	6 months	<u>Home treatment – LMWH</u> (single Subcutaneous injection of LMWH(tinzaparin sodium) in a weight adjusted dose (175 anti Xa IU/Kg) daily for 6 months) Vs <u>Hospital treatment – UFH</u>	Primary: recanalisation of the thrombosed veins, major events Secondary: Recurrent DVT, PE, major bleeding, minor bleeding, thrombocytopenia, death	ALLOCATION CONC: Unclear RANDO: Unclear BLINDING : No Remarks on blinding method: No blinding possible in this study FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions:

		duplex ultrasonography, symptomatic or clinically suspected PE, history of recently diagnosed (within 12 months) DVT or PE, patient already on anticoagulant therapy, bleeding tendency objectively confirmed, hypersensitivity to heparin preparations or coumarin derivatives, uncontrolled hypertension, history of recently diagnosed (< 1 month) cerebrovascular accident, intracranial artery aneurysm, infectious endocarditis, thrombocytopenia, active peptic ulcer, hepatic or renal failure, history of asthma, recent spinal or epidural anaesthesia or intraspinal paracentesis (< 5 days), recent surgery (< 5 days), recently performed thrombolysis or under antiplatelet therapy, body weight < 35 kg, pregnancy, illicit drug addiction, altered mental status or impaired cognitive function with inability to comply with study protocol		(Intravenous bolus of 5000 IU UFH followed by intravenous infusion of UFH for 5 to 7 days. APTT was measured after 4 hours of the initiation of heparin administration and was repeated 6 hours thereafter to reach the therapeutic range (ratio: 1.5 to 2.5) Oral anticoagulant was commenced on the 3rd day following UFH therapy) Did not report duration of hospital stay.		6% Described: Yes Balanced across groups: Unclear ITT: unclear
Koopman 1996(45)	n = 400	Age: 60.5 years (Age > 18 years)	24 weeks	<u>Home treatment – LMWH</u> (Twice daily injections of	Primary: Symptomatic recurrent VTE. Secondary:Major	ALLOCATION CONC: adequate RANDO: adequate

Design RCT PG OL Setting: Outpatient or hospital The Netherlands, France, Italy, New Zealand, Australia		<u>Inclusion criteria:</u> acute symptomatic proximal DVT proven by venography or duplex scan <u>Exclusion criteria:</u> VTE within previous 2 years suspected PE at presentation geographic inaccessibility post-thrombotic syndrome pregnancy life expectancy < 6 months previous treatment with heparin for more than 24 hours		LMWH (nadroparin calcium [Fraxiparine] at a dose adjusted for patient's weight) Vs <u>Hospital treatment – UFH</u> (APTT adjusted dose, continuous intravenous infusion of 1250 IU per hour after initial intravenous bolus of 5000 IU) Oral anticoagulation: Warfarin commenced on day 1 and continued for 3 months, dose adjusted to give INR 2.0 to 3.0 Mean hospital stay was 8.1 days for the hospital-treated 'control' group and 2.7 days for the home-treated 'treatment' group	haemorrhage, death, quality of life comparisons, comparison of costs (in-patient versus home)	BLINDING : No Remarks on blinding method: No blinding possible in this study FOLLOW-UP: Lost-to follow-up: 1% Drop-out and Exclusions: 0.5% Described: Yes Balanced across groups: Yes ITT: unclear (yes by Cochrane authors) Thirty-six per cent of participants in the Koopman trial were treated entirely at home, 39% had a short hospital stay and 25% were entirely hospital treated.
Levine 1996(46) Design RCT PG	n = 500	Mean age: 58 years <u>Inclusion criteria:</u> Acute proximal DVT proven on venography or duplex scan	90 days	<u>Home treatment – LMWH</u> (enoxaparin 1 mg per kg body weight twice a day) Vs	Primary: Symptomatic recurrent DVT or PE within 90 days of randomisation, major bleeding, minor bleeding during study	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : No Remarks on blinding method:

OL Setting Outpatient or hospital Canada		Exclusion criteria: Two or more previous episodes of DVT or PE, active bleeding, active peptic ulcer, coagulation disorder, symptomatic PE, possibility of non-compliance, contraindications to LMWH, pregnancy, pre-treatment with heparin for more than 48 hours, inability to make follow up visits due to geographical inaccessibility, presence of known deficiency of anti-thrombin III, protein C or protein S		Hospital treatment – UFH (APTT adjusted dose, continuous intravenous infusion of 20000 IU after initial intravenous bolus of 5000 IU) Anticoagulants: Warfarin sodium started on evening of day 2 and continued for at least 3 months. First dose 10 mg, thereafter adjusted to maintain INR between 2.0 and 3.0 Mean hospital staywas 6.5 days for the hospital-treated control group and 2.1 days for the home-treated group	period and up to 48 hours after discontinuation of study medication Secondary: Death, economic evaluation.	No blinding possible in this study FOLLOW-UP: Exclusions post-randomisation: Not stated. Losses to follow up: None. ITT: unclear (yes by Cochrane authors) Fifty per cent of participants in the Levine trial were treated entirely at home.
Ramacciotti 2004(47) Design RCT PG OL Setting Outpatient or hospital	n = 201	Mean age for home treatment: 64 Mean age for hospital treatment: 44 (Age ≥ 18 years) Inclusion criteria: weight ≥ 50 and < 110kg DVT symptoms ≥ 10 days proxmal lower limb DVT (confirmed by duplex		Home treatment – LMWH (Once daily Subcutaneous injection of enoxaparin at a dose of 1.5 mg/kg for 5 to 10 days) Vs Hospital treatment – UFH	Primary endpoint: recurrent DVT, PE Secondary outcome: major and minor bleeding.	ALLOCATION CONC: Unclear RANDO: Unclear BLINDING : No Remarks on blinding method: No blinding possible in this study FOLLOW-UP:

Multicenter Brazil		ultrasound or venography) ready access to local health service, capable of using enoxaparin at home <u>Exclusion criteria:</u> - History of HIT or allergy to heparin - haemorrhagic diathesis - surgery within 7 days - symptoms of PE - bilateral DVT - survival prognosis < 6 months - hepatic or renal failure - received therapeutic doses of UFH or LMWH ≥ 24 hrs in the previous 48 hrs - patients in hospital for another reason with stay anticipated to last > 3days, - initial platelet count < 100000/ml, - uncontrolled hypertension with DBP ≥ 180, - initial APTT > 1.3 time the normal value, - INR > 1.5 at enrollment, - indication for thrombolysis or venous thrombectomy		(Intravenous bolus injection of 5000 IU of UFHfollowed **by** intravenous 500 IU/kg/day adjusted to maintain an aPTT of 1.5 to 2.5 times the normal value for 5 to 10 days) <u>Anticoagulant</u>: warfarin (with a targeted INR 2 to 3) for at least 3 months, starting at day 1 or 2 of treatment Mean hospital stay of three days for home-treated patients and seven days for the hospital-treated patients		Lost-to follow-up: 0% Drop-out and Exclusions: Unclear ITT: unclear The trial reported hospitalisation for all hospital-treated patients and 64% of home-treated patients.

Author's conclusions:

Six RCTs involving 1708 participants with comparable treatment arms were included. All six had fundamental problems including high exclusion rates, partial hospital treatment of many in the LMWH arms, and comparison of UFH in hospital with LMWH at home. The trials showed that patients treated at home with LMWH are less likely to have recurrence of venous thromboembolism (VTE) compared with hospital treatment with UFH or LMWH (fixed effect relative risk (RR) 0.61; 95% confidence interval (CI) 0.42 to 0.90). Home-treated patients also had lower mortality (RR 0.72; 95% CI 0.45 to 1.15) and fewer major bleeding (RR 0.67; 95% CI 0.33 to 1.36), but were more likely to have minor bleeding than those in hospital (RR 1.29; 95% CI 0.94 to 1.78) though these were not statistically significant

The limited evidence suggests that home management is cost effective and preferred by patients. Further large trials comparing these treatments are unlikely to occur. Therefore, home treatment is likely to become the norm; further research will be directed to resolving practical issues.

4.5.2 Summary and conclusions. Home treatment versus in-hospital treatment for deep vein thrombosis

Home treatment vs in-patient treatment for deep vein thrombosis			
Bibliography: meta-analysis Othieno 2007(42) included these RCTs: Boccalon 2000(43), Chong 2005(44), Daskalopoulos 2005(10), Koopman 1996(45), Levine 1996(46), Ramacciotti 2004(47)			
Outcomes	**N° of participants (studies) Follow up**	**Relative effect (95% CI)** ***Absolute effect***	**Quality of the evidence (GRADE)**
Mortality	1708 (6 studies) 3m-6m	RR: 0.72 (95%CI, 0.45 to 1.15) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 for trial quality and unclear hospital stay Consistency: OK Directness:-1 for comparing LMWH vs UFH Imprecision: OK
Recurrent VTE	1708 (6 studies) 3m-6m	**RR: 0.61 (95%CI, 0.42 to 0.90)** **SS in favour of home treatment**	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency: OK Directness:-1 Imprecision: OK
Major bleeding	1708 (6 studies) 3m-6m	RR: 0.67 (95%CI, 0.33 to 1.36) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency: OK Directness:-1 Imprecision: OK
Minor bleeding	1708 (6 studies) 3m-6m	RR: 1.29 (95%CI, 0.94 to 1.78) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency: OK Directness:-1 Imprecision: OK

A systematic review compared home treatment to in-hospital treatment for patients with acute deep vein thrombosis. 1708 patients from 6 studies were included. Mean hospital stay for home-treated patients was 1-3 days, mean hospital stay for hospital treated patients was 6.5-9 days.
Follow-up ranged between 3 and 6 months. Some studies compared initial LMWH home treatment with initial UFH in-hospital treatment. The overall study quality was weak.

There was no significant difference in mortality rates observed between home treatment and in-hospital treatment.
GRADE: LOW quality of evidence

There was a significantly lower recurrence rate of VTE with home-treated compared to hospital treated patients.
GRADE: LOW quality of evidence

No significant difference in major or minor bleeding rates was observed.
GRADE: LOW quality of evidence

4.5.3 Home treatment (early discharge) vs in-hospital treatment for pulmonary embolism

Study details	n/Population	Comparison	Outcomes		Methodological
Otero 2010(48) Design: RCT OL PG Setting: Multicenter Duration of follow-up: 14 days + a visit at one and three months after recruitment	n= 132 Mean age: 60 years Previous VTE(DVT/PE): Not mentioned Surgery in the last 2 months: 13.6% Cancer: 4.5% Immobilized (>4days): 9.8% Days of hospitalization: mean 3.4 early discharge vs mean 9.3 standard hospitalization TTR (VKA):NR <u>Inclusion</u> Consecutive patients over 18 years of age who presented with acute symptomatic PE Criteria for PE: - intraluminal filling defect in subsegmental or more proximal pulmonary arteries on spiral CT; high	Early discharge (n=72) (discharge on 3rd day: 61%) (discharge on 5th day: 39%) Vs Hospitalization (n = 60) Treatment: All patients received standard therapy with weight-adjusted doses of Low Molecular Weight Heparin. Vitamin K antagonist therapy was started on day 10 after randomization. After an initial	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no Remarks on blinding method: No blinding possible in this study FOLLOW-UP: Lost-to follow-up: 0 % Drop-out and Exclusions: 0% ITT: Yes (The primary analysis of survival was based on the time from random assignment to death) Power: inadequate The authors assumed an early complication rate less of 1%. It was estimated that at least 671 patients per group would be required to show non-
			Symptomatic recurrent VTE (**PO**) = objective assessment of recurrent PE, DVT or death attributed to PE up to three months. PE: - a new perfusion defect involving -75% or more of a lung segment; - presence of a new intraluminal filling defect or - extension of a previous filling defect on helical CT. New or recurrent DVT was diagnosed by - the appearance of a new noncompressible vein segment, or - a 4-mm or more increase in the diameter of a thrombus on complete lower limb ultrasound testing (CCUS)	Early discharge: 2 (2.8%) Hospitalization: 2 (3.3%) RR: 0.83 (95% CI 0.12 to 5.74) NS (p=0.62)	
			Short term non-fatal recurrences (<10 days after diagnosis)	Early discharge: 1 (1.4%) Hospitalization: 0 (0%) RR: - NS (p=0.54)	

	probability finding on a ventilationperfusion lung scan; nondiagnostic finding with documented deep vein thrombosis A standardized clinical prediction rule was used to identify patients with acute PE and <u>low risk of death and shortterm adverse events</u> <u>Exclusion</u> - a clinical score >2 points; hemodynamic instability atenrolment ; T-troponin concentrations of ≥0.1 ngmL; oxygen saturation <93%; need of hospitalization for other comorbidities; dyspnea ([NYHA] III/IV); severe COPD(FEV1 <50% of predicted), severe asthma; active bleeding or high risk ofbleeding (subjectively assessed by physician); recent surgery (<15d); pregnancy;morbid obesity (	"overlap" treatment period, patients were continued on dose-adjusted acenocoumarol			inferiority in absolute risk for early discharge (80% power; two-sided α=0.05). SELECTIVE REPORTING: no Sponsor: Supported by grants from the Ministry of Health and Consumer Affairs, Instituto de Salud Carlos III (FIS: PI03/0192), and the Sociedad Española de Neumologia y Cirugía Torácica (SEPAR). The authors state : After the first 132 patients were enrolled, the DSMB were alerted by the unsuspected high mortality rate in a carefully selected population. Due to the evaluation by the DSMB, the steering committee decided to apply caution by suspending the study. 'The rate of short-term mortality was unexpectedly high in a (apriori) low-risk group of
			Safety		
			Major bleeding defined as: 1) overt bleeding causing a fall in haemoglobin concentration of >2 g/dL; 2) requirement for transfusion of two or more units of blood; 3) retroperitoneal or intracranial bleeding, or 4) bleeding into a major prosthetic joint.	Early discharge: 1 (1.4%) Hospitalization: 1 (1.6%) RR: 0.83 (95% CI 0.05 to 13.04) NS (p=0.70)	
			Minor bleeding	Early discharge: 3 (4.2%) Hospitalization: 2 (3.3%) RR: 1.25 (95% CI 0.22 to 7.24) NS (p=0.59)	
			Overall mortality Death was classified as due to pulmonary embolism, bleeding or other established diagnoses. PE was considered the cause ofdeath if there was objective documentation or if the cause of death was unexplained and pulmonary embolism could not be confidently ruled out.	Early discharge: 3 (4.2%) Hospitalization: 5 (8.3%) RR: 0.50 (95% CI 0.12 to 2.01) NS (p=0.26)	

	[BMI] >30 Kg m^{-2}); - right ventricular dysfunction assessed by transthoracic echocardiography (TTE) - Patients were also ineligible if they had a life expectancy of less than 3 months.		**Short term mortality** (< 10 days after diagnosis)	Early discharge: 2 (2.8%) Hospitalization: 0 (0%) RR: - NS (p=0.30)	patients with acute PE. The accuracy of clinical prediction scores needs to be validated in well designed clinical trials'

Study details	n/Population	Comparison	Outcomes		Methodological
Aujesky 2011(49) Design: RCT OL PG Non-inferiority trial Setting: International (19 emergency departments in Switzerland, France, Belgium, and the USA) Duration of follow-up: 90 days	n= 344 Mean age: 48 years Previous VTE: 20% Cancer: 1.5% Surgery (<1 week): 7.5% Immobilized (>72h): 8% Time from presentation to emergency department until randomsation: mean 13.5h Duration of treatment with LMWH(days): 11.5 (SD 12.8) outpatient vs 8.9 (SD 10.1) inpatient, p=0.04 TTR (VKA) % of time in the therapeutic INR range : 52% <u>Inclusion</u> Age > 18 years with acute, symptomatic, and objectively verified pulmonary embolism who were at low risk of death based on PE severity index	Outpatients (Discharched < 24h after randomisation) Vs Inpatient treatment <u>Treatment:</u> - subcutaneous enoxaparin 1 mg/kg twice every day - early initiation of oral anticoagulation with vitamin K antagonists (warfarin, acenocoumarol, phenprocoumon, or fluidione) and continuation < 90 days. - The protocol recommended discontinuation	Efficacy		RANDO: adequate ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: yes Data analysers: no FOLLOW-UP: Lost-to follow-up: 2% Drop-out and Exclusions: 0% • Described: yes • Balanced across groups: yes ITT: no (patients lost to follow up were not included in primary analysis) Power: adequate 160 patients per treatment group would provide 80% power a non-inferiority margin of 4% using a one-sided α of 0.05, assuming a 5% drop-
			recurrence VTE, (PO) within **90 days** (= recurrent PE or new or recurrent DVT) <u>Diagnostic criteria for recurrent PE</u> - new intraluminal filling defect on spiral CT or pulmonary angiography, - a cutoff of a vessel more than 2.5 mm in diameter on pulmonary angiography; a new perfusion defect involving 75% or more of a lung segment with corresponding normal ventilation (ie, high probability lung scan); confirmation of a new pulmonary embolism on autopsy <u>Diagnostic criteria for DVT</u> – noncompressibility of a new venous segment or a substantial increase (≥4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography - a new intraluminal filling defect on contrast venography.	<u>Primary analysis</u> Outpatients: 1 (0.6%) Inpatients: 0 (0%) Upper 95% CL for difference: 2.7% **SS** **(p for non-inferiority margin of 4% = 0.011)** <u>Per protocol analysis</u> Outpatients: 1 (0.6%) Inpatients: 0 (0%) Upper 95% CL for difference: 2.9% **SS** **(p for non-inferiority margin of 4% = 0.014)**
			Recurrent VTE within 14 days	<u>Primary analysis</u> Outpatients: 0 (0%) Inpatients: 0 (0%) **Upper 95% CL for difference: 1.7%** **SS (p for non-inferiority margin of 4% = 0.003)**
			Safety	
			Major bleeding within 90 days	<u>Primary analysis</u> Outpatients: 3 (1.8%) Inpatients: 0 (0%)

	(risk classes I or II) PE diagnosis: see outcomes <u>Exclusion</u> - arterial hypoxaemia, systolic BP < 100 mm Hg, chest pain necessitating parenteral opioids, active bleeding, stroke <10 days, GI bleeding <14 days or - < 75000 platelets per mm^3, severe renal failure (creatinine clearance <30 mL per min), BMI >150 kg), history of heparin-induced thrombocytopenia, allergy to heparins, therapeutic oral anticoagulation at the time of diagnosis of PE, barriers to adherence or follow-up (eg, current alcohol abuse, illicit drug use, psychosis, dementia, or homelessness), pregnancy, imprisonment, diagnosis of PE> 23 h before the time of screening , previous enrolment in the trial.	of enoxaparin after 5 or more days of treatment when the INR was 2.0 or more for 2 consecutive days	(= fatal bleeding, bleeding at critical sites (ie, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or bleeding with a reduction of haemoglobin of 20 g/L or more or resulting in transfusion of two units or more of packed red cells	Upper 95% CL for difference: 4.5% NS (p for non-inferiority margin of 4% = 0.086) <u>Per protocol analysis</u> **Outpatients: 2 (1.2%)** **Inpatients: 0 (0%)** **Upper 95% CL for difference: 3.8%** **SS (p for non-inferiority margin of 4% = 0.04)**	out rate SELECTIVE REPORTING: no Sponsor: Swiss National Science Foundation, Programme Hospitalier de Recherche Clinique, and the US National Heart, Lung, and Blood Institute. Sanofi - Aventis provided free drug supply in the participating European centres.
			All-cause mortality within 90 days	**<u>Primary analysis</u>** **Outpatients: 1 (0.6%)** **Inpatients: 1 (0.6%)** **Upper 95% CL for difference: 2.1%** **SS (p for non-inferiority margin of 4% = 0.005)** **<u>Per protocol analysis</u>** **Outpatients: 1 (0.6%)** **Inpatients: 1 (0.6%)** **Upper 95% CL for difference: 2.1%** **SS (p for non-inferiority margin of 4% = 0.007)**	
			Major bleeding within 14 days	<u>Primary analysis</u> Outpatients: 2 (2.1%) Inpatients: 0 (0%) Upper 95% CL for difference: 3.6% **SS** (p for non-inferiority margin of 4% = 0.031)	
			All-cause mortality within 14 days	<u>Primary analysis</u> Outpatients: 0 (0%) Inpatients: 0 (0%) Upper 95% CL for difference: 1.7% **SS** (p for non-inferiority margin of 4% = 0.003)	

4.5.4 Summary and conclusions: Home treatment (early discharge) versus in-hospital treatment for pulmonary embolism

Outpatient (early discharge) versus inpatient treatment for pulmonary embolism with low mortality risk			
Bibliography: Otero 2010(48), Aujesky 2011(49)			
Outcomes	**N° of participants (studies) Follow up**	**Relative effect (95% CI)** ***Absolute effect***	**Quality of the evidence (GRADE)**
Mortality	476 (2 studies) 3m	Otero 2010: 4.2% vs 8.3% RR: 0.50 (95% CI 0.12 to 2.01) Aujesky 2011: 0.6% vs 0.6% P for non-inferiority 0.005	⊕⊕⊖⊖ **LOW** Study quality: -1 unblinded data analysis Consistency: OK Directness: OK Imprecision:-1 power and design
Recurrent VTE	476 (2 studies) 3m	Otero 2010: 2.8% vs 3.3% RR: 0.83 (95% CI, 0.12 to 5.74) Aujesky 2011: 0.6% vs 0% P for non-inferiority 0.011	⊕⊕⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision:-1
Major bleeding	476 (2 studies) 3m	Otero 2010: 1.4% vs 1.6% RR: 0.83 (95% CI 0.05 to 13.04) Aujesky 2011: 1.8% vs 0% Noninferiority margin not reached in primary analysis, but reached in per protocol-analysis	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 Consistency: -1 Directness: OK Imprecision:-1
Minor bleeding	132 (1 studies) 3m	Otero 2010: 4.2% vs 3.3% RR: 1.25 (95% CI 0.22 to 7.24)	⊕⊕⊖⊖ **LOW** Study quality: -1 unblinded Consistency: NA Directness: OK Imprecision:-1 insufficient power

Two RCTs compared outpatient treatment (early discharge) versus inpatient treatment for pulmonary embolism, in patients with a low risk of mortality (assessed with a clinical prediction tool). One of the trials (Otero 2010) was stopped early due to high complication rates in both treatment groups. The other trial (Aujesky 2011) was a non-inferiority trial.

Patients randomized to the outpatient treatment were discharged after 3-5 days in the first trial (Otero 2010) and after one day in the second trial (Aujesky 2011).

The overall quality of the evidence is low, due to the different study designs and low patient numbers.

No significant difference in mortality was observed between outpatient treatment and inpatient treatment.

GRADE: LOW quality of evidence

No significant difference in recurrent venous thromboembolism rates was observed between outpatient and inpatient treatment.

GRADE: LOW quality of evidence

No significant difference in major bleeding was observed in one trial, with a very wide confidence interval (Otero 2010). In the second trial (Aujesky 2011), outpatient treatment was found to be non-inferior to inpatient treatment in the per protocol analysis, but not in the primary analysis (modified intention to treat).
GRADE: VERY LOW quality of evidence

One trial (Otero 2010) reported on minor bleeding. No significant difference was observed between outpatient and inpatient treatment. This trial was underpowered.
GRADE: LOW quality of evidence

4.6 Prevention of post-thrombotic syndrome

4.6.1 Graduated compression stockings vs no graduated compression stockings

Ref	Comparison	N/n	Outcomes	Result**
ref* Nice 2012(8) Design: SR +MA Search date: dec 2011	Graduated compression stockings vs No graduated compression stockings	N= 2 n= 374 (Brandjes 1997, Prandoni 2004)	Post-thrombotic Syndrome	**Stockings: 42/186 (22.6%)** **No stockings: 90/188 (47.9%)** **RR: 0.47 (95% CI 0.35 to 0.64)** **SS in favour of stockings** **Absolute effect: 254 fewer per 1000 (95%CI from 172 to 311 fewer)**
		N= 0	Skin adverse events	
		N= 2 (Brandjes 1997) (Prandoni 2004)	Compliance	Brandjes 1997: frequency of wear 1st 2 years Did not /only occasionally: 7/96 (7%) Usually: 16/96 (17%) Always: 73/96 (76%) Prandoni 2004: 78/84 (93%) patients wore stockings 80% of day time hours 1 patient withdrew due to inability to put on stockings
		N= 0	Fitting	
		N= 0	Quality of life	
		N= 0	VTE related mortality	

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Brandjes 1997(50) **Study design:** RCT open label **Setting:** The Netherlands	194 (out of 315 patients with 1st episode venogram proven DVT)	1st episode of venogram proven proximal DVT **Inclusion criteria:** consecutive outpatients with a first episode of venogram-proven proximal DVT. **Age (mean):** 60±17 **Exclusion criteria:** - Bilateral thrombosis - Leg ulcers or extensive varicosity; - Current use of compression stockings - e.a. (not VTE-related)	**Duration of follow-up:** 60 to 96 months	**Group 1** Below-knee elastic compression stockings, made-to-measure (Neodurelna Varitex) with an ankle pressure of 40 mm Hg. Each patient received 2 pairs, which were replaced every 6 months Stockings were custom made for each patient Start: 2-3weeks after 1st episode. Duration: At least 2 years Vs. **Group 2** No compression stockings	**Post Thrombotic syndrome** (PTS only start being diagnosed after 6 months to distinguish it from the initial symptoms from DVT) Standardised score used (see Notes)	ALLOCATION CONC: NR in NICE 2012 RANDO: NR in NICE 2012 BLINDING : No (open label) outcome assessor blinded FOLLOW-UP: Drop outs:6/194 ITT: probably yes Unclear whether the scale used to classify PTS was validated
Prandoni 2004(51) **Study design:** RCT, open label **Country of study:** Italy **Setting:** University hospital	180	All consecutive inpatients and outpatients referred to 19 Italian participating centres from 1 October 1998- 30 April 2001 with the clinical suspicion of an acute (<3 weeks old) DVT of the lower extremities and/or PE , provided that suspicion was objectively confirmed. Age: mean 62y	**Duration of follow-up:** Minimum 3 years up to 5 years	**Group 1** Below knee ready-made elastic compression stockings with an ankle pressure of 30-40 mm Hg (Flebysan, Rovigo). Start: at discharge (5-10 days) after admission Duration : minimum 2	PTS was evaluated using a scoring method based on the presence of symptoms and signs, including: Heaviness, pain, cramps, pruritis, paraesthesia, pretibial oedema, skin induration, hyperpigmentation, venous ectasia, redness,	ALLOCATION CONC: NR in NICE 2012 RANDO: NR in NICE 2012 BLINDING : (open label) Participants: no (open)/personnel: no (open)/assessors: yes FOLLOW-UP: Drop outs and exclusions: 4/720

		Inclusion criteria: **At least 1 of the following:** - Ascending phlebography - Compression ultrasound of the proximal vein system - For DVT-Echo colour Doppler scan of the calf vein system - Ventilation-perfusion scanning, spiral computed tomographic scanning, and pulmonary angiography in the case of clinical suspicion of PE. - In the presence of abnormal results of ultrasound test of lower extremities, diagnosis of PE was also accepted if perfusion lung scan was compatible with high probability of PE when compared with chest x-ray. **Exclusion criteria:** - Previous (less than 1 year earlier) episode of VTE		years Stockings must be used during the day or longer. Patients given two pair of stocking, replaced every 6 months. **Group 2** No intervention **Anticoagulant therapy:** all patients received heparin (UFH or LMWH) , followed by at least 3 months of vitamin K antagonists.. Patients with transient risk factors - 3 months; idiopathic thrombosis – 6 months; permanent risk factors – entire study period	compression pain and the presence of a venous ulcer. On the PTS rating scale, A score of 0-4 indicates mild severity; 5-14 moderate and ≥15 severe.	ITT: yes **Funding:** New Medical Service, Linear Flebollogical Flebysan, Rovigo

4.6.2 Summary and conclusions. Graduated compression stockings vs no graduated compression stockings

Compression stockings vs. no compression stockings in patients with proximal DVT			
Bibliography: meta-analysis: NICE 2012(8) selected 2 RCTs: Brandjes 1997(50); Prandoni 2004(51)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Post-thrombotic syndrome	374 (2 studies) 3 to 8y	22.6% vs. 47.9% RR: 0.47 (95% CI 0.35 to 0.64) SS in favour of stockings	⊕⊕⊕⊕ **HIGH** ⊕⊕⊕⊖ **MODERATE** ⊕⊕⊖⊖ **LOW** ⊕⊖⊖⊖ **VERY LOW** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

NICE 2012 conducted a meta-analysis of 2 studies comparing the effect of compression stockings with no compression stockings in patients with a first episode of objectively confirmed proximal DVT. Patients had to wear the stockings for at least 2 years. The duration of follow-up varied from 3 to 8 years.
Overall, compliance with the compression stockings was good in both studies, with more than 90% of patients wearing them for most time of the day.

The rate of post-thrombotic syndrome was lower in patients wearing compression stockings than in patients wearing no compression stockings.
GRADE: HIGH quality of evidence

4.6.3 Compression stockings versus no compression stockings, after 6 months of pharmacological therapy + compression stockings

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: G010 Aschwanden 2008(52) Design: RCT OL PG (treatment crossover occurred during follow-up) Setting: Single center study in Switzerland Duration of follow-up: 3.2 years (treatment group) and 2.9 years (control group)	n= 169 Mean age: 64y Previous VTE(DVT/PE): 22.5% Current malignancy: NR Recent surgery: NR Recent trauma: NR Immobilized: NR <u>Inclusion</u> Patients, with first or recurrent proximal DVT confirmed by duplex ultrasound (DUS) imaging, which completed a <u>6 month</u> recommended standard therapy (Therapy consisted of heparin in the initial phase, followed by oral anticoagulation (target INR 2.0 to 3.0) and compression stockings (anklepressure, 26.3 to 36.1 mm Hg) for at + Age > 18 years	Compression stockings (a ready-to-wear, flat-knitted, below knee stocking with an applied pressure at the ankle of 26.3 to 36.1 mm Hg) during the day **vs** No compression stockings	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: Lost-to follow-up: 23 % Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: Yes Power: inadequate for the primary outcome (which was a study limitation according to the authors of the study) SELECTIVE REPORTING: no Other important remarks: Seven patients in each group had a crossover from their assigned treatment. Five of the seven crossovers in the control
			Emerging post-thrombotic skin changes (PO) (C4-C6 according to the CEAP classification; confirmed by a consensus of two outcome assessors at a second visit)	<u>Intent to treat -analysis</u> Treatment: 11 patients (13.1%) Control: 17 patients (20.0%) Crude HR= 0.60 (95% CI 0.28 to 1.28); NS, p=0.19 HR adjusted for previous DVT, age and sex= 0.61 (95% CI 0.30 to 1.42), NS, p=0.20 <u>As treated analysis</u> Unadjusted HR= 0.65 (95%CI 0.31-1.40), NS, p=0.27 HR adjusted for previous DVT, age and sex= 0.65 (95% CI 0.30 tp 1.42), NS, p=0.28	
			Symptoms associated with post-thrombotic syndrome A patient was considered symptomatic if at least one of five PTS-associated symptoms was present.	Intervention: in 12.2% of follow-up visits, PTS associated symptoms were reported at any follow-up visit examination. Control: in 16.5% of follow-up visits, PST associated symptoms were reported at any follow-up examination . **At 3 months:** **OR: 0.35 (95% CI 0.17 to 0.73)** **SS in favour of the intervention**	

	<u>Exclusion</u> Chronic venous insufficiency C4 to C6 by the CEAP classification, advanced malignancy or death anticipated to occur 2 years, long-lasting immobilization, geographic inaccessibility, dementia, peripheral arterial disease contraindicating compression therapy, anticipated lack of compliance, or refused informed consent			**At 1 year:** **OR: 0.46 (95% CI 0.23 to 0.90)** **SS in favour of the intervention** Symptom relief was significant in favor of compression treatment during the first year but **not thereafter** (graphical presentation only)	group were caused by development of post-thrombotic pain swelling, or venous claudication, and all the remaining in both groups were because of patients' wishes. To deal with treatment crossover during follow-up, an as-treated analysis using time dependent covariates was additionally performed. Power calculation was based on the outcome PTS, which was not the primary outcome of the trial. Sponsor: NR
			Non-adherence	Treatment: 8.4%	
			Safety		
			Adverse events from stockings	NR	

4.6.4 Summary and conclusions. Compression stockings versus no compression stockings, after 6 months of pharmacological therapy + compression stockings

Compression stockings versus no compression stockings in patients with a first or recurrent proximal deep vein thrombosis, after 6 months of pharmacological therapy + compression stockings			
Bibliography: Aschwanden 2008(52)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Symptoms associated with post-thrombotic syndrome	169 (1 study) 3y	At 3 months: OR= 0.35 (95% CI 0.17 to 0.73) **SS in favour of compression stockings** At 1 year: OR=0.46 (95% CI 0.23 to 0.90) **SS in favour of compression stockings**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 loss to FU 23%, open label + assessor not blinded Consistency: NA Directness: OK Imprecision: OK
Emerging post-thrombotic skin changes (PO)	169 (1 study) 3y	13.1% vs. 20.0% HR=0.61 (95% CI 0.30 to 1.42), NS	⊕⊕⊖⊖ **LOW** Study quality: -1 loss to FU 23%, open label + assessor not blinded Consistency: NA Directness: OK Imprecision: -1 insufficient power

In this trial, continued use of compression stockings was compared to no continued use in patients who had received 6 months of pharmacological treatment + compression stockings for a first or recurrent proximal deep vein thrombosis. Duration of follow-up was 3 years.

There was no statistically significant difference in the rate of emerging post-thrombotic skin changes (primary outcome of the trial) between patients with continued use of compression stockings and patients with no continued use of compression stockings
GRADE: LOW quality of evidence

At three months and one year follow-up, but not thereafter, patients with continued use of compression stockings had a lower risk of post-thrombotic syndrome associated symptoms than patients with no continued use of compression stockings.
GRADE: MODERATE quality of evidence

There was no information on treatment safety.

4.6.5 Thigh-length versus below-knee compression elastic stockings

Study details	n/Population	Comparison	Outcomes		Methodological
Prandoni 2012(53) Design: OL PG RCT Setting: Patients referred to 8 Italian university or hospital centers Duration of follow-up: 3 years	n= 267 Mean age: 68y Location of DVT: Popliteal only 43% ; common femoral 57% Clinical presentation: unprovoked 61% ; secondary 39% Current malignancy: 10% Recent trauma or surgery: 14% DVT treatment: LMWH/VKA 91%; UFH/VKA 9%; VKA duration 10 months INR ≥ TTR (INR, 2.0-3.0) on at least 70% of measurements was reached in 66.7% of patients <u>Inclusion</u> patients with a first episode of proximal-vein thrombosis, confirmed by compression ultrasonography	Thigh-length versus below-knee compression elastic stockings (CES) for 2 years Patients were treated with low-molecular-weight heparin, overlapping with and followed by at least 3 months of vitamin K antagonist therapy (INR 2.0-3.0), except for selected patients with active cancer or pregnancy, in which a low-molecular-weight heparin monotherapy was used	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: yes FOLLOW-UP: Lost-to follow-up: 4% Drop-out and Exclusions: • Described: yes • Balanced across groups: yes ITT: Yes (cumulative incidences of PTS were calculated using the Kaplan-Meier method) Power: inadequate (313 patients required in each group according to sample size calculation) SELECTIVE REPORTING: no
			3 year cumulative incidence of PTS (PO) (using the Villalta scale, with scores the presence of 5 leg symptoms and 6 objective signs)	<u>Total group</u>: Thigh-length: 44/135 (32.6%) Below-knee: 47/132 (35.6%) HR= 0.93 (95% CI 0.62 to 1.41), NS <u>Popliteal vein</u>: Below-knee: 19/51 (37.3%) Thigh-length: 23/64 (35.9%) HR= 1.01 (95% CI 0.55 to 1.85), NS <u>Proximal DVT</u>: Below-knee: 25/84 (29.8%) Thigh-length: 24/68 (24/68 (35.3%) HR= 0.86 (95% CI 0.49 to 1.51), NS
			Severe PTS	3 patients in each group	
			Safety		
			CES related side-effects (i.e., itching, erythema, or other forms of allergic reaction)	Thigh-length: 55/135 (40.7%) Below-knee: 36/132 (27.3%) HR not reported, **SS in favour of below-knee, p=0.017**	
			Premature discontinuation of use	Thigh-length: 29/135 (21.5%) Below-knee: 18/132 (13.6%) HR not reported, NS, p=0.11	

	Exclusion recurrent ipsilateral DVT, preexisting leg ulcers or signs of chronic venous insufficiency, bilateral thrombosis, a short life expectancy, or contraindication for the use of CES (eg, advanced-stage peripheral arterial insufficiency or allergy to stockings)				Sponsor: NR; the authors declare no competing financial interests

4.6.6 Summary and conclusions. Thigh-length versus below-knee compression elastic stockings

Thigh-length versus below-knee compression elastic stockings (CES) for prevention of post-thrombotic syndrome (PTS) in patients with a first episode of proximal-vein thrombosis			
Bibliography: Prandoni 2012(53)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Cumulative incidence of PTS (PO)	267 (1 study) 3y	Thigh-length 32.6% Below-knee 35.6% HR= 0.93 (95% CI 0.62 to 1.41), NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 power inadequate
CES related side-effects	267 (1 study) 2y	Thigh-length 40.7% Below-knee 27.3% HR not reported, **SS in favour of below-knee, p=0.017**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 no primary endpoint, only 1 trial Consistency: NA Directness: OK Imprecision: OK
Premature discontinuation of CES use	267 (1 study) 2y	Thigh-length 21.5% Below-knee 13.6% HR not reported, NS, p=0.11	⊕⊕⊕⊖ **MODERATE** Study quality: -1 no primary endpoint, only 1 trial Consistency: NA Directness: OK Imprecision: OK

In this trial, thigh-length compression elastic stockings (CES) were compared to below-knee CES for prevention of post-thrombotic syndrome (PTS) in patients with a first episode of proximal-vein thrombosis. All patients received pharmacological treatment during 10 months and had to wear the CES for two years.

There was no statistically significant difference between thigh-length CES and below-knee CES for the incidence of post-thrombotic syndrome in the follow-up period of 3 years, which was the primary outcome of the trial.
GRADE: MODERATE quality of evidence

Thigh-length CES resulted in a higher rate of CES related side-effects (itching, erythema, or other forms of allergic reactions) than below-knee CES.
GRADE: MODERATE quality of evidence

There was no statistically significant difference between thigh-length CES and below-knee stockings for the rate of premature discontinuation.
GRADE: MODERATE quality of evidence

5 Evidence tables and conclusions: thromboprophylaxis in major hip surgery

5.1 Pharmacological treatment versus placebo in elective hip surgery

5.1.1 UFH vs placebo in elective hip surgery

Ref	Comparison	N/n	Outcomes	Result**
ref* NICE 2010(54) Design: SR+MA Search date: dec 2008	UFH vs nil	N= 8 n= 515 (Bergqvist 1979, Dechavanne 1974, Dechavanne 1975, Gallus 1973, Hampson 1974, Lowe 1981, Anon 1975, Welin-Berger 1982)	**DVT**	**UFH: 67/257 (26.1%)** **Nil: 116/258 (45.0%)** **RR: 0.53 (95% CI 0.32 to 0.89)** **SS in favour of UFH** **Absolute effect: -20% (95% CI -31% to -9%)**
		N= 3 n= 283 (Bergqvist 1979, Lowe 1981, Welin-Berger 1982)	**Pulmonary embolism**	UFH: 20/143 (14.0%) Nil: 19/140 (13.6%) RR: 0.88 (95% CI 0.30 to 2.61) NS Absolute effect: -1% (95% CI -8% to 5%)
		N= 9 n= 687 (Bergqvist 1979, Dechavanne 1974, Dechavanne 1975, Hampson 1974, Lowe 1981, Mannucci 1976 I and II, Anon 1975, Welin-Berger 1982)	**Major bleeding**	UFH: 26/342 (7.6%) Nil: 19/345 (5.5%) RR: 1.42 (95% CI 0.84 to 2.41) NS Absolute effect: 0% (95% CI -2% to 2%)

* Characteristics of included studies as reported in NICE 2010: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Dechavanne 1975(55) Study type: RCT	60 Aspirin/dipyridamol n = 20 UFH n = 20 No intervention : n = 20)	Type of surgery: Hip replacement for patients with osteoarthritis	15 days postoperatively	3 arm study Aspirin 1.5g/day and dipyridamole 150mg/day <u>Timing:</u> Started day before surgery and continued until postoperative day 10 Vs Control: unfractionated heparin Dose: 5000 IU every 12 hours for first 48 hours post-operatively, then every 8 hours until postoperative day 8, progressively decreased until stopped on postoperative day 15 Timing: Started 2 hours preoperatively continued until postoperative day 15 Vs No intervention	DVT: confirmed by 125 I-labelled fibrinogen test.	ALLOCATION CONC:NR RANDO: NR BLINDING : NR FOLLOW-UP: NR ITT: NR Evidence level: 1+ Funding not Reported Additional noncomparative prophylaxis: none stated

The other RCTs were not individually reported in NICE 2010. They were extracted, as were the two RCTs reported above, from this systematic review.

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Collins 1988(56) (74 studies included; o.a. Bergqvist 1979(57),	15598	Type of surgery: general, orthopaedic and urological.	Given for 2-16 days or until ambulatory or discharged.	**UFH** Dose: Subcutaneous and given perioperatively. Additional noncomparative prophylaxis: GCS: 8 studies Aspirin: 2 studies	DVT confirmed by Radiolabelled fibrinogen or scanning	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: NR % in safety analysis NR % in efficacy analysis)

Dechavanne 1974(58), Dechavanne 1975(55), Gallus 1973(59), Hampson 1974(60), Lowe 1981(61), Anon 1975(62), Welin-Berger 1982(63), Mannucci 1976(64) which were all included in the guideline review) Study design: SR				Dextran: 1 study IPCD: 1 study Vs. **No prophylaxis** Additional noncomparative prophylaxis: GCS: 8 studies Aspirin: 2 studies Dextran: 1 study IPCD: 1 study		ITT: NR Evidence level: 1+ Not reported: Funding, QoL, LoS or PTS.

NICE 2010 reports:

- All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).
- All cause mortality was not identified as a key outcome during the development of the surgical guideline. Much of the data were identified from systematic reviews where all cause mortality was not reported. There was not time during the development of this guideline to review all cause mortality for this population
- The orthopaedic subgroup noted that although all cause mortality is the most important outcome for this population the studies were not powered to detect a difference in mortality for
- Overall the quality of the evidence is good. There is a large body of evidence for this population comprising 72 RCTs providing thromboprophylaxis for between 7-21days

The SR by Collins 1988 was discussed in the literature review that was undertaken for the consensus conference venous thromboembolism 2002. It was given a quality score of 6.5/12. Here is the detailed appraisal:

		Reference + scoring date

	Quality criterium	COLLINS
	N° of studies examined	74
	N° of patients examined	15.598
	Duration of outcome measurement	1 w
	Design of studies (CO/RCT/CT)	RCT
	Journal of publication	N Engl J Med
	Year of publication	1988
	Financial support	British Heart Research
	Setting in general practice	hospital
1	Effect clinically relevant	1
2	Clinical question clear	1
3	Effect measure given (OR/RR/...)	1
4	Confidence interval of effect/difference reported	0.5
5	Adequate search strategy	0.5
6	Publication bias examined	0
7	Inclusion/exclusion criteria for studies	1
8	Quality of studies examined	0
9	Statistical method described	1
10	Variability of studies examined	0.5
11	Quality score in analysis	0
12	Assessor blinded or double-blind RCTs	0
SCORE TOTAL 1 to 12		**6.5**

5.1.2 Summary and conclusions. UFH vs placebo in elective hip surgery

UFH versus placebo or no treatment for thromboprophylaxis in elective hip replacement			
Bibliography: Systematic review NICE 2010(54), selected these RCTs: Bergqvist 1979(57), Dechavanne 1974(58), Dechavanne 1975(55), Gallus 1973(59), Hampson 1974(60), Lowe 1981(61), Anon 1975(62), Welin-Berger 1982(63), Mannucci 1976(64). All RCTs extracted from Collins 1988(56)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
DVT (both symptomatic and asymptomatic)	515 (8 studies) 2-16d treatment	UFH: 26.1% Nil: 25.0% **RR: 0.53 (95% CI 0.32 to 0.89)** **SS in favour of UFH** Absolute effect: -20% (95% CI -31% to -9%)	Not applied
PE	283 (3 studies) 2-16d treatment	UFH: 14.0% Nil: 15.6% RR: 0.88 (95% CI 0.30 to 2.61) NS	Not applied
Major bleeding	687 (9 studies) 2-16d treatment	UFH: 7.6% Nil: 5.5% RR: 1.42 (95% CI 0.84 to 2.41) NS	Not applied

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

In this meta-analysis by NICE 2010, UFH is compared to placebo or no treatment in patients undergoing elective hip replacement. 9 RCTs were included. All RCTs were extracted from an old SR (Collins 1988) that was discussed in the previous literature search for the consensus conference on VTE in 2002. No new trials comparing UFH to placebo or no treatment in elective hip surgery were published since the previous consensus conference.

We have insufficient information whether all trials screened the patients for the outcome DVT at some point after surgery. This does seem to be the case for many of the trials. The reported rate of DVT consists therefore of both symptomatic and asymptomatic DVT.
Treatment with UFH resulted in a lower rate of deep vein thrombosis compared to placebo or no treatment.

There was no statistically significant difference between UFH and placebo or no treatment in the rate of pulmonary embolism.

There was no statistically significant difference between both groups in the rate of major bleeding.

We did not score this comparison using GRADE because insufficient data on the included RCTs could be obtained.
For the totality of trials in elective hip replacement, NICE 2010 rates the quality of evidence as good. Our previous literature review was less positive about the quality of the SR by Collins (lack of reporting on quality of included RCT, inclusion of unblinded RCTs).

5.1.3 LMWH vs placebo in elective hip replacement

Ref	Comparison	N/n	Outcomes	Result**
ref* NICE 2010(54) Design: SR+MA Search date: dec 2008	LMWH vs nil	N= 4 n= 492 (Lassen 1988, Tørholm 1991, Turpie 1986, Yoo 1997)	**DVT**	LMWH: 49/252 (19.4%) Nil: 100/ 240 (41.7%) **RR= 0.40 (95% CI 0.22 to 0.71)** **SS in favour of LMWH** **Absolute effect: -22% (95%CI -33% to -12%)**
		N= 3 n= 312 (Tørholm 1991, Turpie 1986, Yoo 1997)	**Pulmonary embolism**	LMWH: 1/158 (0.6%) Nil: 4/154 (2.6%) RR: 0.33 (95% CI 0.05 to 2.02) NS Absolute effect: -1% (95%CI -4% to 2%)
		N= 2 n= 334 (Lassen 1988, Turpie 1986)	**Major bleeding**	LMWH: 2/168 (1.2%) Nil: 4/166 (2.4%) RR: 0.50 (95% CI 0.09 to 2.66) NS Absolute effect: -1% (95%CI -4% to 2%)

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Turpie 1986(65) DB PG RCT	100	Patients with total hip replacement	Treatment duration 14 days Follow-up duration 14 days or discharge	Enoxaparin 3000x2 Vs. Placebo Time of first administration postop. 12-24h	DVT 1st part confirmed by venography if positive fibrinogen uptake test, or plethysmography; 2nd part by bilateral venography All patients were to be screened	"The study did not meet the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography)" ITT
Lassen 1988(66) DB PG RCT	234	Patients with total hip replacement	Treatment duration 7 days Follow-up duration 6 days	Certoparin 3000 + 0.5mg Dihydroergotamine x1 Vs. Placebo Time of first administration preop 2h	Diagnosis of DVT confirmed by venography if positive plasminogen uptake test screening in all patients? unclear	"The study did not meet the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography)" no ITT
Tørholm 1991(67) DB PG RCT	120	Patients with total hip replacement	Treatment duration 7 days Follow-up duration 9 days	Dalteparin 5000x1 vs. placebo Time of first administration preop 2h	DVT confirmed by venography if positive plasminogen uptake test All patients were to be screened	"The study did not meet the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography)" no ITT
Yoo 1997(68) OL PG RCT	100	Patients with total hip replacement	Treatment duration 10 days Follow-up duration 10 days	Nadroparin 41/kg x 1 days 1-3, 62/kg x1 days 4-11 +Elastic stockings Vs. No treatment Time of administration preop 12h	DVT screened by bilateral venography	"The study did not meet the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography)" ITT

All above RCTs were not reported in detail in the NICE 2010 document. They were extracted by NICE from this systematic review:

Zufferey 2003(69) (13 studies, o.a. Lassen 1988, Tørholm 1991, Turpie 1986, Yoo 1997: all of them included in the guideline review) Study design: SR	1925 Note: 2 studies did not give total distribution of randomized patients and only gave number for those that had detection test.	Type of surgery: Hip fracture: 3 studies Knee surgery: 2 studies Hip replacement 8 studies	Studies ranged from 6 to 14 days follow-up.	**LMWH**: (Enoxaparin, certoparin, tinzaparin, dalteparin, nadroparin, ardeparin) Doses: Ranged from 3000 anti-Xa IU to over 6000 anti-Xa IU. Timing: Treatment started preoperatively in 9 studies and postoperatively in 4 studies. The treatment varied from 3 to 14 days. Additional noncomparative prophylaxis: NR Vs. **Placebo** (11 studies) or **No treatment** (2 studies) background: GCS in 4 studies. Electrical stimulation 2 studies	DVT confirmed by fibrinogen or Plasminogen uptake test, duplex US or venography. Major bleeds defined as major haemorrhage.	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: NR% in safety analysis NR% in efficacy analysis) ITT: NR Evidence level: 1+ Not reported: QoL, LoS, PTS and funding.

5.1.4 Summary and conclusions. LMWH vs placebo in elective hip replacement

LMWH versus placebo or no treatment for thromboprophylaxis in elective hip replacement.			
Bibliography: Meta-analysis NICE 2010(54), selected these RCTs: Turpie 1986(65), Lassen 1988(66), Tørholm 1991(67), Yoo 1997(68). All RCTs extracted from this SR: Zufferey 2003(69)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
DVT (symptomatic and asymptomatic)	492 (4 studies) 6-14d	LMWH: 19.4% Nil: 41.7% **RR= 0.40 (95%CI 0.22 to 0.71)** **SS in favour of LMWH** Absolute effect: -22% (95%CI -33% to -12%)	⊕⊕⊕⊖ **MODERATE** Study quality:-1 (1 open label, 3 no ITT) Consistency: OK Directness:OK Imprecision:OK
Pulmonary embolism	312 (3 studies) 6-14d	LMWH: 0.6% Nil: 2.6% RR: 0.33 (95%CI 0.05 to 2.02) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 (low rating in SR Consistency: OK Directness: OK Imprecision:-1 wide CI
Major bleeding	334 (2 studies) 6-14d	LMWH: 1.2% Nil: 2.4% RR: 0.50 (95%CI 0.09 to 2.66) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 (low rating in SR) Consistency: OK Directness: OK Imprecision:-1 wide CI

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

In this meta-analysis by NICE 2010, LMWH was compared to placebo or no treatment in patients undergoing elective hip replacement.

Most patients in these trials were screened for the outcome DVT using imaging techniques, so the reported rate of DVT consists of both symptomatic and asymptomatic DVT.

There is a lower rate of deep vein thrombosis in patients receiving LMWH compared to placebo or no treatment.
GRADE: MODERATE quality of evidence

No statistically significant difference in the rate of pulmonary embolism is observed.
GRADE: LOW quality of evidence

There is no statistically significant difference in the rate of major bleeding.
GRADE: LOW quality of evidence

5.2 Pharmacological treatment versus no thromboprophylaxis in hip fracture surgery

5.2.1 UFH versus no thromboprophylaxis in hip fracture surgery

Ref	Comparison	N/n	Outcomes	Result**
ref*NICE 2010(54) Design: SR + MA Search date: dec 2008	UFH vs nil	N= 6 n= 464 (Bergqvist 1979, Gallus 1973, Lahnborg 1980, Morris 1977, Svend-Hansen 1981, Xabregas 1978)	**DVT**	**UFH: 63/236 (26.7%)** **Nil: 115/228 (50.4%)** **RR: 0.56 (95% CI 0.39 to 0.81)** **SS in favour of UFH** **Absolute effect: -23% (95% CI -35% to -12%)**
		N= 2 n= 148 (Morris 1977, Galasko 1976)	**Pulmonary embolism**	UFH: 1/74 (1.4%) Nil: 2/74 (2.7%) RR: 0.50 (95% CI 0.05 to 5.34) NS Absolute effect: -1% (95% CI -6% to 4%)
		N= 4 n= 252 (Bergqvist 1979, Morris 1977, Galasko 1976, Xabregas 1978)	**Major bleeding**	UFH: 4/129 (3.1%) Nil.: 6/123 (4.9%) RR: 0.69 (95% CI 0.23 to 2.13) NS Absolute effect: -1% (95% CI -5% to 3%)
		N=3 n=380 (Bergqvist 1979, Galasko 1976, Svend-Hansen 1981)	**All cause mortality**	UFH: 20/193 (10.4%) Nil: 20/187 (10.7%) RR: 0.96 (95 % CI 0.55 to 1.67) NS Absolute effect: -1 % (95% CI -8% to 7%)

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

The included RCTs were not individually reported in NICE 2010. They were extracted (by NICE) from this systematic review.

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Collins 1988 (74 trials included; o.a. Bergqvist 1979(57), Gallus 1973(59), Lahnborg 1980(70), Morris 1977, Svend-Hansen 1981(71), Xabregas 1978(72), Galasko 1976(73)) Study design: SR	15598	Type of surgery: general, orthopaedic and urological.	Given for 2-16 days or until ambulatory or discharged.	**UFH** Dose: Subcutaneous and given perioperatively. Additional noncomparative prophylaxis: GCS: 8 studies Aspirin: 2 studies Dextran: 1 study IPCD: 1 study Vs. **No prophylaxis** Additional noncomparative prophylaxis: GCS: 8 studies Aspirin: 2 studies Dextran: 1 study IPCD: 1 study	DVT confirmed by Radiolabelled fibrinogen or scanning	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: NR % in safety analysis NR % in efficacy analysis) ITT: NR Evidence level: 1+ Not reported: Funding, QoL, LoS or PTS.

The SR by Collins 1988 was discussed in the literature review that was undertaken for the consensus conference venous thromboembolism 2002. It was given a quality score of 6.5/12.
Here is the detailed appraisal:

		Reference + scoring date
	Quality criterium	COLLINS
	N° of studies examined	74
	N° of patients examined	15.598
	Duration of outcome measurement	1 w
	Design of studies (CO/RCT/CT)	RCT
	Journal of publication	N Engl J Med
	Year of publication	1988
	Financial support	British Heart Research
	Setting in general practice	hospital
1	Effect clinically relevant	1
2	Clinical question clear	1
3	Effect measure given (OR/RR/...)	1
4	Confidence interval of effect/difference reported	0.5
5	Adequate search strategy	0.5
6	Publication bias examined	0
7	Inclusion/exclusion criteria for studies	1
8	Quality of studies examined	0
9	Statistical method described	1
10	Variability of studies examined	0.5
11	Quality score in analysis	0
12	Assessor blinded or double-blind RCTs	0
SCORE TOTAL 1 to 12		**6.5**

5.2.2 Summary and conclusions. UFH versus no thromboprophylaxis in hip fracture surgery

UFH versus placebo or no treatment for thromboprophylaxis in hip fracture surgery			
Bibliography: meta-analysis NICE 2010(54) included these RCTs: Bergqvist 1979(57), Gallus 1973(59), Lahnborg 1980(70), Morris 1977, Svend-Hansen 1981(71), Xabregas 1978(72), Galasko 1976(73)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Mortality	n=380 (3 studies) 2-16 d	10.4% vs10.7% RR: 0.96 (95 % CI 0.55 to 1.67) NS	Not applied
DVT (both symptomatic and asymptomatic)	n= 464 (6 studies) 2-16 d	**26.7% vs 50.4%** **RR: 0.56 (95% CI 0.39 to 0.81)** **SS in favour of UFH** Absolute effect: -23% (95% CI -35% to -12%)	Not applied
PE	n= 148 (2 studies) 2-16 d	1.4% vs 2.7% RR: 0.50 (95% CI 0.05 to 5.34) NS	Not applied
Major bleeding	n= 252 (4 studies) 2-16 d	3.1% vs 4.9% RR: 0.69 (95% CI 0.23 to 2.13) NS	Not applied

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

NICE 2010 examined UFH versus placebo or no treatment in hip fracture surgery. Six RCTs were found and included in a meta-analysis. All RCTs were extracted from an old systematic review (Collins 1988), already discussed in the previous literature search for the consensus conference on VTE in 2002.

We have insufficient information whether all trials screened the patients for the outcome DVT at some point after surgery. This does seem to be the case for many of the trials. The reported rate of DVT consists therefore of both symptomatic and asymptomatic DVT.

In this meta-analysis no statistically significant difference was observed between unfractionated heparin and placebo or no thromboprophylaxis on the following endpoints: mortality, pulmonary embolism and major bleeding.

In patients treated with unfractionated heparin during two to sixteen days, a significantly smaller number of deep vein thrombosis was reported in comparison with placebo or no treatment.

We did not score this comparison using GRADE because insufficient data on the included RCTs could be obtained.
NICE rates the quality of evidence as good. Our previous literature review was less positive about the quality of the SR by Collins (lack of reporting on quality of included RCT, inclusion of unblinded RCTs, …).

5.2.3 LMWH versus placebo in hip fracture surgery

Ref	Comparison	N/n	Outcomes	Result**
ref*NICE 2010(54) Design: SR+MA Search date: DEC 2008	LMWH vs nil	N= 2 n= 218 (Jørgensen 1992, Sourmelis 1995)	**DVT**	LMWH: 33/102 (32.4%) Nil: 78/116 (67.2%) **RR= 0.48 (95% CI 0.35 to 0.65)** **SS in favour of LMWH** **Absolute effect: -35% (95%CI -48% to -23%)**
		N= 1 n= 82 (Jørgensen 1992)	**Major bleeding**	LMWH: 0/41 (0%) Nil: 0/41 (0%) RR: not estimable Absolute effect: 0% (95%CI -5% to 5%)
		N= 1 n= 68 (Jørgensen 1992)	**All cause mortality**	LMWH: 3/30 (10%) Nil: 4/38 (10.5%) RR= 0.95 (95% CI 0.23 to 3.92) NS Absolute effect: -1% (95%CI -15% to 14%)

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Jørgensen 1992(74) DB PG RCT (reported from Zufferey 2003 and abstract)	82	Patients with surgery for hip fracture	Duration of treatment 7 days Duration of follow-up 9 days	Dalteparin 5.000x1 (n=41) vs. Placebo (n=41) Time of first administration preop. 2h	DVT confirmed by venography if positive fibrinogen uptake test	The study did not meet the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography) no ITT FU: 83% evaluable population
Sourmelis 1995(75) DB PG RCT (reported from Zufferey 2003)	150	Patients with surgery for hip fracture	Duration of treatment postop. 12 days Duration of Follow-up 10-12 days	Nadroparin 3.075x1 preop, 6.150x1 postop (n=72) vs. Placebo (n=78) Time of first administration preop. at diagnosis	DVT confirmed by unilateral venography	The study did not meet the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography) ITT

Additional information from above RCTs extracted from this systematic review:

Zufferey 2003(69) Study design: SR 13 studies (met o.a. Jørgensen 1992, Sourmelis 1995; both included in the guideline review)	1925 Note: 2 studies did not give total distribution of randomized patients	**Type of surgery:** Hip fracture: 3 studies Knee surgery: 2 studies Hip replacement 8 studies	Studies ranged from 6 to 14 days follow-up.	**LMWH:** (Enoxaparin, certoparin, tinzaparin, dalteparin, nadroparin, ardeparin) **Doses:** Ranged from 3000 anti-Xa IU to over 6000 anti-Xa IU. **Timing**: Treatment started preoperatively in 9 studies and postoperatively in 4	DVT confirmed by fibrinogen or plasminogen uptake test, duplex US or venography. Major bleeds: defined as major haemorrhage	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: NR% in safety analysis NR% in efficacy analysis) ITT: NR Evidence level: 1+

9 of these studies were included in the guideline review	and only gave number for those that had detection test.			studies. The treatment varied from 3 to 14 days **Additional noncomparative prophylaxis**: Not reported Vs **Placebo** (11 studies) or **No treatment** (2 studies) **Background**: GCS in 4 studies. electrical stimulation 2 studies		Not reported: QoL, LoS, PTS and funding. Note: RR and CI reported by SR authors.

5.2.4 Summary and conclusions. LMWH versus placebo in hip fracture surgery

LMWH versus placebo for thromboprophylaxis after hip fracture surgery			
Bibliography: meta-analysis NICE 2010(54) included 2 RCT: Jørgensen 1992(74), Sourmelis 1995(75)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Mortality	n= 68 (1 study) 9 d	10% vs 10.5% RR= 0.95 (95%CI 0.23 to 3.92) NS	⊕⊕⊖⊖ **V LOW** Study quality: -1, no ITT, 82% evaluable, only 1 trial Consistency: NA Directness: OK Imprecision: -1, wide CI
DVT (symptomatic and asymptomatic)	n= 218 (2 studies) 9-12 d	32.4% vs 67.2% **RR= 0.48 (95% CI0.35 to 0.65)** **SS in favour of LMWH** Absolute effect: -35% (95%CI -48% to -23%)	⊕⊕⊕⊖ **MODERATE** Study quality: -1, defined as low quality by SR, limited information available Consistency: OK Directness: OK Imprecision:OK
Major bleeding	n= 82 (1 study) 9 d	0 vs 0 RR: not estimable	⊕⊕⊖⊖ **LOW** Study quality: -1, no ITT, defined as low quality by SR Consistency: NA Directness: OK Imprecision: -1 lack of power

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

This meta-analysis included two small RCTs comparing LMWH with placebo during 7 to 12 days for thromboprophylaxis after hip fracture surgery.

The outcome DVT was checked for in all patients using imaging techniques, so the reported rate of DVT consists of both symptomatic and asymptomatic DVT.

Mortality was reported in only one trial. No statistically significant difference between LMWH and placebo was found for this endpoint .
GRADE: LOW quality of evidence

The rate of DVT (symptomatic and asymptomatic) observed in two small studies was about twice as high in the placebo group compared to the group treated with LMWH.
GRADE: MODERATE quality of evidence

No cases of major bleeding were reported in one trial. The relative risk was not estimable.
GRADE: LOW quality of evidence

5.2.5 Vitamin K antagonists versus no thromboprophylaxis in hip fracture surgery

Ref	Comparison	N/n	Outcomes	Result**
ref*NICE 2010(54) Design: SR + MA Search date: dec 2008	VKA vs. nil	N= 5 n= 485 (Borgstrom 1965, Hamilton 1970, Morris 1976, Myhre 1969, Powers 1989)	**DVT**	**VKA: 57/245 (23.3%)** **Nil: 132/240 (55.0%)** **RR: 0.44 (95% CI 0.34 to 0.56)** **SS in favour of VKA** **Absolute effect: -32% (95%CI -40% to -24%)**
		N= 5 n= 610 (Borgstrom 1965, Eskeland 1966, Morris 1976, Myhre 1969, Powers 1989)	**Pulmonary embolism**	**VKA: 4/307 (1.3%)** **Nil: 28/303 (9.2%)** **RR: 0.21 (95% CI 0.08 to 0.53)** **SS in favour of VKA** **Absolute effect: -7% (95% CI -11% to -3%)**
		N= 5 n= 622 (Borgstrom 1965, Eskeland 1966, Hamilton 1970, Morris 1976, Powers 1989)	**Major bleeding**	VKA: 26/312 (8.3%) Nil: 18/310 (5.8%) RR: 1.35 (95% CI 0.70 to 2.62) NS Absolute effect: 2% (95%CI -3% to 6%)
		N= 6 n=727 (Borgstrom 1965, Eskeland 1966, Hamilton 1970, Morris 1976, Myhre 1969, Powers 1989)	**All cause mortality**	VKA: 47/362 (13.0%) Nil: 62/365 (17.0%) RR: 0.76 (95% CI 0.54 to 1.07) NS Absolute effect: -1% (95% CI -5% to 3%)

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration of FU	Comparison	Definition of outcomes	Methodology
Borgstrom 1965(76) OL RCT	58	Hip fracture surgery	3-4w	Dicoumarol, pt 40ms vs no treatment start preop, duration not stated	Diagnosis of DVT venography unilateral	rando: adequate blinded assessment: yes
Eskeland 1966(77) OL RCT	200	Hip fracture surgery	3m	Phenindione vs no treatment postop until discharge	Not stated	blinded assessment: no
Hamilton 1970(78) OL RCT	76	Hip fracture surgery	3-10m	phenprocoumon pt 2-2.5 vs no treatment postop, duration not stated	Venography unilateral	allocation concealment: unclear blinded assessment: no
Morris 1976(79) OL RCT	160	Hip fracture surgery	3m	Warfarin TT 10% vs no treatment start preop, continue until ambulation or 3 months	Fibrinogen uptake	allocation concealment: adequate rando: adequate blinded assessment:no
Myrhe 1969(80) DB RCT	105	Hip fracture surgery	3w	Warfarin vs placebo start postop, duration not stated	DVT diagnosis: venography	blinded assessment:no
Powers 1989(81) OL RCT	128	Hip fracture surgery	3m	Warfarin INR 2-2,7 vs no treatment start postop, until discharge or 3 weeks	DVT diagnosis: venography	allocation concealment: adequate blinded assessment:yes

Information from above trials extracted from these 2 systematic reviews.

- Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. Health technology assessment. 2005;9(49):iii-iv, ix-x, 1-78.
- Mismetti P, Laporte S, Zufferey P, Epinat M, Decousus H, Cucherat M. Prevention of venous thromboembolism in orthopedic surgery with vitamin K antagonists: a meta-analysis. Journal of thrombosis and haemostasis : JTH. 2004;2(7):1058-70.

Roderick 2005 Design: SR 9 RCT's included (waaronder Borgstrom 1965, Hamilton 1970, Morris 1976, Powers 1989) All of these studies were included in the guideline review.	884	Type of surgery: orthopaedic: 6 studies gynaecological: 3 studies Pre-existing risk factors: not reported	End time varied from 1 week to 3 months	Oral anticoagulant Dose: Adjusted dose: 6 studies Fixed dose: 2 studies Adjusted/fixed: 1 study Timing: Start time varied from admission or 1 week preoperatively to postoperatively. Additional noncomparative prophylaxis: none Vs. No prophylaxis: 5 studies Placebo: 4 studies Additional noncomparative prophylaxis: none	DVT Confirmed by venography or FUT PE (scan, x-ray or post-mortem for fatal) Major bleeding: definition not given	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: NR ITT: NR Evidence level: 1+ Not reported: LoS, QoL, PTS
Mismetti 2004 Design: SR 2 RCTs included Eskeland 1966 and Myhre 1969 All of these studies were included in the guideline	305	Type of surgery: Orthopaedic: 2 studies	3 months (I study) 3 weeks (1 study)	Type: Oral anticoagulant (adjusted) Phenindione (1 study) Warfarin (1 study) Timing: Postoperative: 2 studies Administered until discharge (1 study) Vs.	DVT: Confirmed by venography or FUT Fatal PE: Defined as specified in each report.	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: NR ITT: NR Evidence level: 1+ Not reported: LoS, QoL, PTS

review.				No prophylaxis: 1 study Placebo: 1 study Additional noncomparative prophylaxis: none		Funding: Sanofi- Synthelabo grant

Remarks:
Quality of the evidence as evaluated by NICE 2010
"All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).
…These studies tended to be small, 61% (14/23) and had less than 100 patients. In addition, 78% (18/23) were published before 1990. Some studies reported bleeding outcomes using different criteria. After a review of the techniques used for fixation of the fractures of the proximal femur used within individual studies it was noted that there was a wide variety of techniques including some which were no longer used in current practice. This may limit the applicability of the evidence."

5.2.6 Summary and conclusions. Vitamin K antagonists versus no thromboprophylaxis in hip fracture surgery

VKA versus no treatment for thromboprophylaxis in hip fracture surgery			
Bibliography: meta-analysis NICE 2010(54) included these RCTs: Borgstrom 1965(76), Eskeland 1966(77), Hamilton 1970(78), Morris 1976(79), Myrhe 1969(80), Powers 1989(81)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Mortality	n=727 (6 studies) 3w-10m	13.0% vs 17.0% RR: 0.76 (95% CI 0.54 to 1.07) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 mostly OL, quite small trials, limited information available Consistency:OK Directness:OK Imprecision: CI does not exclude possible benefit
DVT (both symptomatic and asymptomatic)	n= 485 (5 studies) 3w-10m	23.3% vs 55.0% **RR: 0.44 (95% CI 0.34 to 0.56)** **SS in favour of VKA** Absolute effect: -32% (95%CI -40% to -24%)	⊕⊕⊖⊖ **LOW** Study quality:-1 mostly OL, quite small trials, limited information available Consistency:OK Directness:-1unclear wheter all trials screened patients Imprecision: OK
Pulmonary embolism	n= 610 (5 studies) 3w-3m	1.3% vs 9.2% **RR: 0.21 (95% CI 0.08 to 0.53)** **SS in favour of VKA** -7% (95% CI -11% to -3%)	⊕⊕⊕⊖ **MODERATE** Study quality:-1 mostly OL, quite small trials, limited information available Consistency:OK Directness:OK Imprecision: OK
Major bleeding	n= 727 (6 studies) 3w-10m	8.3% vs 5.8% RR: 1.35 (95% CI 0.70 to 2.62) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 mostly OL, quite small trials, limited information available Consistency:OK Imprecision: CI does not exclude possible harm

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

This meta-analysis included six (mostly open-label) RCTs that compared (various durations of) VKA thromboprophylaxis with no treatment in patients undergoing surgery for hip fracture. All trials were quite old: published between 1965 and 1989.

We have insufficient information whether all trials screened the patients for the outcome DVT at some point after surgery. This does seem to be the case for many of the trials. The reported rate of DVT consists therefore of both symptomatic and asymptomatic DVT.
NICE 2010 remarks: there was a wide variety of techniques used for fixation of fractures, including some which were no longer used in current practice. This may limit the applicability of the evidence.

There was no statistically significant difference in mortality between the two treatment groups.
GRADE: LOW quality of evidence (quality estimate based on limited data)

Significantly more cases of deep vein thrombosis and pulmonary embolism were observed in the group that received no treatment in comparison with the group that received VKA .
GRADE: MODERATE quality of evidence (quality estimate based on limited data)

The difference in major bleeding outcomes was not statistically significant.
GRADE: LOW quality of evidence (quality estimate based on limited data)

5.3 Pharmacological treatment versus pharmacological treatment for thromboprophylaxis in elective hip replacement

5.3.1 Vitamin K antagonists versus LMWH in elective hip replacement

Ref	Comparison	N/n	Outcomes	Result**
ref* NICE 2010(54) Design: SR+MA Search date: DEC 2008	VKA vs LMWH	N= 2 n= 1393 (Francis 1997, Hull 2000)	**DVT**	**VKA: 130/528 (24.6%)** **LMWH: 108/865 (12.5%)** **RR: 1.94 (95 % CI 1.53 to 2.44)** **SS in favour of LMWH** **Absolute effect: 12% (95% CI 7% to 16%)**
		N= 1 n= 3011 (Colwell 1999)	**Pulmonary embolism**	VKA: 12/1495 (0.8%) LMWH: 15/1516 (1.0%) RR: 0.81 (95% CI 0.38 to 1.73) NS Absolute effect: 0% (95% CI -1% to 0%)
		N= 3 (staat 4 in Nice) n= 5082 (Colwell 1999, Francis 1997, Hull 2000)	**Major bleeding**	**VKA: 30/2288 (1.3%)** **LMWH: 91/2794 (3.3%)** **RR: 0.57 (95% CI 0.38 to 0.85)** **SS in favour of VKA** **Absolute effect: -1% (95% CI -4% to 1%)**

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Colwell 1999(82) Design: RCT	3011	Type of surgery: Elective total hip arthroplasty <u>Pre-existing risk factors:</u> Significantly more obese patients in enoxoparin arm (p=0.0055)	Both groups: 14 days treatment, 3 month follow up	**Coumadin (adjusted dose warfarin)** Dose: Started at 7.5mg, adjusted to maintain INR ratio between 2.0 to 3.0 Timing: Started between 48 hours preoperatively (at the discretion of the investigator) and 24 hours postoperatively. Administered until Discharge (n=1495) vs **Enoxoparin (LMWH)** Dose: 30mg Timing: Every 12 hours, started within 24 hours postoperatively once haemostasis (cessation of active bleeding as determined by the investigator) had been established. Administered until discharge (n=1516) Additional non-comparative prophylaxis: Stockings permitted but not reported how many patients received these	Symptomatic DVT: Confirmed by US or venography PE: Confirmed by ventilation perfusion scan or pulmonary angiography Major bleeds: NR	ALLOCATION CONC: NR RANDO: NR BLINDING : participants inadequate; personnel inadequate (open label); assessors: probably inadequate FOLLOW-UP: 26% did not complete study of which 2.8 % lost to follow up, and 16,1% protocol deviations ITT: yes Evidence level (NICE 2010): +1 Funding: No direct funding for this study. Indirect funding (i.e. authors" institution funding) Rhone Poulenc Rorer Pharmaceuticals Not reported: PTS, LoS, QoL, fatal PE
Francis 1997(83) Design: RCT (based on Roderick	580	Patients with unilateral primary or revision total hip arthroplasty	NR	**Warfarin** PT 1.4-1.5 preop. Night once daily postoperative – discharge (n=292) Vs.	DVT diagnosed by venography, mean timing of assessment day 7	RANDO: unclear ALLOCATION CONCEALMENT: unclear BLINDING: participants inadequate; personnel

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
2005 and abstract)				**LMWH** 2h preop. 5000 IU subcutaneously once daily – discharge (n=288)	PE not applicable Major bleeds: NR	inadequate; assessors adequate FOLLOW-UP: 65% had evaluable venography ITT: no FUNDING: NR
Hull 2000(84) Design: RCT (based on Roderick 2005 and abstract)	1501	Patients with elective hip arthroplasty	NR	**Warfarin** INR 2-3 + placebo Heparin night of surgery - ? (n=501) Vs. **LMWH** 2500-5000 IU subcutaneous + placebo warfarin (n=1000) (immediately before or immediately after surgery)	DVT diagnosed by venography, timing of assessment day 4-8 postoperative or at discharge PE diagnosed by scan/angiography/ post- mortem	RANDO: adequate ALLOCATION CONCEALMENT: unclear BLINDING: participants unclear; personnel unclear; assessors unclear FOLLOW-UP: 67% evaluable venography ITT: no FUNDING: NR

NICE 2010 did not report all included trials in detail, but extracted them form this systematic review.

Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. Health technology assessment. 2005;9(49):iii-iv, ix-x, 1-78.

Roderick et al., 2005 Design: MA 8 RCT's included (a.o. Francis 1997, Hull 2000); all included in the NICE guideline review	7260	Orthopedic surgery	1 – 14 days	**OAC-adjusted Warfarin** (5 studies), warfarin fixed (3 studies) and acenocoumarin adjusted INR 2-3 (1 study) Timing: Ranged from time admitted to 14 days postoperatively/discharge Vs. **LMWH** Timing: Ranged from time admitted to 14 days postoperatively/discharge	DVT: confirmed by fibrinogen uptake, venography or doppler US PE by scan, angiogram, X-ray or post-mortem Major bleeds: NR	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: NR ITT: NR

5.3.2 Summary and conclusions. Vitamin K antagonists versus LMWH in elective hip replacement

VKA versus LMWH for thromboprophylaxis in hip replacement			
Bibliography: Meta-analysis NICE 2010(54), selected these RCTs: Colwell 1999(82), Francis 1997(83), Hull 2000(84)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
DVT	1393 (2 studies) Treatment 14d, FU 3m or NR	VKA: 24.6% LMWH: 12.5% **RR: 1.94 (95 % CI 1.53 to 2.44)** **SS in favour of LMWH** Absolute effect: 12% (95% CI 7% to 16%)	⊕⊕⊕⊖ **MODERATE** Study quality:-1, low FU and no ITT Consistency: OK Directness: OK Imprecision: OK
Pulmonary embolism	3011 (1 study) Treatment 14d, FU 3m	VKA: 0.8% LMWH: 1.0% RR: 0.81 (95% CI 0.38 to 1.73) NS	⊕⊕⊕⊖ **MODERATE** Study quality: unblinded assessment and only 1 trial Consistency:NA Directness:OK Imprecision:OK
Major bleeding	5082 (3 studies) Treatment 14d, FU 3m or NR	VKA: 1.3% LMWH: 3.3% **RR: 0.57 (95% CI 0.38 to 0.85)** **SS in favour of VKA** Absolute effect: -1% (95% CI -4% to 1%)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unblinded assessment in 2/3 Consistency:OK Directness:OK Imprecision: OK

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

In this meta-analysis by NICE 2010, vitamin K antagonists are compared to low molecular weight heparins in patients undergoing elective hip artrhoplasty. 3 RCTs were included.

The rate of DVT is higher in patients treated with VKA compared to patients treated with LMWH.
GRADE: MODERATE quality of evidence

There is no statistically significant difference in rate of pulmonary embolism between both treatments.
GRADE: MODERATE quality of evidence

The rate of major bleeding is lower in patients treated with VKA compared to patients treated with LMWH.
GRADE: MODERATE quality of evidence

5.3.3 Dabigatran versus enoxaparin in elective hip replacement

Study details	n/Population	Comparison	Outcomes		Methodological
588 Eriksson 2011 RE-NOVATE II(85) Design: RCT DB PG Double dummy Non-inferiority trial Setting: Multinational (86.1% from EU or USA) Duration of follow-up: 3 months ± 7 days after surgery	n= 2055 Mean age: 62 y Previous VTE or DVT: 2.5% <u>Inclusion</u> Age ≥ 18 years primary, unilateral, elective total hip arthroplasty <u>Exclusion:</u> - bleeding-related contraindications, - contraindications to enoxaparin or dabigatran treatment; - elevated liver enzymes (alanine aminotransferase level [ALT] > three times the upper limit of the normal range [ULN]); -severe renal insufficiency [creatinine clearance <30 ml/minute)].	Dabigatran (2 X 110 mg /d) + placebo injection vs Enoxaparin (40 mg /d) + placebo tablets Duration of treatment: 28 to 35 days	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 98.0% in safety analysis 76.7 % in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: no modified ITT = all randomised and treated patients who underwent elective total hip arthroplasty and had evaluable adjudicated data on VTE or died during the treatment period. <u>Excluded from efficacy analysis:</u> Patients with inadequate or missing bilateral venography who neither died nor experienced symptomatic thromboembolic events <u>Safety analysis</u>: All randomised patients who received at least one dose of study drug
			Total VTE and all cause mortality (PO) (venographic or symptomatic DVT and/or PE) (PE was established by ventilation-perfusion scintigraphy and chest X-ray, pulmonary angiography, spiral chest computer tomography, or by autopsy. Symptomatic DVT was confirmed by compression ultrasound, venography or by autopsy)	<u>primary efficacy analysis</u> Dabigatran: 61/792 (7.7%) Enoxaparin: 69/785 (8.8%) **Absolute risk difference:** **-1.1% (95%CI, -3.8% to 1.6%)** **P value for non-inferiority: < 0.0001** P-value for superiority: 0.43	
			Total DVT (venography or symptomatic)	Dabigatran: 60/791 (7.6%) Enoxaparin: 67/783 (8.6%) Absolute risk difference: -1.0% (95%CI, -3.7% to 1.7%) P-value for superiority: 0.48	
			Total proximal DVT (venography or symptomatic)	**Dabigatran: 17/804 (2.1%)** **Enoxaparin: 31/792 (3.9%)** **P-value for superiority: 0.04** **SS**	
			Symptomatic VTE	Dabigatran: 1/1001 (0.1%) Enoxaparin: 6/992 (0.6%) P-value for superiority: not reported	
			Symptomatic DVT	Dabigatran: 0/1001 (0.0%) Enoxaparin: 4/992 (0.4%) P-value for superiority: 0.06	
			Symptomatic non-fatal PE	Dabigatran: 1/1001 (0.1%)	

	from participation. - Concomitant treatment with long-acting NSAID, - aspirin > 162 mg/day - requirement for continued anticoagulation or planned intermittent pneumatic compression was prohibited. - If spinal or epidural anesthesia was performed, less than three attempts or non-traumatic placement was required for patient eligibility.			Enoxaparin: 2/992 (0.2%) P-value for superiority: 0.62	Power: adequate? (planned sample size: 1920 (720 evaluable patients per group)) Sample size determination for the study was based on an expected rate of the primary efficacy outcome of up to 20% in each group and the requirement for at least 95% power to exclude an absolute increase in risk of 7.7% for the primary outcome with dabigatran, at a one-sided alpha level of 0.025. This non-inferiority margin was estimated to correspond to preservation of 67% of the lower boundary of the 95% confidence interval (CI) for the efficacy of enoxaparin compared with placebo, as assessed in three studies. SELECTIVE REPORTING: no Sponsor: Boehringer Ingelheim
			Death	Dabigatran: 0/1001 (0.1%) Enoxaparin: 1/992 (0.1%) P-value for superiority: 0.50	
			Major VTE and VTE related mortality (SO) (Major VTE = venographic and symptomatic proximal DVT and/or non-fatal PE. VTE-related mortality = fatal PE and deaths where VTE cannot be excluded)	**Dabigatran: 18/805 (2.2%)** **Enoxaparin: 33/794 (4.2%)** **Absolute risk difference:** **-1.9% (95%CI, -3.6% to -0.2%)** **P-value for superiority: 0.03**	
			Total VTE and all cause mortality during total study period (treatment + follow up)	Dabigatran: 3/942 (0.3%) Enoxaparin: 10/951 (1.1%) P-value: not reported	
			Safety		
			Major bleeding events (Fatal; In a critical organ (e.g. retroperitoneal, intracranial, intraocular or intraspinal); Clinically overt associated with 20 g/L or more fall in haemoglobin in excess of that expected by the investigator; Clinically overt leading to transfusion of 2 or more units of packed cells or whole blood in excess of that expected by the investigator; Leading to re-operation; Warranting treatment cessation)	Dabigatran: 14/1010 (1.4%) Enoxaparin: 9/1003 (0.9%) P-value for superiority: 0.40	
			Clinically relevant non-major bleeding (Spontaneous skin haematomas ≥ 25 cm2; Wound haematoma ≥ 100 cm2; Spontaneous nose	Dabigatran: 23/1010 (2.3%) Enoxaparin: 20/1003 (2.0%) P-value for superiority: not reported	

			bleeding > 5 minutes; Spontaneous gingival bleeding > 5 minutes; Macroscopic haematuria that was spontaneous or lasted >24 hours, if associated with an intervention; Spontaneous rectal bleeding creating more than a spot on toilet paper; Any other bleeding event judged as clinically significant by the investigator)		
			Minor bleeding	Dabigatran: 61/1010 (6.0%) Enoxaparin: 54/1003 (5.4%) P-value for superiority: not reported	
			Any bleeding event	Dabigatran: 98/1010 (9.7%) Enoxaparin: 83/1003 (8.3%) P-value for superiority: 0.26	
			Adverse events		
			Any adverse events	Dabigatran: 684/1010 (67.7%) Enoxaparin: 696/1003 (69.4%)	
			Serious adverse events	Dabigatran: 57/1010 (5.7%) Enoxaparin: 59/1003 (5.9%)	
			ALT elevation > 3 x ULN anytime post baseline	Dabigatran: 37/984 (3.8%) Enoxaparin: 55/975 (5.6%)	
			Myocardial infarction	Dabigatran: 1/1010 (<0.1%) Enoxaparin: 1/1003 (<0.1%)	

Study detail	n/population	Comparison	Outcomes		Methodological
G007 Eriksson 2007 RE- NOVATE I(86) RCT DB PG Double dummy Non inferiority trial Setting: Multinational (Europe, Australia and South Africa) Duration of follow up: 94 d	n= 3494 dabi 220 n=1157 dabi 150 n=1174 pla n= 1162 Mean age: 64 Previous VTE(DVT/PE): 3% <u>Inclusion</u> Age > 18 years Weight ≥ 40 kg scheduled for primary elective unilateral total hip replacement <u>Exclusion</u> - any bleeding diathesis; - history of acute intracranial disease or haemorrhagic stroke; - major surgery, trauma, - uncontrolled hypertension, or myocardial infarction in the past 3 months; - gastrointestinal or urogenital bleeding, or ulcer disease in the past 6 months; severe	Dabigatran (220 mg/d) Vs Enoxaparin (40 mg/d) Duration of treatment: 28 tot 35 days until mandatory bilateral venography Concomitant therapy allowed: Administration of low-dose aspirin (< 160 mg) and selective cyclo- oxygenase-2 inhibitors - Elastic compression stockings	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: unclear Assessors: yes Remarks on blinding method: Nothing was mentioned about the blinding of the personnel FOLLOW-UP: 99 % in safety analysis 76 % in efficacy analysis • Described: yes • Balanced across groups: yes ITT: no (<u>Efficacy analysis</u>: Patients who were untreated, had no surgery or with inadequate or missing mandatory bilateral venography who neither died nor experienced venous thromboembolic events were excluded from effi cacy analyses) (patients in <u>safety analysis</u>: patients who were untreated were excluded from safety analysis) Power: adequate
			Total VTE + all cause mortality (PO) (venographic or symptomatic)	<u>Primary efficacy analysis</u> Dabigatran 220: 53/880 6.0% (95%CI, 4.5% to 7.6%) Enoxaparin: 60/897 6.7% (95%CI, 5.1% to 8.3%) **Absolute difference vs enoxaparin** **-0.7% (95%CI, -2.9% to 1.6%)** **P value for non-inferiority : < 0.0001**	
			Total asymptomatic DVT	Dabigatran 220 : 40/874 (4.6%) Enoxaparin : 56/894 (6.3%) NT	
			Symptomatic DVT	Dabigatran 220: 6/1137 (0.5%) Enoxaparin : 1/1142 (0.1%) NT	
			Symptomatic PE	Dabigatran 220: 5/1137 (0.4%) Enoxaparin: 3/1142 (0.3%) NT	
			Death	Dabigatran 220: 3/1137 (0.3%) Enoxaparin: 0/1142 (0%) NT	
			Major VTE and VTE related death (proximal deep-vein thrombosis and pulmonary embolism) (Includes all deaths where venous thromboembolism cannot be excluded)	<u>Efficacy analysis</u> Dabigatran 220: 28/909 3.1% (95%CI, 2.0% to 4.2%) Enoxaparin: 36/917 3.9% (95%CI, 2.7% to 5.2%) Absolute difference vs enoxaparin -0.8% (95%CI, -2.5% to 0.8%) P value for non-inferiority : 0.33	
			Safety		
			Major bleeding	Dabigatran 220: 23/1146 2.0% (95%CI, 1.3% to 3.0%)	

	liver disease; - alanine or aspartate aminotransferase concentrations greater than two times the upper limit of the normal range in the past month; - severe renal insuffi ciency (creatinine clearance less than 30 mL/min); - use of long-acting NSAID (also contraindicated during treatment); - childbearing potential; - allergy to radiopaque contrast media or Heparin - active malignant disease. - If spinal or epidural anaesthesia was done, less than three attempts or non-traumatic placement was required for patient eligibility.	- But intermittent pneumatic compression devices were prohibited.		Enoxaparin: 18/1154 1.6% (95%CI, 0.9 to 2.5%) P=0.44	Non-inferiority margin: "In the absence of placebo-controlled trials with enoxaparin given for 28–35 days, we used a pooled analysis of published rates of venous thromboembolism for enoxaparin versus placebo given for 8–14 days.19–21 showed an absolute difference in rates of 32·8% (95% CI 23·2–42·6), from which we chose a conservative non-inferiority margin of 7·7%, which preserves two- thirds of the 95% CI difference between enoxaparin and placebo" SELECTIVE REPORTING: no Sponsor: Boehringer Ingelheim
			Clinically relevant non-major bleeding	Dabigatran 220: 48/1146 (4.2%) Enoxaparin: 40/1154 (3.5%)	
			Minor bleeding	Dabigatran 220: 70/1146 (6.1%) Enoxaparin: 74/1154 (6.4%)	
			Adverse events		
			Serious adverse events	Dabigatran 220: 89/1146 (8%) Enoxaparin: 82/1154 (7%)	
			Total adverse events	Dabigatran 220: 879/1146 (77%) Enoxaparin: 892/1154 (77%)	
			Adverse events leading to treatment discontinuation	Dabigatran 220: 74/1146 (6.0%) Enoxaparin: 66/1154 (6.0%)	
		Comparison	Outcomes		
		Dabigatran (150 mg/d) Vs Enoxaparin (40 mg/d)	Efficacy		
			Total VTE + all cause mortality (PO) (venographic or symptomatic)	<u>Primary efficacy analysis</u> Dabigatran 150: 75/874 8.6% (95%CI, 6.7% to 10.4%) Enoxaparin: 60/897 6.7% (95%CI, 5.1% to 8.3%) Absolute difference vs enoxaparin -1.9% (95%CI, -0.6% to 4.4%) P value for non-inferiority : < 0.0001	
			Total asymptomatic DVT	Dabigatran 150: 63/871 (7.2%) Enoxaparin : 56/894 (6.3%)	
			Symptomatic DVT	Dabigatran 150: 9/1156 (0.8%) Enoxaparin : 1/1142 (0.1%)	
			Symptomatic PE	Dabigatran 150: 1/1156 (0.1%) Enoxaparin: 3/1142 (0.3%)	

			Death	Dabigatran 150: 3/1156 (0.3%) Enoxaparin: 0/1142 (0%)	
			Major VTA and VTE related death (Includes all deaths where venous thromboembolism cannot be excluded)	<u>Efficacy analysis</u> Dabigatran 150: 38/888 4.3% (95%CI, 2.9% to 5.6%) Enoxaparin: 36/917 3.9% (95%CI, 2.7% to 5.2%) Absolute difference vs enoxaparin 0.4% (95%CI, -1.5% to 2.2%) P value for non-inferiority : 0.71	
			Safety		
			Major bleeding	Dabigatran 150: 15/1163 1.3% (95%CI, 0.7% to 2.1%) Enoxaparin: 18/1154 1.6% (95%CI, 0.9 to 2.5%) P=0.60	
			Clinically relevant non-major bleeding	Dabigatran 150: 55/1163 (4.7%) Enoxaparin: 40/1154 (3.5%)	
			Minor bleeding	Dabigatran 150: 72/1163 (6.2%) Enoxaparin: 74/1154 (6.4%)	
			Adverse events		
			Serious adverse events	Dabigatran 150: 91/1163 (8%) Enoxaparin: 82/1154 (7%)	
			Total adverse events	Dabigatran 150: 895/1163 (77%) Enoxaparin: 892/1154 (77%)	
			Adverse events leading to treatment discontinuation	Dabigatran 150: 88/1163 (8.0%) Enoxaparin: 66/1154 (6.0%)	

5.3.4 Summary and conclusions. Dabigatran versus enoxaparin in elective hip replacement

Dabigatran 220 mg versus enoxaparin 40mg/d for 28-35 days for the prevention of VTE after hip arthroplasty			
Bibliography: Eriksson 2007 RE-NOVATE I(86), Eriksson 2011 RE-NOVATE II(85)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	4374 (2 studies) 3 months	**Eriksson 2007** 0.3% vs 0% NT **Eriksson 2011** 0.1% vs 0.1% NS	⊕⊕⊕⊖ **MODERATE** Study quality: non-inferiority trial, but OK Consistency:OK Directness:OK Imprecision:-1 low event rates
Total VTE + all cause mortality (venographic or symptomatic) (PO)	4374 (2 studies) 3 months	**Eriksson 2007** 6.0% vs 6.7% **ARD= -0.7% (95%CI -2.9% to 1.6%)** **P for non-inferiority : <0.0001** **Eriksson 2011** 7.7% vs 8.8% **ARD= -1.1% (95%CI -3.8% to 1.6%)** **P for non-inferiority: < 0.0001**	⊕⊕⊖⊖ **LOW** Study quality:-1 non-inferiority trial, no ITT, 24% exclusions Consistency: OK Directness:-1 asymptomatic VTE in composite Imprecision: OK
Symptomatic DVT	4374 (2 studies) 3 months	**Eriksson 2007** 0.5% vs 0.1% NT **Eriksson 2011** 0.0% vs 0.4% NS	⊕⊕⊕⊖ **MODERATE** Study quality: non-inferiority trial, but OK Consistency: OK Directness: OK Imprecision:-1 low event rates
Major bleeding	4374 (2 studies) 3 months	**Eriksson 2007** 2.0% vs 1.6% NS **Eriksson 2011** 1.4% vs 0.9% NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency:OK Directness:OK Imprecision: -1 low event rates

Two RCTs compared dabigatran 220mg to enoxaparin 40mg/d for the prevention of VTE after total hip arthroplasty. Treatment duration was 28-35 days. Both trials were non-inferiority trials.

Mortality rates were low in both groups. Only one trial did a statistical test for this outcome.
There was no significant difference in mortality rates.
GRADE: MODERATE quality of evidence

The primary endpoint was a composite of total venous thromboembolic events (both symptomatic and asymptomatic) and all-cause mortality. Dabigatran 220mg was found to be non-inferior to enoxaparin for this outcome.
GRADE: LOW quality of evidence
Rates of symptomatic DVT were low in both groups. Only one trial did a statistical test for this outcome. There was no significant difference in symptomatic DVT between dabigatran 220mg and enoxaparin 40 mg.
GRADE: MODERATE quality of evidence

No significant difference in major bleeding events was found.
GRADE: MODERATE quality of evidence

Clinically relevant non-major bleeding rates and minor bleeding rates were reported, but not statistically tested.
GRADE: Not applicable

Dabigatran 150 mg versus enoxaparin 40mg/d for 28-35 days for the prevention of VTE after hip arthroplasty			
Bibliography: Eriksson 2007 RE-NOVATE I(86)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	2336 (1 study) 3 months	0.3% vs 0% NT	Not applicable
Total VTE + all cause mortality (venographic or symptomatic) (PO)	2336 (1 study) 3 months	8.6% vs 6.7% ARD= 1.9% (95%CI -0.6% to 4.4%) **P for non-inferiority : < 0.0001**	⊕⊕⊖⊖ **LOW** Study quality:-1 non-inferiority trial, no ITT, 24% exclusions Consistency: OK Directness:-1 asymptomatic VTE in composite Imprecision: OK
Symptomatic DVT	2336 (1 study) 3 months	0.8% vs 0.1% NT	Not applicable
Major bleeding	2336 (1 study) 3 months	1.3% vs 1.6% P=0.60; NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency:OK Directness:OK Imprecision: -1 low event rates

One RCT compared dabigatran 150mg to enoxaparin 40mg/d for the prevention of VTE after total hip arthroplasty. Treatment duration was 28-35 days. This was a non-inferiority trial.

Mortality rates were low in both groups. No statistical test was done.
GRADE: Not applicable

The primary endpoint was a composite of total venous thromboembolic events (both symptomatic and asymptomatic) and all-cause mortality. Dabigatran 150mg was found to be non-inferior to enoxaparin for this outcome.
GRADE: LOW quality of evidence

Rates of symptomatic DVT were low in both groups. No statistical test was done
GRADE: Not applicable

No significant difference in major bleeding events was found.
GRADE: MODERATE quality of evidence

Clinically relevant non-major bleeding rates and minor bleeding rates were reported, but not statistically tested.
GRADE: Not applicable

5.3.5 Apixaban versus enoxaparin in elective hip replacement

Study details	n/Population	Comparison	Outcomes		Methodological
595_Lassen 2010-ADVANCE-3(87) Design: Non-inferiority RCT DB PG Setting: patients from 160 sites in 21 countries (European majority) Duration of follow-up: 60 days (after 35 d treatment)	n= 5407 Mean age: 60y Previous VTE(DVT/PE): DVT : 1.6% PE : 0.5% Current malignancy: Previous orthopaedic surgery: -4.4% (knee replacement) -23% (hip replacement) -7.2% (hip or knee fracture surgery) Recent trauma: Immobilized: Baseline demographic and clinical characteristics of all the patients who underwent randomization and of all the patients	Apixaban at a dose of 2.5 mg orally twice daily plus placebo injections once daily vs enoxaparin at a dose of 40 mg subcutaneously once daily plus placebo tablets twice daily (Apixaban therapy was initiated 12 to 24 hours after closure of the surgical wound; enoxaparin therapy was initiated 12 hours before surgery. Prophylaxis was continued for 35 days after surgery,	Efficacy (n patients)		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 98.6% in safety analysis 71.5 % in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: no (The primary efficacy analysis was performed on data from all patients who underwent randomization and who had a primary efficacy outcome that could be evaluated; safety analysis: all randomized patients who received at least one dose of the study drug) Power: probably adequate SELECTIVE REPORTING: no
			All venous thromboembolism and death from any cause (composite of asymptomatic or symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause during the treatment period)(PO) (all patients underwent bilateral venography after treatment period)	**Intended treatment period** **Apixaban: 27/1949 (1.4%)** **Enoxaparin: 74/1917 (3.9%)** **RR : 0.36 (0.22 to 0.54)** **one-sided P<0.001 for non inferiority and two sided P<0.001 for superiority**	
			Major venous thromboembolism (composite of adjudicated symptomatic or asymptomatic proximal deep-vein thrombosis (popliteal, femoral, or iliac-vein thrombosis), nonfatal pulmonary embolism, or death related to venous thromboembolism, during the same period.)	**Intended treatment period** **Apixaban: 10/2199 (0.5%)** **Enoxaparin:25/2195 (1.1%)** **RR : 0.40 (0.15 to 0.80)** **one-sided P<0.001 for non inferiority and two sided P = 0.01 for superiority** **NNT : 147**	
			Symptomatic venous thromboembolism and	**Intended treatment period** Apixaban: 4/2708 (0.1%)	

	who could be evaluated for the primary efficacy outcome were similar between the study groups <u>Inclusion</u> Patients were eligible if they were scheduled to undergo elective total hip replacement or revision of a previously inserted hip prosthesis…. documented by … <u>Exclusion</u> Major exclusion criteria were active bleeding, a contraindication to anticoagulant prophylaxis, or the need for ongoing anticoagulant or antiplatelet treatment.	followed by bilateral venographic studies) followed for an additional 60 days after the last intended dose of study medication	**death from venous thromboembolism**	Enoxaparin:10/2699 (0.4%) RR : 0.40 (0.01 to 1.28) P=0.11	Other important methodological remarks : -Authors tested the hypothesis that apixaban would be noninferior to enoxaparin with respect to the primary efficacy outcome, using prespecified noninferiority margins in which the maximum value for the upper limit of the 95% confidence interval for relative risk was 1.25. If noninferiority was established for the primary efficacy outcome, the secondary efficacy outcome would be tested for noninferiority with the use of a prespecified margin in which the maximum value for the upper limit of the 95% confidence interval for relative risk was 1.5. Finally, if apixaban met the prespecified criteria for noninferiority with respect to both the primary and secondary efficacy outcomes, we would test for superiority using Pearson's chisquare test. This sequential testing procedure maintained the one-sided alpha level at 0.025. -All P values reported for
			Symptomatic deep-vein thrombosis	**Intended treatment period** Apixaban: 1/2708 (<0.1%) Enoxaparin:5/2699 (0.4%) NT **Intended follow-up period** Apixaban: 0/2598 Enoxaparin:3/2577 (0.1%) NT	
			Pulmonary embolism	**Intended treatment period** Non fatal: Apixaban: 2/2708 (<0.1%) Enoxaparin:5/2699 (0.2%) NT Fatal: Apixaban: 1/2708 (<0.1%) Enoxaparin:0/2699 NT **Intended follow-up period** Non fatal: Apixaban: 0/2598 Enoxaparin: 4/2577 (0.2%) NT Fatal: Apixaban: 0/2598 Enoxaparin:0/2577	

			Deep-vein thrombosis	**Intended treatment period** Apixaban: 22/1944 (1.1%) Enoxaparin: 68/1911 (3.6%) NT	noninferiority tests on primary and key secondary end points are based on one-sided tests. All other reported P values are based on two-sided tests. Sponsor: Bristol-Myers Squibb and Pfizer
			Death	**Intended treatment period** Apixaban: 3/2708(0.1%) Enoxaparin: 1/2699 (<0.1%) NT **Intended follow-up period** Apixaban: 2/2598 (<0.1%) Enoxaparin: 1/2577 (<0.1%) NT	
			Safety(Treatment period)		
			All bleeding events	Apixaban: 313/2673 (11.7%) Enoxaparin: 334/2659 (12.6%) ARR : -0.9 (-2.6 to 0.9) P=0.34	
			Adjudicated major bleeding events (The definition of major bleeding was acute, clinically overt bleeding accompanied by one or more of the following findings: a decrease in the hemoglobin level of 2 g per deciliter or more over a 24-hour period; transfusion of 2 or more units of packed red cells; bleeding at a critical site (including intracranial, intraspinal, intraocular, pericardial, and retroperitoneal bleeding); bleeding into the operated joint, necessitating reoperation or intervention; intramuscular bleeding with the	Apixaban: 22/2673 (0.8%) Enoxaparin: 18/2659 (0.7%) ARR : 0.10 (-0.3 to 0.6) P=0.54	

			compartment syndrome; or fatal bleeding.		
			Adjudicated clinically relevant nonmajor bleeding (Clinically relevant nonmajor bleeding included acute, clinically overt episodes such as wound hematoma, bruising or ecchymosis, gastrointestinal bleeding, hemoptysis, hematuria, or epistaxis that did not meet the criteria for major bleeding)	Apixaban: 109/2673 (4.1%) Enoxaparin: 120/2659 (4.5%) ARR : -0.4 (-1.5 to 0.7) P=0.43	
			Adjudicated major or clinically relevant nonmajor bleeding events	Apixaban: 129/2673 (4.8%) Enoxaparin: 134/2659 (5.0%) ARR : -0.2 (-1.4 to 1.0) P=0.72	
			Minor bleeding event (Bleeding was categorized as minor if it was clinically overt but was not adjudicated as major or clinically relevant nonmajor bleeding.)	Apixaban: 184/2673 (6.9%) Enoxaparin: 200/2659 (7.5%)	

5.3.6 Summary and conclusions. Apixaban versus enoxaparin in elective hip replacement

Apixaban (2x2.5mg/d) versus Enoxaparin (40mg/d) for 35d for thromboprophylaxis after hip replacement			
Bibliography: Lassen 2010 ADVANCE-3(87)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	5407 (1 study) 35d treatment	Treatment: 0.1% vs <0.1% No statistical test	Not applicable
Composite of asymptomatic or symptomatic DVT, nonfatal PE, or death from any cause during the treatment period (PO)	5407 (1 study) 35d	1.4% vs 3.9% **RR=0.36 (95%CI 0.22 to 0.54) SS, p<0.001 for superiority, in favour of apixaban**	⊕⊕⊖⊖ **LOW** Study quality: -1 no ITT and <80% FU in efficacy analysis Consistency: NA Directness: -1 asymptomatic DVT included in composite outcome Imprecision: OK
Symptomatic DVT	5407 (1 study) 35d	Treatment: <0.1% vs 0.4% No statistical test	Not applicable
PE	5407 (1 study) 35d	Treatment: <0.1% vs 0.2% No statistical test	Not applicable
Major bleeding	5407 (1 study) 2 days after last dose	0.8% vs 0.7% ARR=0.10 (95% CI -0.3 to 0.6), NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: NA Directness: OK Imprecision: OK
Any bleeding	5407 (1 study) 2 days after last dose	11.7% vs 12.6% ARR=-0.9 (95% CI -2.6 to 0.9), NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: NA Directness: OK Imprecision: OK

This RCT was a non-inferiority trial comparing 35 days of treatment of apixaban 2x2.5mg/d with 35 days of treatment with enoxaparin 40mg/d for the prevention of VTE after hip surgery. In case of non-inferiority, a superiority test was also done for the efficacy outcomes.

The event rates for mortality, PE and symptomatic DVT were low and no statistical test was reported for these outcomes.
GRADE: not applicable

The primary outcome was a composite of asymptomatic DVT, symptomatic DVT, nonfatal PE, and death from any cause, with a lower event rate during 35 days of treatment with apixaban 2x2.5mg/d than during 35 days of treatment with enoxaparin 40 mg/d.
GRADE: LOW quality of evidence

There was no statistically significant difference in the rate of major bleeding between 35 days of treatment of apixaban 2x2.5mg/d with 35 days of treatment with enoxaparin 40mg/d
GRADE: HIGH quality of evidence

There was no statistically significant difference in the rate of any bleeding between 35 days of treatment of apixaban 2x2.5mg/d with 35 days of treatment with enoxaparin 40mg/d
GRADE: HIGH quality of evidence

5.3.7 Rivaroxaban versus enoxaparin in elective hip replacement

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: 757 Eriksson 2008 RECORD1(88) Design: Noninferiority and superiority trial RCT (DB) (PG) Setting: NR Duration of follow-up: 30 to 35 days after the last dose of the study drug.	n= 4541 Mean age: 63.2 Previous VTE(DVT/PE): 102 (of safety population= 2462 patients) Current malignancy: NR Recent surgery: 990 had previous orthopedic surgery of the safety population Recent trauma: NR Immobilized:NR <u>Inclusion</u> - At least 18 years of age - Scheduled to undergo elective total hip arthroplasty… <u>Exclusion</u> - Scheduled to undergo staged, bilateral hip	10mg of oral rivaroxaban once daily, beginning after surgery vs 40mg of enoxaparin subcutaneously once daily, beginning the evening before surgery + a placebo tablet/injection For 35 days	Efficacy		RANDO: adequate ALLOCATION CONC: unclear BLINDING : adequate Participants:yes Personnel: yes Assessors: yes FOLLOW-UP: 97.6% in safety analysis 69.4% in efficacy analysis 67% in per protocol-analysis Drop-outs and Exclusions: • Described: no • Balanced across groups: yes (1537 vs 1492) ITT: no (PP and modified ITT, "*if noninferiority was shown, a second analysis would determine whether the efficacy of rivaroxaban was superior to that of enoxaparin in the modified ITT-population. The modified intention-to-treat analysis included patients who had undergone planned surgery, had taken a study drug, and had undergone an adequate assessment for*
			The composite of DVT (symptomatic or detected by bilateral venography if the patient was asymptomatic), nonfatal pulmonary embolism and death from any cause at end of treatment (PO) confirmed by by means of systematic ascending, bilateral venography with the use of the Rabinov and Paulin technique), Nonfatal PE (confirmed by spiral computed tomography, perfusion– ventilation lung scintigraphy, or pulmonary angiography)	**<u>Per protocol</u> Rivaroxaban: 13/1537 (0.8%) Enoxaparin: 50/1492 (3.4%) Weighted ARR 2.5% (95%CI 1.5 to 3.5) Rivaroxaban is non-inferior to enoxaparin (p not reported) <u>Modified ITT (superiority analysis)</u> Rivaroxaban: 18/1595 (1.1%) Enoxaparin: 58/1558 (3.7%) ARR: 2.6% (95% CI 1.5 to 3.7) P<0.001 SS in favour of Rivaroxaban**	
			Major VTE (proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death from venous thromboembolism)	**<u>Per protocol</u> Rivaroxaban: 2/1622 (0.1%) Enoxaparin: 29/1604 (1.8%) Weighted ARR: 1.7% (95% CI 1.0 to 2.4) Rivaroxaban is non-inferior to enoxaparin (p not reported) <u>Modified ITT</u> Rivaroxaban: 4/1686 (0.2%) Enoxaparin: 33/1678 (2.0%) ARR: 1.7% (95% CI 1.0 to 2.5) P<0.001**	

	arthroplasty - Were pregnant or breastfeeding - Had active bleeding or a high risk of bleeding - Had a contraindication for prophylaxis with enoxaparin or a condition that might require an adjusted dose of enoxaparin. - Conditions preventing bilateral venography - Substantial liver disease - Severe renal impairment (creatinine clearance, <30 ml per minute) - Concomitant use of protease inhibitors for the treatment of human immunodeficiency virus infection - Planned intermittent pneumatic compression			**SS in favour of Rivaroxaban**	*thromboembolism.* *These patients were included in the per-protocol analysis, provided they had no major deviation from the protocol (for details, see Table 1)")* Power: lower numbers than planned in per protocol analysis SELECTIVE REPORTING: no Other important methodological remarks : *"The aim of the trial was first to test the null hypothesis that the efficacy of rivaroxaban was inferior to that of enoxaparin in the per-protocol population.If noninferiority was shown, a second analysis would determine whether the efficacy of rivaroxaban was superior to that of enoxaparin in the modified intention-to-treat population."* *"Margin of 3.5% for the primary efficacy outcome and an absolute margin of 1.5% for major venous thromboembolism."* Sponsor: Bayer HealthCare and
			Death during on-treatment period	**<u>Modified ITT</u>** Rivaroxaban: 4/1595 (0.3%) Enoxaparin: 4/1558 (0.3%) ARR: 0.0 (95% CI –0.4 to 0.4) p=1.00 NS	
			Nonfatal pulmonary embolism	**<u>Modified ITT</u>** R: 4/1595 (0.3%) E: 1/1558 (0.1%) ARR: 0.2 (95% CI–0.1 to 0.6) p=0.37 NS	
			Deep-vein thrombosis	**<u>Modified ITT</u>** **R: 12/1595 (0.8%)** **E: 53/1558 (3.4 %)** **ARR: –2.7 (95% CI–3.7 to –1.7)** **p<0.001** **SS in favour of Rivaroxaban** **<u>Proximal DVT</u>** **R: 1/1595(0.1%)** **E: 31/1558 (2.0%)** **ARR: –1.9 (95% CI–2.7 to –1.2)** **p<0.001** **SS in favour of Rivaroxaban** <u>Distal DVT</u> R: 11/1595 (0.7%) E: 22/1558 (1.4%) ARR: –0.7 (95% CI –1.5 to 0.0) p=0.04; NS	
			Symptomatic venous	R: 6/2193 (0.3%)	

	- A requirement for anticoagulant therapy that could not be stopped.		**thromboembolism during treatment**	E: 11/2206 (0.5%) ARR: –0.2 (95% CI–0.6 to 0.1) p=0.22 NS	Johnson & Johnson
			Symptomatic venous thromboembolism during follow-up	R: 1/2193 (<0.1%) E: 4/2206 (0.2%) ARR: –0.1 (95% CI –0.4 to 0.1) p=0.37; NS	
			Death during follow-up	**<u>Modified ITT</u>** R: 1/1595(0.1%) E: 0/1558 (0.0%) ARR: 0.1 (95 % CI–0.2 to 0.4) p=1.00; NS	
			Safety		
			Major bleeding (PO) (defined as bleeding that was fatal, occurred in a critical organ (e.g., retroperitoneal, intracranial, intraocular, and intraspinal bleeding), or required reoperation or extrasurgical-site bleeding that was clinically overt and was associated with a fall in the hemoglobin level of at least 2 g per deciliter or that required transfusion of 2 or more units of whole blood or packed cells.)	Rivaroxaban: 6/2209 (0.3%) Enoxaparin: 2/2224 (0.1%) p=0.18 NS	
			Any on-treatment bleeding	Rivaroxaban: 133/2209 (6.0%) Enoxaparin: 131/2224 (5.9%) p=0.94 NS	

5.3.8 Summary and conclusions. Rivaroxaban versus enoxaparin in elective hip replacement

Rivaroxaban 10 mg versus enoxaparin 40 mg for 35 days for thromboprophylaxis after hip arthroplasty			
Bibliography: Eriksson 2008 RECORD1(88)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	4541 (1 study) 35 d	0.3% vs 0.3% ARR: 0.0 (95% CI –0.4 to 0.4) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 >30% exclusions, no ITT, non-inferiority trial Consistency: NA Directness:OK Imprecision:OK
DVT (symptomatic or asymptomatic), nonfatal PE and death from any cause (PO)	4541 (1 study) 35 d	**Non-inferiority** 0.8% vs 3.4% **ARR 2.5% (95%CI 1.5 to 3.5)** **Rivaroxaban non-inferior to enoxaparin** **Superiority** 1.1% vs 3.7% **ARR: 2.6% (95% CI 1.5 to 3.7)** **SS in favour of rivaroxaban**	⊕⊕⊖⊖ **LOW** Study quality:-1 >30% exclusions, no ITT, non-inferiority trial Consistency: OK Directness: -1 asymptomatic vte in composite Imprecision: OK
Nonfatal PE		0.3% vs 0.1% ARR: 0.2% (95% CI–0.1 to 0.6) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Consistency: NA Directness:OK Imprecision:OK
Symptomatic VTE	4541 (1 study) 35 d	0.3% vs 0.5% ARR: –0.2% (95% CI–0.6 to 0.1) NS	⊕⊕⊕⊖ **MODERATE** Study quality:non-inferiority trial, secondary outcome Consistency: NA Directness:OK Imprecision:OK
Major bleeding	4541 (1 study) 35 d	0.3% vs 0.1% NS	⊕⊕⊕⊖ **MODERATE** Study quality: non-inferiority trial, secondary outcome Consistency: NA Directness:OK Imprecision:OK
Any bleeding	4541 (1 study) 35 d	6.0% vs 5.9% NS	⊕⊕⊕⊖ **MODERATE** Study quality: non-inferiority trial, secondary outcome Consistency: NA Directness:OK Imprecision:OK

This RCT compares rivaroxaban 10 mg to enoxaparin 40mg daily for the thromboprophylaxis after hip arthroplasty. The trial is designed as a non-inferiority trial, with superiority testing if non-inferiority is proven. Both treatments were given for 35 days.

Mortality rates during treatment were low and not significantly different between treatment groups.
GRADE: MODERATE quality of evidence

The primary outcome for this trial is a composite of symptomatic and asymptomatic DVT, non-fatal PE and death from any cause. Rivaroxaban is first found to be non-inferior and in a subsequent analysis even superior to enoxaparin for this outcome. However, exclusion rates were very high, mainly due to lack of diagnostic testing for asymptomatic DVT.
GRADE: LOW quality of evidence

No significant difference in rates of non-fatal pulmonary embolism was found. Nor was there a significant difference in symptomatic DVT observed.
GRADE: MODERATE quality of evidence

No significant difference in major bleeding events or any bleeding events was found.
GRADE: MODERATE quality of evidence

5.3.9 Extended duration Rivaroxaban versus short duration enoxaparin in elective hip replacement

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: 755_Kakkar 2008 RECORD II(89) Design: RCT DB PG Setting: 123 centres across 21 countries worldwide Duration of follow-up: 32-40 days treatment + period of 30–35 days after the last dose of study medication.	n= 2509 Mean age: 61.5y Previous VTE(DVT/PE): 1.2% Current malignancy: NR Previous orthopaedic surgery: 18.6% Immobilized:NR <u>Inclusion</u> Patients, aged 18 years or over, who were scheduled to undergo elective total hip arthroplasty <u>Exclusion</u> - bilateral hip arthroplasty, active bleeding or a high risk of bleeding, or contraindication to enoxaparin or that might require enoxaparin dose	Oral rivaroxaban 10 mg once daily for 31–39 days (with placebo injection for 10–14 days) vs enoxaparin 40 mg once daily subcutaneously for 10–14 days (with placebo tablet for 31–39 days) (Mean duration of rivaroxaban therapy was 33·5 (SD 6·9) days, and 12·4 (3·0) days with enoxaparin)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 98% in safety analysis 69% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: No -modified intention-to-treat population for primary efficacy (all patients who had received at least one dose of study medication, had undergone planned surgery, and had adequate assessment of thromboembolism) -modified intention-to-treat population for major VTE (Patients could be valid for the
			Composite of deep-vein thrombosis (symptomatic or asymptomatic detected by mandatory, bilateral venography), non-fatal pulmonary embolism, and all-cause mortality up to day 30–42. (PO) (Deep-vein thrombosis was assessed on day 32–40, or earlier if symptomatic, by ascending, bilateral venography using the Rabinov and Paulin technique. All suspected deep-vein thromboses had to be confirmed by venography (positive ultrasound had to be confirmed). In cases of suspected pulmonary embolism, pulmonary angiography, perfusion/ventilation lung scintigraphy with chest radiography, or spiral computed tomography was done)	<u>Modified intention to treat</u> population for primary efficacy **Rivaroxaban: 17/864 (2.0%)** **Enoxaparin: 81/869 (9.3%)** **ARR : 7.3% (5.2 to 9.4)** **SS; p two-sided <0.0001**	
			Major venous thromboembolism (proximal DVT, non-fatal PE, and VTE-related death)	Treatment period <u>Modified intention to treat</u> population for major VTE **Rivaroxaban: 6/961 (0.6%)** **Enoxaparin: 49/962 (5.1%)** **ARR : 4.5% (3.0 to 6.0)** **SS; p two-sided <0.0001**	

	adjustment, including severe renal impairment; significant liver disease, pregnancy or breastfeeding, concomitant use of HIV protease inhibitors, use of fibrinolytic therapy or planned intermittent pneumatic compression during the study period, conditions preventing bilateral venography, or the requirement for an anticoagulant that could not be discontinued.				assessment of major venous thromboembolism if proximal veins were evaluable on the venogram, irrespective of whether distal veins were.) Power: adequate (lower than expected venography rates but sensitivity analysis "showed that the missing data did not affect the power.." SELECTIVE REPORTING: no Other methodological remarks: - comparison of 5 weeks rivaroxaban with 2 weeks enoxaparin… - major bleeding did not include surgical-site bleeding events unless they required re-operation or were fatal; this could explain the low event rates Sponsor: Bayer HealthCare AG, Johnson & Johnson Pharmaceutical Research and
			Symptomatic venous thromboembolism	Treatment period <u>Safety population who underwent surgery</u> **Rivaroxaban: 3/1212 (0.2%)** **Enoxaparin: 15/1207 (1.2%)** **ARR : 1.0% (0.3 to 1.8)** **SS; p two-sided =0.0040** Follow-up period <u>Safety population who underwent surgery</u> Rivaroxaban 1/1212 (0.1%) Enoxaparin: 2/1207 (0.2%) ARR : 0.1% (-0.2 to 0.4) NS; p two-sided =0.62	
			Death	Treatment period <u>Modified intention to treat population for primary efficacy</u> Rivaroxaban: 2/864 (0.2%) Enoxaparin: 6/869 (0.7%) ARR : 0.5% (-0.2 to 1.1) NS; p two-sided =0.29 Follow-up period <u>Safety population</u> Rivaroxaban: 0/1228 (0.0%) Enoxaparin: 2/1229 (0.2%) ARR : 0.2% (-0.1 to 0.6) NS; p two-sided =0.50	

			Non-fatal pulmonary embolism	Treatment period Modified intention to treat population for primary efficacy Rivaroxaban: 1/864 (0.1%) Enoxaparin: 71/869 (0.5%) ARR : 0.3% (-0.2 to 1.1) NS; p two-sided =0.37	Development LLC.
			Deep-vein thrombosis	Treatment period Modified intention to treat population for primary efficacy **Rivaroxaban: 14/864 (1.6%)** **Enoxaparin: 71/869 (8.2%)** **ARR : 6.5% (4.5 to 8.5)** **SS; p two-sided <0.0001** proximal DVT only **Rivaroxaban: 5/864 (0.6%)** **Enoxaparin: 44/869 (5.1%)** **ARR : 4.5% (3.0 to 6.0)** **SS; p two-sided <0.0001**	
			Safety (safety population)		
			Any on-treatment bleeding (beginning after initiation of study medication and up to 2 days after the last intake of study medication)	Rivaroxaban: 81/1228 (6.6%) Enoxaparin: 68/1229 (5.5%) NS; p =0.25	

			Major bleeding events (beginning after initiation of study medication and up to 2 days after the last intake of study medication) Major bleeding was defined as bleeding that was fatal, was into a critical organ (eg, retroperitoneal, intracranial, intraocular, intraspinal), required re-operation, or clinically overt extra-surgical-site bleeding associated with a fall in haemoglobin of 20 g/L or more, calculated from the day 1 post-operative baseline value, or requiring infusion of two or more units of whole blood or packed cells.	Rivaroxaban:1/1228 (<0.1%) Enoxaparin: 1/1229 (<0.1%) NT	
			Non-major bleeding	Rivaroxaban: 80/1228 (6.5%) Enoxaparin: 67/1229 (5.5%) NT	
			Clinically relevant non-major bleeding (Clinically relevant non-major bleeding events included events such as multiple source bleeding, spontaneous haematoma >25 cm2 and excessive wound haematoma.)	Rivaroxaban:40/1228 (3.3%) Enoxaparin:33/1229 (2.7%) NT	
			Any on-treatment adverse event	Rivaroxaban: 768/1228 (62.5%) Enoxaparin: 807/1229 (65.7%) NT	
			Skin and subcutaneous tissue disorders	Rivaroxaban: 130/1228 (10.6%) Enoxaparin: 94/1229 (7.7%) NT *"Although there seems to have been an increase in skin and subcutaneous*	

				tissue disorders, and in blistering in the rivaroxaban group compared with the enoxaparin group, no discernible trend can be seen if all three RECORD trials are considered together"	
			Cardiovascular adverse events	Rivaroxaban: 8/1228 (0.7%) Enoxaparin: 4/1229 (0.3%) NT *"there exists an apparent excess of cardiovascular adverse events after discontinuation of rivaroxaban in this trial.This difference could be due to chance, and no trend is apparent when viewed across all three RECORD trials"*	
			Adverse events leading to discontinuations	Rivaroxaban: 46/1228 (3.8%) Enoxaparin: 64/1229 (5.2%) NT	

5.3.10 Summary and conclusions. Extended duration Rivaroxaban versus short duration enoxaparin in elective hip replacement

Extended oral rivaroxaban (10 mg/d) versus short-term subcutaneous enoxaparin (40 mg/d) for thromboprophylaxis after total hip arthroplasty			
Bibliography: Kakkar 2008 RECORD II(89)			
Outcomes	**N° of participants (studies) Follo w up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	2509 (1 study) 30-42d + 30-35d FU	Treatment period: 0.2% vs 0.7% ARR=0.5% (95% CI -0.2 to 1.1) NS, p=0.29 Follow-up period: 0.1% vs 0.2% ARR=0.1% (95% CI -0.1 to 0.6) NS,p=0.50	⊕⊕⊖⊖ **LOW** Study quality: -1 <80% follow-up and no ITT for efficacy analysis Consistency: NA Directness: -1 comparing different durations of treatment Imprecision: OK
Composite outcome: DVT (symptomatic or asymptomatic), nonfatal PE and death from any cause (PO)	2509 (1 study) 30-42d	2.0% vs 9.3% **ARR=7.3% (95% CI 5.2 to 9.4), SS, p<0.0001 in favour of 31-39d oral rivaroxaban**	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 <80% follow-up and no ITT for efficacy analysis Consistency: NA Directness: -2 composite outcome and comparing different durations of treatments Imprecision: OK
Nonfatal PE	2509 (1 study) 30-42d	0.1% vs 0.5% ARR=0.3% (95% CI -0.2 to 1.1) NS, p=0.37	⊕⊕⊖⊖ **LOW** Study quality: -1 <80% follow-up and no ITT for efficacy analysis Consistency: NA Directness: -1 comparing different durations of treatments Imprecision: OK
Symptomatic VTE	2509 (1 study) 30-42d + 30-35d FU	0.2% vs 1.2% **ARR=1.0% (95% CI 0.3 to 1.8) SS, p=0.004 in favour of 31-39d oral rivaroxaban**	⊕⊕⊖⊖ **LOW** Study quality: -1 <80% follow-up and no ITT for efficacy analysis Consistency: NA Directness: -1 comparing different durations of treatments Imprecision: OK
Major bleeding	2509 (1 study) 30-42d	<0.1% vs <0.1% No statistical test	Not applicable
Any on treatment bleeding	2509 (1 study) 31-39d for rivaroxaban; 10-14d for enoxaparin	6.6% vs 5.5% NS, p=0.25	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: -1 comparing different durations of treatments Imprecision: OK

In this trial, extended treatment with oral rivaroxaban (10 mg/d) during 31-39 days was compared to short-term treatment with subcutaneous enoxaparin (40 mg/d) during 10-14 days to prevent venous thromboembolic events in patients undergoing hip surgery. Because the treatment durations of

rivaroxaban and enoxaparin were different, no conclusions can be drawn on the superiority of either drug as such.

There was no statistically significant difference in mortality between extended treatment with oral rivaroxaban and short-term treatment with subcutaneous enoxaparin.
GRADE: LOW quality of evidence

The primary outcome was a composite of symptomatic DVT, asymptomatic DVT, nonfatal PE and death from any cause, with a lower event rate after extended treatment with oral rivaroxaban than after short-term treatment with subcutaneous enoxaparin.
GRADE: VERY LOW quality of evidence

There was no statistically significant difference in non-fatal PE between extended treatment with oral rivaroxaban and short-term treatment with subcutaneous enoxaparin.
GRADE: LOW quality of evidence

There was a lower incidence of symptomatic VTE after extended treatment with oral rivaroxaban than after short-term treatment with subcutaneous enoxaparin.
GRADE: LOW quality of evidence

No statistical test was reported for the outcome major bleeding, which occurred in less than 0.1% of the patients .
GRADE: not applicable

There was no statistically significant difference in on-treatment bleeding between extended treatment with oral rivaroxaban and short-term treatment with subcutaneous enoxaparin.
GRADE: MODERATE quality of evidence

5.3.11 Aspirin versus dalteparin after initial 10 days of dalteparin for extended thromboprophylaxis in elective hip replacement

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: 002 Anderson 2013(90) Design: RCT DB PG Non-inferiority trial Setting: multicenter, 12 tertiary care orthopedic referral centers in Canada. Duration of follow-up: 90days	n= 786 Mean age: 57y. Previous VTE (DVT or PE): 1.6% Recent surgery: 3.3% in past 6m Recent trauma: NR Immobilized: yes Active cancer in past 5y: 2.7% <u>Inclusion</u> Patients undergoing elective unilateral THA <u>Exclusion</u> hip fracture in the previous 3 months, metastatic cancer, life expectancy less than 6 months, bleeding that precluded use of anticoagulant prophylaxis (per the investigator's judgment), active	81mg/d Aspirin Vs 5000 U once daily dalteparin during 28 days After initial 10 days of dalteparin	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions: 1.0 % (After randomly assigned - Withdrew consent or consent not signed.) • Described: yes • Balanced across groups: yes (398 vs. 380) ITT: No "The primary analysis was by intention to treat" (excluding paients who withdrew consent after randomization (n=2 LMWH, n= 6 aspririn) The safety analysis was performed on all randomly assigned patients who received at least 1 dose of the study drug Power: inadequate for
			Total VTE event (PO) (symptomatic DVT or PE) (confirmed by objective testing)	Aspirin: 1 patient (0.3%) Dalteparin: 5 patients (1.3%) Absolute difference: 1.0% (95% CI -0.5 to 2.2); p=0.22 **P for noninferiority <0.001**	
			Net clinical benefit (combined VTE and clinically relevant major and nonmajor bleeding complications)	Aspirin: 3 patients (0.8%) Dalteparin: 10 patients (2.5%) Absolute difference: 1.7% (95% CI -0.3 to 3.8); p=0.091 NS	
			Other secondary outcomes (Wound infection, Myocardial infarction, Death, Stroke or transient ischemic attack, Thrombocytopenia)	NS	
			Mortality	Aspirin: 0 patients Dalteparin: 1 patient (0.3%) P=1.00 NS	
			Safety		
			Major bleeding (if it was overt and fulfilled at least one of thefollowing criteria: fatal bleeding, symptomatic bleeding into a critical area or organ,	Aspirin: 0 patients Dalteparin: 1 patient (0.3%) Absolute difference: 0.25% (95% CI -4.9 to 1.0); p=1.00 NS	

	peptic ulcer disease or gastritis that precluded aspirin use (per the investigator's judgment), aspirin allergy, heparin-induced thrombocytopenia or heparin allergy, creatinine clearance less than 30 mL/min per 1.73 m2, platelet count less than 100 x 10^9 cells/L, need for long-term anticoag due to a preexisting comorbid condition or VTE developing after surgery but before randomization, and unwillingness or inability to give informed consent.		or bleeding that caused a 20-g/L decrease or more in hemoglobin level or led to transfusion of 2 or more units of whole blood or red blood cells.)		noninferiority, not clear for superiority (A sample size of 1100 patients per group was required to achieve 95% power) SELECTIVE REPORTING: no Non-inferiority margin: Method of determining margin not stated. "We required a sample size of 1100 patients per group to achieve 95% power at a 5% significance level, based on the noninferiority design, a baseline event rate of 1.5%, and a minimal clinically important difference of 2.0%" Other important methodological remarks: The trial stopped early because of slow enrollment, so the findings are based on very few events Sponsor: Canadian Institutes of Health Research
			Clinically significant nonmajor bleeding (if it resulted in hospitalization, reoperation, aspiration, or a wound hematoma complicated by infection)	Aspirin: 2 patients (0.5%) Dalteparin: 4 patients (1.0%) Absolute difference: 0.48% (95% CI -1.0 to 2.0); p=0.68	
			Minor bleeding (overt bleeding that did not fall into one of the aforementioned categories)	Aspirin: 8 patients (2.1%) Dalteparin: 18 patients (4.5%) Absolute difference: 2.4% (95% CI -3.1 to 5.2); p= 0.164 NS	

5.3.12 Summary and conclusions. Aspirin versus dalteparin after initial 10 days of dalteparin for extended thromboprophylaxis in elective hip replacement

Aspirin 81 mg versus dalteparin 5000U for extended thromboprophylaxis in patients with total hip arthroplasty			
Bibliography: Anderson 2013(90)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	786 (1 study) Treatment 28d FU 90d	0% vs 0.3% NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 noninferiority trial with inadequate power, not clear if power was adequate for superiority test
VTE (symptomatic DVT or PE) (PO)	786 (1 study) Treatment 28d FU 90d	0.3% vs 1.3% ARD= 1% (95% CI -0.5 to 2.2) NS **P for noninferiority <0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1
Major bleeding	786 (1 study) Treatment 28d FU 90d	0% vs. 0.3% ARD=0.25% (95% CI 4.9 to 1.0) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1
Clinically significant non-major bleeding	786 (1 study) Treatment 28d FU 90d	0.5% vs. 1.0% ARD=0.48% (95% CI 1.0 to 2.0) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1

In this noninferiority trial, aspirin in a daily dose of 81 mg was compared to dalteparin 5000 U for extended prophylaxis in patients undergoing total hip arthroplasty, after 10 days of initial treatment with dalteparin. Both treatments were given during 28 days; the duration of follow-up for all outcomes was 90 days and a superiority test was reported. There was no information on the rate of pulmonary events.

There was no statistically significant difference in the mortality rate between both groups.
GRADE: MODERATE quality of evidence

There was no statistically significant differenc in the rate of venous thromboembolic events (primary outcome) between both groups. Aspirin was found to be non-inferior to dalteparin for this outcome.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in the rate of major bleedings between both groups.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in the rate of clinically relevant non-major bleedings between both groups.
GRADE: MODERATE quality of evidence

5.4 Pharmacological and mechanical prophylaxis versus mechanical prophylaxis in elective hip surgery

5.4.1 LMWH + graduated compression stockings versus graduated compression stockings in elective hip replacement

Ref	Comparison	N/n	Outcomes	Result**
ref* NICE 2010(54) Design: SR+MA Search date: dec 2008	LMWH+GCS vs GCS	N= 4 n= 836 (Fuji 2008, Lassen 1991, Samama 1997, Warwick 1995)	**DVT**	**LMWH+GCS: 128/500 (26%)** **GCS: 141/ 336 (42%)** **RR: 0.62 (95% CI 0.51 to 0.76)** **SS in favour of LMWH+GCS** **Absolute effect: -17% (95% CI -23% to -10%)**
		N= 3 n= 663 (Fuji 2008, Samama 1997, Warwick 1995)	**Pulmonary embolism**	LMWH+GCS: 2/414 (0.5%) GCS: 2/249 (0.8%) RR: 0.65 (95% CI 0.10 to 4.37) NS Absolute effect: 0% (95% CI -1% to 1%)
		N= 2 n= 577 (Samama 1997; Fuji 2008)	**Major bleeding**	LMWH+GCS: 7/391 (1.8%) GCS: 1/186 (0.5%) RR: 2.02 (95% CI 0.28 to 14.72) NS Absolute effect: 1% (95% CI 0% to 3%)

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Fuji 2008(91) Country of study: Japan Setting: Department of Orthopaedic Surgery Study design: RCT	436	Patient group: Study 1: Total knee replacement (TKR) Study 2: Total hip replacement (THR)(n=436) all Japanese patients Inclusion criteria: Patients of either gender if their age was 20 years or greater, and they were scheduled for TKR or THR surgery or revision surgery for TKR or THR Age (mean): 71.0 (sd = 8.0) Additional risk factors: BMI ≥ 30 kg/m2 = 64 (15.0%)	Duration of follow-up: 11-17 days	Study 1 (TKR) Group 1 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 20mg subcutaneous injection Group 2 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 40 mg subcutaneous injection Group 3 LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Twice daily 20mg subcutaneous injections Group 4 Placebo (saline) Start time: 24-36 hrs after surgery Duration: 14 days Subcutaneous injections (no frequency stated) Additional noncomparative	Major bleeding: fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with a bleeding index of 2 or more Minor bleeding: not defined Deep vein thrombosis (determined by venography) Symptomatic pulmonary embolism (confirmed by appropriate objective methods).	ALLOCATION CONC: unclear ("*No details provided on allocation concealment"*) RANDO: unclear ("*Method of randomization not given"*) BLINDING : unclear *("Paper states that study is double blind and that the endpoint assessors were blinded.")* FOLLOW-UP: 93% in safety analysis 77% in efficacy analysis ITT: no ('modified' ITT) Evidence level: 1+ Incidence of combined VTE was recorded **Study 1 (TKR)** Group 1: 16.2% Group 2: 65.3% P value: <0.05* **Study 2 (THR)** Group 3: 7.4% Group 4: 33.8% P value: <0.05* Funding: GlaxoSmithKlein, Sanovi-synthelabo and NV Organon Study was a dose ranging study with separate groups receiving

				prophylaxis: More than 50% of patients received elastic stockings/ bandages for part of the study. No other prophylaxis was used.		0.75, 1.5, 2.5 and 3.0mg fondaparinux. Only the group receiving 2.5 mg fondaparinux is analysed here as this is the licensed dose.
Lassen 1991(92) DB PG RCT (from MA Zufferey 2003 and abstract)	210	Patients with total hip replacement	Treatment duration 7 days Follow-up duration 8-10 days	Tinzaparin 50/kgx1 + elastic stockings Vs. Placebo + elastic stockings Time of first administration preop. 2h	DVT diagnoses by bilateral venography (all patients, day 8-10)	"The study met the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography)" 10% excluded from evaluation Remark: ITT: no
Samama 1997(93) DB PG RCT (from MA Zufferey 2003 and abstract)	170	Patients with total hip replacement, undergoing spinal anesthesia	Treatment duration 8-12 days Follow-up duration 8-12 days	Enoxaparin 4000x1 + elastic stockings Vs. Placebo + elastic stockings Time of first administration postop. 6-8h	DVT diagnosed by bilateral venography (all patients, day 10+/-2)	"The study met the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography)" 10% excluded from analysis (no data available) Remark ITT: no
Warwick 1995(94) OL PG RCT (from MA Zufferey 2003 and abstract)	213 (actually 153 randomised)	Patients with total hip replacement	Treatment duration 3 days Follow-up duration 8-10 days	Enoxaparin 4000x1 + elastic stockings Vs. No treatment + elastic stockings Time of first administration preop.	DVT diagnosed by routine unilateral venography day 8-10	"The study did not meet the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography)" Remark:

				12h		no post-randomisation exclusions no ITT

NICE 2010 did not report all included trials in detail, but extracted them form this systematic review.

Zufferey 2003(69) Study design: MA 13 studies (with a.o. Lassen 1991, Samama 1997, and Warwick 1995; not included in the NICE-guideline review) 9 of these studies were included in the NICE-guideline review	1925 Note: 2 studies did not give total distribution of randomized patients and only gave number for those that had detection test.	**Type of surgery:** Hip fracture: 3 studies Knee surgery: 2 studies Hip replacement 8 studies	Studies ranged from 6 to 14 days follow-up.	**LMWH:** (Enoxaparin, certoparin, tinzaparin, dalteparin, nadroparin, ardeparin) **Doses:** Ranged from 3000 anti-Xa IU to over 6000 anti-Xa IU. **Timing**: Treatment started preoperatively in 9 studies and postoperatively in 4 studies. **Duration**: The treatment varied from 3 to 14 days **Additional non-comparative prophylaxis**: Not reported Vs **Placebo** (11 studies) or **No treatment** (2 studies) **Background**: GCS in 4 studies. electrical stimulation 2 studies	DVT confirmed by fibrinogen or plasminogen uptake test, duplex US or venography. Major bleeds: defined as major haemorrhage	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: % in safety analysis NR % in efficacy analysis NR ITT: NR Evidence level: 1+ Not reported: QoL, LoS, PTS and funding. Note: RR and CI reported by MA authors.

5.4.2 Summary and conclusions. LMWH + graduated compression stockings versus graduated compression stockings in elective hip replacement

LMWH + GCS versus GCS for thromboprophylaxis in patients with hip replacement surgery			
Bibliography: Meta-analysis NICE 2010(54), selected these RCTs: Fuji 2008(91), Lassen 1991(92), Samama 1997(93), Warwick 1995(94)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
DVT	836 (4 studies) treatment 3-16d FU 8-17d	26% vs 42% **RR: 0.62 (95% CI 0.51 to 0.76)** **SS in favour of LMWH+GCS** Absolute effect: -17% (95% CI -23% to -10%)	⊕⊕⊕⊖ **MODERATE** Study quality:-1 no ITT, >10% exclusions, variety of durations Consistency: OK Directness: see study quality Imprecision: OK
Pulmonary embolism	663 (3 studies) treatment 3-16d FU 8-17d	0.5% vs 0.8% RR: 0.65 (95% CI 0.10 to 4.37) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 no ITT, >10% exclusions, variety of durations Consistency: OK Directness: see study quality Imprecision:-1 wide CI
Major bleeding	577 (2 studies) treatment 8-16d FU 8-17d	1.8% vs 0.5% RR: 2.02 (95% CI 0.28 to 14.72) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 no ITT, some exclusions, 1 trial all Japanese Consistency: OK Directness: see study quality Imprecision:-1 wide CI

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

In this meta-analysis by NICE 2010, low molecular weight heparin combined with graduated compression stockings is compared to compression stockings only in patients undergoing hip replacement surgery. 4 RCTs were included.

Patients in these trials were screened for the outcome DVT using imaging techniques, so the reported rate of DVT consists of both symptomatic and asymptomatic DVT.

DVT rates are lower with LMWH + GCS compared to GCS only.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in the rate of pulmonary embolism.
GRADE: LOW quality of evidence

There was no statistically significant difference in the rate of major bleeding between both groups. However, the confidence interval is quite wide.
GRADE: LOW quality of evidence

5.5 Duration of thromboprophylaxis in elective hip replacement

5.5.1 Post discharge LMWH versus placebo in patients with elective hip replacement

Ref	Comparison	N/n	Outcomes	Result**
ref*NICE 2010(54) Design: SR+MA Search date: dec 2008	Post discharge LMWH vs control	N= 5 n= 1093 (Bergqvist 1996B, Comp 2001, Dahl 1997, Lassen 1998, Planes 1996)	**DVT**	**LMWH: 58/560 (10.4%)** **Control: 136/533 (25.5%)** **RR: 0.41 (95% CI 0.31 to 0.55)** **SS in favour of LMWH** **Absolute effect: -14% (95% CI -19% to -9%)**
		N= 6 n= 1817 (Bergqvist 1996B, Comp 2001, Dahl 1997, Heit 2000, Lassen 1998, Planes 1996)	**Pulmonary embolism**	LMWH: 0/923 (0%) Control: 5/894 (0.55%) RR: 0.16 (95% CI 0.02 to 1.35) NS Absolute effect: 0% (95% CI -1% to 1%)
		N= 3 (6 staat in Nice, maar slechts 3 vermeld) n= 1086 (Comp 2001, Heit 2000, Planes 1996)	**Major bleeding**	LMWH: 0/555 (0%) Control: 1/531 (0.2%) RR: 0.32 (95 % CI 0.01 to 7.80) NS Absolute effect: 0% (95% CI -1% to 1%)

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Most of these RCTs were appraised using information from different systematic reviews.

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Bergqvist 1996(95) (based on NICE 2010(54), Hull 2001(96) and Sobieraj 2012(97)) PG RCT	262	Patients with elective hip arthroplasty Mean age: 70 y Previous VTE: 20/262 (8%) Cancer: 0%	Duration of prophylaxis: in-hospital 10-11 days out-of hospital 18-19 days	In-hospital initiation of enoxaparin once daily (initial + subsequent doses 4000 IU) + preoperative initiation of extended therapy with enoxaparin (n=131) Vs In-hospital initiation of enoxaparin once daily (initial + subsequent doses 4000 IU) + preoperative initiation of extended therapy with placebo (n=131)	DVT confirmed by Bilateral ascending phlebography PE Confirmed by ventilation – perfusion lung scan or a pulmonary angiography.	ALLOCATION CONC: unclear RANDO: unclear BLINDING : patients unclear; personnel unclear; assessors adequate FOLLOW-UP: 89% of patients undergoing successful venography ITT: yes FUNDING: NR
Comp 2001(98) (based on Hull 2001(96) and Sobieraj 2012(97)) PG RCT	435	Patients with elective hip arthroplasty Mean age: 64y Previous VTE: patients did not have clinical evidence of chronic or acute VTE in the past 12 months Cancer: NR	Duration of prophylaxis: in-hospital 8 days out-of hospital 19 days Duration of follow-up: 90d	Prolonged: In-hospital initiation of enoxaparin (30 mg twice daily during the in-hospital treatment period and starting 12-24h after surgery, then 40mg once daily during the out-of-hospital study interval) + postoperative initiation of extended therapy with enoxaparin Vs. Standard: In-hospital initiation of enoxaparin	Patients were examined for clinical evidence of PE. At the end of the double-blind phase, all patients underwent bilateral venography and ultrasonography.	ALLOCATION CONC: adequate RANDO: adequate BLINDING : unclear FOLLOW-UP: 67% of patients undergoing successful venography ITT: yes FUNDING: NR

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
				(30 mg twice daily, during the in-hospital treatment period and starting 12-24h after surgery, then 40mg once daily during the out-of-hospital study interval) + postoperative initiation of extended therapy with placebo		
Dahl 1997(99) (based on Hull 2001(96) and Sobieraj 2012(97)) PG RCT	265	Patients with elective hip arthroplasty Mean age: 71 y Previous VTE: 15/227 (7%) Cancer: 21/227 (9%)	Duration of prophylaxis: in-hospital 7 days out-of hospital 28 days Duration of follow-up: 35d	Prolonged: In-hospital initiation of dalteparin once daily (initial + subsequent doses 5000 IU), starting the evening before surgery and continued for 35d Vs. Standard: In-hospital initiation of dalteparin once daily (initial + subsequent doses 5000 IU), starting the evening before surgery until day 7, then placebo injections for 35d	Bilateral ascending venography, ventilation-perfusion scintigraphy, and chest radiography were performed on day 35 after surgery	ALLOCATION CONC: unclear RANDO: unclear BLINDING : patients unclear; personnel unclear; assessors adequate FOLLOW-UP: 69% of patients undergoing successful venography ITT: yes FUNDING: NR
Lassen 1998(100) (based on Hull 2001(96) and Sobieraj 2012(97)) PG RCT	281	Patients with elective hip arthroplasty Mean age: 79y Previous VTE: 15/281 (5%) Cancer: 6/281 (2%)	Duration of prophylaxis: in-hospital 7 days out-of hospital 28	Prolonged: In-hospital initiation of dalteparin once daily (initial + subsequent doses 5000 IU), starting 12h before surgery and continuing for 7 days after surgery, then continued once daily for	Bilateral ascending phlebography was performed on day 35	ALLOCATION CONC: adequate RANDO: adequate BLINDING : patients unclear; personnel unclear; assessors adequate FOLLOW-UP:

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
			days Duration of follow-up: 35d	35 days Vs. Standard: In-hospital initiation of dalteparin (initial + subsequent doses 5000 IU), starting 12h before surgery and continuing for 7 days after surgery, then placebo once daily for 35 days		76% of patients undergoing successful venography ITT: no FUNDING: NR
Planes 1996(101) (based on Hull 2001(96) and Sobieraj 2012(97)) PG RCT	179	Patients with elective hip arthroplasty Mean age: 79y Previous VTE: 3/179 (2%) Cancer: 0%	Duration of prophylaxis: in-hospital 14 days out-of hospital 21 days	Prolonged: In-hospital initiation of enoxaparin (initial + subsequent doses 4000 IU)), starting immediately before surgery until just before hospital discharge, then continuing for 21d after discharge Vs. Standard: In-hospital initiation of enoxaparin (initial + subsequent doses 4000 IU), starting immediately before surgery until just before hospital discharge, then placebo injections for 21d after discharge	At the end of 21 days of randomized treatment, patients were reviewed and underwent a second bilateral phlebographic examination as outpatients.	ALLOCATION CONC: adequate RANDO: adequate BLINDING : patients adequate, personnel adequate, assessors adequate FOLLOW-UP: 97% of patients undergoing successful venography ITT: no FUNDING: NR
Heit 2000(102)	1.195	Type of surgery:	Duration of	Extended (6 week)	MEASUREMENTS:	ALLOCATION CONC: adequate

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
DB PG RCT Multicenter RCT conducted at 33 clinical centres		Orthopaedic (total hip or knee replacement) *Only THRpatients used in above meta-analysis* Intervention: Mean age: 65±11 yrs M/F:265/342 Control: Mean age: 66±11 M/F:275/313 Pre-existing risk factors: Not reported	extended prophylaxis 6 weeks	ardeparin sodium 50 IU/kg body weight twice daily to discharge, then ardeparin sodium 100 IU/kg once daily. Timing: begun with 24 hours post-op; continued until 6 weeks post-op (n=607). vs. ardeparin sodium 50 IU/kg body weight twice daily), then placebo. Timing: begun within 24 hours of surgery and continued until discharge (4-10 days). Placebo as per intervention schedule (n=588) Additional noncomparative Prophylaxis not reported	Symptomatic, objectively documented venous thromboembolism or death, along with major bleeding, from time of hospital discharge to 12 weeks after surgery Symptomatic DVT confirmed by venous duplex ultrasonography or venography Symptomatic PE Confirmed by ventilation perfusion lung scanning or pulmonary angiography. Major bleeding defined as overt bleeding with a Haemoglobin decrement of at least 20g/L or transfusion of at least 2 units of blood or any intracranial, retroperitoneal, intraocular or mediastinal bleeding that occurred after at least one does of drug	RANDO: adequate BLINDING : particpants yes, staff: unclear, assessors: yes FOLLOW-UP: % in efficacy analysis NR ITT: NR Evidence level (NICE 2010) 1+ FUNDING: Wyth-Ayerst Research

5.5.2 Summary and conclusions. Post discharge LMWH vs placebo in patients with elective hip replacement

LMWH post discharge versus placebo after 1-2 weeks of in-hospital LMWH for thromboprophylaxis in total hip replacement			
Bibliography: meta-analysis NICE 2010(54) included these RCTs: Bergqvist 1996(95), Comp 2001(98), Dahl 1997(99), Lassen 1998(100), 1996(101), Heit 2000(102)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
DVT (symptomatic and asymptomatic)	n= 1093 (5 studies) 28-90 d	10.4% vs 25.5% **RR: 0.41 (95% CI 0.31 to 0.55)** **SS in favour of LMWH** Absolute effect: -14% (95% CI -19% to -9%)	⊕⊕⊕⊖ **MODERATE** Study quality: -1: low FU and no ITT Consistency: OK Directness: OK Imprecision: OK
PE	n= 1817 (6 studies) 28-90 d	0% vs 0.55% RR: 0.16 (95% CI 0.02 to 1.35) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1, two trials with low FU and no ITT Consistency: OK Directness: OK Imprecision: OK
Major bleeding	n= 1086 (3 studies) 35-90 d	0% vs 0.2% RR: 0.32 (95 % CI 0.01 to 7.80) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 wide CI

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

In this meta-analysis, LMWH post discharge (during four to six weeks) was compared to control after one or two weeks of in-hospital thromboprophylaxis in patients who had total hip replacement.

The outcome DVT consisted of both symptomatic and asymptomatic DVT in 5 trials. One trial (Heit 2000) was designed to detect only symptomatic DVT, but it was not included in the meta-analysis for the outcome DVT.

Unfortunately, the mortality rate was not reported.

A significantly lower number of patients suffered from deep vein thrombosis in the prolonged LMWH group compared to the control group.
GRADE: MODERATE quality of evidence

No statistically significant difference was observed for the outcome 'pulmonary embolism' between both treatment groups.
GRADE: MODERATE quality of evidence

Only one case of major bleeding (in the control group) was reported throughout the RCTs. However, the difference was not statistically significant.
GRADE: MODERATE quality of evidence

5.5.3 Warfarin extended duration versus warfarin until discharge in elective hip replacement

Study details	n/Population	Comparison	Outcomes		Methodological
Prandoni 2002(103) Design: OL PG non-inferiority RCT Setting: university hospital in Italy Duration of follow-up: 4 weeks	n= 360 Median age: 69y Current malignancy: 2% Recent trauma: NR Immobilisation: 10% TTR (VKA): NR <u>Inclusion</u> Patients with total hip arthroplasty with no previous hip surgery on the same side and no history of thromboembolic disorders <u>Exclusion</u> patients who developed venous thromboembolic complications or major bleeding during hospitalization; patients with	Extended warfarin 5mg 2nd day pre-op, then adjusted dose INR 2.0 – 3.0 continued for 4 weeks (n=184) Vs. Warfarin 5mg 2nd day pre-op, then adjusted dose INR 2.0 – 3.0 until discharge (mean 9 days) (n=176)	Efficacy		RANDO: adequate ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: adequate FOLLOW-UP: 100% in safety analysis 100% in efficacy analysis Drop-outs and exclusions: 3% ITT: Yes (all patients randomized) Power: 600 patients were needed for non-inferiority test, however the study was prematurely terminated after inclusion of 360 patients, because of an unexpected statistically significant and clinically relevant superiority of extended over short-term prophylaxis observed. SELECTIVE REPORTING: no
			VTE (**PO**) (DVT confirmed by bilateral Doppler US of proximal venous system at 1,2, and 4 weeks post-op; PE confirmed by V/Q, spiral CT or angiography)	Overall VTE: EXT. warf: 1/184 (0.5%) Warf: 9/176 (5.1%) **ARR= 4.57% (95% CI 1.15 to 7.99)** **SS in favour of extended warfarin** **RR=9.4 (95% CI 1.2 to 73.5** **SS in favour of extended warfarin** NNT=22 (CI or p-value NR) Symptomatic VTE: Ext. warf: 0/184 (0%) Warf: 4/176 (2.3%) NT	
			Proximal DVT	Ext. warf.: 1/184 (0.5%) Warf: 8/176 (4.5%) (3 symptomatic DVT) NT	
			PE	Ext. warf.: 0/184 (0%) Warf: 1/176 (0.6%) RR= 0.32 (95% CI 0.01 to 7.78), NS	
			Fatal PE confirmed by: autopsy or where PE could not be ruled out	Ext. warf.: 0/184 (0%) Warf: 0/176 (0%)	
			Safety		
			Death	No patients died during the follow-up period	
			Major bleeding.	Ext. warf.: 1/184 (0.5%)	

	asymptomatic proximal DVT as shown by a bilateral compression ultrasound examination before hospital discharge; those who needed long-term anticoagulation; unavailable for long-term follow-up		Defined as: 1. clinically overt and associated with either a decrease in haemoglobin of at least 2.0 g/dL or requiring transfusion of 2 or more units of red blood cells 2. Intracranial or retroperitoneal 3. resulted in permanent discontinuation of anticoagulation	Warf: 0/176 (0%) RR=2.87 (95% CI 0.12 to 69.99), NS (superiority test)	Sponsor: NR

5.5.4 Summary and conclusions. Warfarin extended duration versus warfarin until discharge in elective hip replacement

Warfarin extended duration (4w) vs. warfarin until discharge (mean 9 days) in patients with hip arthroplasty			
Bibliography: Prandoni 2002(103)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	360 (1 study) 4w	0% vs 0% No statistical test	Not applicable
VTE (PO)	360 (1 study) 4w	0.5% vs. 5.1% **RR=9.4 (95% CI 1.2 to 73.5)** **In favour of warfarin extended duration**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 not blind, prematurely terminated Consistency: NE Directness: OK Imprecision: OK
Proximal DVT	360 (1 study) 4w	0.5% vs. 4.5% No statistical test	Not applicable
PE	360 (1 study) 4w	0% vs. 0.6% No statistical test	Not applicable
Major bleeding	360 (1 study) 4w	0.5% vs. 0% RR=2.87 (95% CI 0.12 to 69.99)	⊕⊕⊖⊖ **LOW** Study quality: -1 not blind, prematurely terminated Consistency: NA Directness: OK Imprecision: -1 wide CI

In this trial extended warfarin treatment for 4 weeks was compared with warfarin until discharge (mean 9 days) in patients undergoing hip surgery. The trial was set up as a non-inferiority trial but was prematurely terminated because of a statistically significant and clinically relevant superiority of extended warfarin over short-term prophylaxis.

There was no statistical test for the outcomes proximal DVT and PE separately.
GRADE: not applicable

There was no statistically significant difference in mortality between extended warfarin and short-term warfarin treatment.
GRADE: LOW quality of evidence

There was a higher incidence of the primary outcome venous thromboembolic events with short-term warfarin treatment than with extended warfarin treatment.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in major bleeding between extended warfarin and short-term warfarin treatment.
GRADE: LOW quality of evidence

6 Evidence tables and conclusions: thromboprophylaxis in elective knee replacement

6.1 Pharmacological treatment versus placebo for thromboprophylaxis in elective knee replacement

6.1.1 LMWH versus placebo or no prophylaxis in elective knee replacement

Ref	Comparison	N/n	Outcomes	Result**
ref* NICE 2010(54) Design: SR+MA Search date: dec 2008	LMWH vs placebo	N= 1 n= 129 (Leclerc 1992)	**DVT**	**LMWH: 11/65 (17%)** **Nil.: 37/64 (58%)** **RR: 0.29 (95% CI 0.16 to 0.52)** **SS** **Absolute effect: -41% (95%CI -56% to -26%)**
		N= 1 n= 131 (Leclerc 1992)	**Major bleeding**	LMWH: 0/66 (0%) Nil.: 1/65 (1.5%) RR: 0.33 (95% CI 0.01 to 7.92) NS Absolute effect: -2% (95%CI -6% to 3%)

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Leclerc 1992(104) RCT, 'double blind' (reported from Zufferey 2003 and abstract)	131	Consecutive patients undergoing knee arthroplasty or tibial osteotomy at four participating hospitals		Enoxaparin 30mg bid versus placebo for 14 days	Patients underwent surveillance with 125I-fibrinogen leg scanning and impedance plethysmography. Bilateral contrast venography was performed routinely at Day 14 or at time of discharge,	"The study met the criteria defining high quality trials (double-blind design, intention-to-treat principle, and systematic bilateral venography)" Remark: ITT: no

The above RCTs was not reported in detail in the NICE 2010 document. It were extracted by NICE from this systematic review

Zufferey 2003(69) (13 studies, o.a. Lassen 1988, Tørholm 1991, Turpie 1986, Yoo 1997: all of them included in the guideline review) Study design: SR	1925 Note: 2 studies did not give total distribution of randomized patients and only gave number for those that had detection test.	Type of surgery: Hip fracture: 3 studies Knee surgery: 2 studies Hip replacement 8 studies	Studies ranged from 6 to 14 days follow-up.	**LMWH**: (Enoxaparin, certoparin, tinzaparin, dalteparin, nadroparin, ardeparin) Doses: Ranged from 3000 anti-Xa IU to over 6000 anti-Xa IU. Timing: Treatment started preoperatively in 9 studies and postoperatively in 4 studies. The treatment varied from 3 to 14 days. Additional noncomparative prophylaxis: NR Vs. **Placebo** (11 studies) or **No treatment** (2 studies) background: GCS in 4 studies. Electrical stimulation 2 studies	DVT confirmed by fibrinogen or Plasminogen uptake test, duplex US or venography. Major bleeds defined as major haemorrhage.	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: NR% in safety analysis NR% in efficacy analysis) ITT: NR Evidence level: 1+ Not reported: QoL, LoS, PTS and funding.

No prophylaxis versus GCS versus low-molecular-weight heparin (enoxaparin) in patients undergoing TKA

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: 715 Chin 2009(105) Design: RCT OL PG Setting: Asian patients, probably single centre Duration of follow-up: 1 month	n= 440 Mean age:66 years <u>Inclusion</u> Low-risk patients undergoing TKA and those who did not have any predisposition to thromboembolism <u>Exclusion</u> The use of anticoagulants or aspirin; A history of pulmonary embolism (PE) or DVT in the previous year; BMI >30 kg/m2); prolonged immobilisation or wheelchair bound; Bleeding tendency or a history of gastro-intestinal bleeding; < 6 months; Cerebrovascular accident< 3 months; Uncontrolled hypertension; Congestive cardiac failure; Renal or liver impairment; Allergy to heparin or heparin-induced thrombocytopenia; Varicose veins or chronic venous insufficiency; Peripheral vascular disease; Skin ulcers Dermatitis or wounds; Malignancy.	No prophylaxis (control) vs GCS vs low-molecular-weight heparin (enoxaparin) *(versus intermittent pneumatic compression – not considered by our review)* Continued for 5-7 days	Efficacy		RANDO: Unclear ALLOCATION CONC: Unclear BLINDING : Participants: no Personnel: no Assessors: ok(*"based on bilateral duplex ultrasonography (carried out by one of 3 dedicated ultrasonographers blinded to the prophylactic method used)")* FOLLOW-UP: 100% in safety analysis 100% in efficacy analysis Drop-outs and Exclusions: • Described: no • Balanced across groups: NR ITT: No Power: NR SELECTIVE REPORTING: no Other important methodological remarks: - Differences were
			DVT (PO) (confirmed by loss of compressibility of a vein or visualisation of thrombosis based on bilateral duplex ultrasonography)	**DVT (overall)** Control: 24 (22%) GCS: 14 (13%) Enoxaparin: 6 (6%) *IPC: 9 (8%)* p=0.001 overall Control vs GCS; p=0.119 Control vs enoxaparin; p=0.001 **Proximal DVT:** Control: 3 (3%) GCS: 1 (1%) Enoxaparin: 1 (1%) *IPC: 0 (0%)* p=0.279 **Distal DVT** Control: 21 (19%) GCS: 13 (12%) Enoxaparin: 5 (5%) *IPC: 9 (8%)* p=0.003	
			Symptomatic PE (diagnosis with ventilation-perfusion scanning and spiral computed tomography)	Control: 1 (1%) GCS: 1 (1%) Enoxaparin: 0 (0%) *IPC: 0 (0%)* p=0.571	

					considered significant when the p value was <0.05. - It is not totally clear whether all patients were routinely screened with duplex ultrasonography at a certain point in time; but this seems to be the case. Sponsor: NR
			Safety		
			Development of bleeding complications Haemarthrosis necessitating aspiration or arthrotomy for drainage was categorised as a major complication. Severe bruising around a wound (extending to the popliteal region, midcalf or mid-thigh) and haemarthrosis not requiring intervention were categorised as minor complications.	Control: 3 (2.7%) GCS: 3 (2.7%) Enoxaparin: 9 (8.2%) *IPC: 4 (3.6%)* p(difference between 4 arms of this study) =0.304	

6.1.2 Summary and conclusions. LMWH versus placebo or no prophylaxis in elective knee replacement

Enoxaparin versus placebo or no treatment for 5-14 days for thromboprophylaxis in elective knee surgery			
Bibliography: Meta-analysis NICE 2010(54) selected 1 RCT: Leclerc 1992(104); subsequent RCT: Chin 2009(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
DVT (symptomatic and asymptomatic)	349 (2 studies) 14d-1m	Leclerq 1992 17% vs 58% **RR: 0.29 (95% CI 0.16 to 0.52)** **SS** Absolute effect: -41% (95%CI -56% to -26%) Chin 2009 6% vs 22% **p=0.001 (no RR or CI reported)** **SS in favour of LMWH**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 Asian patients 1 trial, different assessment DVT Imprecision: OK
Major bleeding	131 (1 study) 14d	Leclerq 1992 0% vs 1.5% RR: 0.33 (95% CI 0.01 to 7.92) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 only 1 small trial Consistency: NA Directness:OK Imprecision:-1 wide CI
All bleeding complications	220 (1 study) 1m	Chin 2009 8.2% vs 2.7% p(difference between 4 arms of RCT) =0.304 (No RR or CI reported)	⊕⊕⊖⊖ **LOW** Study quality: -1 only 1 trial Consistency: NA Directness:OK Imprecision:-1

NICE 2010 found only 1 RCT comparing LMWH (enoxaparin 30 mg bid) to placebo in patients undergoing elective knee arthroplasty or tibial osteotomy. We found one more recent RCT comparing enoxaparin 40mg/d to control (4-arm study: control vs GCS vs enoxaparin vs IPC).

The outcome DVT was checked for in all patients using imaging techniques, so the reported rate of DVT consists of both symptomatic and asymptomatic DVT.
The rate of DVT is lower with enoxaparin compared to placebo.
GRADE: MODERATE quality of evidence

There is no statistically significant difference in the rate of major bleeding. However, the confidence interval is quite wide.
GRADE: LOW quality of evidence

There is no statistically significant difference in the rate of all bleeding complications. However, power is probably inadequate for this outcome.
GRADE: LOW quality of evidence

6.2 Pharmacological treatment versus graduated compression stockings for thromboprophylaxis in elective knee replacement

6.2.1 Enoxaparin versus graduated compression stockings in elective knee replacement

No prophylaxis versus GCS versus low-molecular-weight heparin (enoxaparin) in patients undergoing TKA

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: 715 Chin 2009(105) Design: RCT OL PG Setting: Asian patients, probably single centre Duration of follow-up: 1 month	n= 440 Mean age:66 years <u>Inclusion</u> Low-risk patients undergoing TKA and those who did not have any predisposition to thromboembolism <u>Exclusion</u> The use of anticoagulants or aspirin; A history of pulmonary embolism (PE) or DVT in the previous year; BMI >30 kg/m2); prolonged immobilisation or wheelchair bound; Bleeding tendency or a history of gastro-intestinal bleeding; < 6 months; Cerebrovascular accident< 3 months; Uncontrolled hypertension; Congestive cardiac failure; Renal or liver impairment; Allergy to heparin or heparin-induced thrombocytopenia;	No prophylaxis (control) vs GCS vs low-molecular-weight heparin (enoxaparin) *(versus intermittent pneumatic compression – not considered by our review)* Continued for 5-7 days	Efficacy		RANDO: Unclear ALLOCATION CONC: Unclear BLINDING : Participants: no Personnel: no Assessors: ok(*"based on bilateral duplex ultrasonography (carried out by one of 3 dedicated ultrasonographers blinded to the prophylactic method used)"*) FOLLOW-UP: 100% in safety analysis 100% in efficacy analysis Drop-outs and Exclusions: • Described: no • Balanced across groups: NR ITT: No Power: NR
			DVT (PO) (confirmed by loss of compressibility of a vein or visualisation of thrombosis based on bilateral duplex ultrasonography)	**DVT (overall)** Control: 24 (22%) GCS: 14 (13%) Enoxaparin: 6 (6%) *IPC: 9 (8%)* p=0.001 overall Control vs GCS; p=0.119 Control vs enoxaparin; p=0.001 **Proximal DVT:** Control: 3 (3%) GCS: 1 (1%) Enoxaparin: 1 (1%) *IPC: 0 (0%)* p=0.279 **Distal DVT** Control: 21 (19%) GCS: 13 (12%) Enoxaparin: 5 (5%) *IPC: 9 (8%)* p=0.003
			Symptomatic PE	Control: 1 (1%)	

	Varicose veins or chronic venous insufficiency; Peripheral vascular disease; Skin ulcers Dermatitis or wounds; Malignancy.		(diagnosis with ventilation-perfusion scanning and spiral computed tomography)	GCS: 1 (1%) Enoxaparin: 0 (0%) *IPC: 0 (0%)* p=0.571	SELECTIVE REPORTING: no Other important methodological remarks: - Differences were considered significant when the p value was <0.05. - It is not totally clear whether all patients were routinely screened with duplex ultrasonography at a certain point in time; but this seems to be the case. Sponsor: NR
			Safety		
			Development of bleeding complications Haemarthrosis necessitating aspiration or arthrotomy for drainage was categorised as a major complication. Severe bruising around a wound (extending to the popliteal region, midcalf or mid-thigh) and haemarthrosis not requiring intervention were categorised as minor complications.	Control: 3 (2.7%) GCS: 3 (2.7%) Enoxaparin: 9 (8.2%) *IPC: 4 (3.6%)* p(difference between 4 arms of this study) =0.304	

6.2.2 Summary and conclusions. Enoxaparin versus graduated compression stockings in elective knee replacement

Enoxaparin 40mg/d versus GCS for 5-7 days for thromboprophylaxis in elective knee arthroplasty			
Bibliography: Chin 2009(105)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
DVT (both symptomatic and asymptomatic)	220 (1 study) 1 month	6% vs 13% NT	Not applicable
All bleeding complications	220 (1 study) 1 month	8.2% vs 2.7% p (difference between 4 arms of this study) =0.304	⊕⊕⊖⊖ **LOW** Study quality: -1 only 1 trial Consistency: NA Directness:OK Imprecision:-1

One RCT compared LMWH (enoxaparin 40mg/d) to graduated compression stockings in Asian patients. This was a 4-arm trial (control vs GCS vs enoxaparin vs IPC).

The outcome DVT was checked for in all patients using duplex ultrasonography, so the reported rate of DVT consists of both symptomatic and asymptomatic DVT.
DVT rates were 6% in the enoxaparin group compared to 13% in the GCS-group. No statistical test was done for this specific comparison.
GRADE: not applicable

There is no statistically significant difference in the rate of bleeding complications. However, power is probably inadequate for this outcome.
GRADE: LOW quality of evidence

6.3 Pharmacological treatment versus pharmacological treatment for thromboprophylaxis in elective knee replacement

6.3.1 Vitamin K antagonists versus LMWH in elective knee replacement

Ref	Comparison	N/n	Outcomes	Result**
ref*NICE 2010(54) Design: SR+MA Search date: dec 2008	VKA vs LMWH	N= 3 n= 1220 (Fitzgerald 2001, Heit 1997, Leclerc 1996)	**DVT**	**VKA: 274/609 (45.0%)** **LMWH: 182/611 (29.8%)** **RR: 1.50 (95% CI 1.29 to 1.74)** **SS in favour of LMWH** **Absolute effect: 15% (95% CI 10% to 20%)**
		N= 3 n= 1220 (Fitzgerald 2001, Heit 1997, Leclerc 1996)	**Pulmonary Embolism**	VKA: 3/609 (0.5%) LMWH: 2/611 (0.3%) RR: 1.39 (0.19 to 10.16) NS Absolute effect: 0% (95% CI -0% to 1%)
		N= 3 n= 1575 (Fitzgerald 2001, Heit 1997, Leclerc 1996)	**Major bleeding**	**VKA: 22/789 (2.8%)** **LMWH: 38/786 (4.8%)** **RR: 0.58 (95% CI 0.34 to 0.97)** **SS in favour of VKA** **Absolute effect: -2% (95% CI -4% to 1%)**

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Fitzgerald 2001(106) OL RCT (reported from Roderick 2005 and full publication)	349	Elective knee arthroplasty		warfarin adjusted (INR 2-3) vs LMWH(enoxaparin) 30mg sc bid 8h postop – 4-14d postop	DVT: venography (all patients were to be screened) PE: angiogram	ALLOCATION CONC: unclear RANDO: adequate BLINDING : assessors: unclear (NR) FOLLOW-UP: 69% evaluable ITT: no no timing on DVT assessment reported
Heit 1997(107) DB RCT (reported from Roderick 2005 and abstract)	566	Elective total knee replacement		Warfarin adjusted (INR 2-3) vs LMWH (ardeparin) 60IU/kg sc 1 d preop – 14 d postop or discharge dose ranging study. Only doses +/- 60IU/kg considered	DVT: venography (all patients to be screened) PE: scan, angiography, postmortem for fatal PE	ALLOCATION CONC: NR RANDO: NR BLINDING :DVT assessors yes, PE assessment not reported FOLLOW-UP: 79% evaluable ITT: no no timing on DVT assessment reported
Leclerc 1996(108) DB RCT (reported from Roderick 2005 and abstract)	670	Elective knee arthroplasty		Warfarin adjusted INR 2-3 vs enoxaparin 30mg sc bid, placebo warfarin 1d postop – 14 d postop or discharge	DVT: venography (all patients to be screened), confirmed by Doppler ultrasound or impedance phlethysmograph 14 d postop PE: scan	ALLOCATION CONC: NR RANDO: adequate BLINDING : assessors yes FOLLOW-UP: 62% evaluable ITT: no

All above RCTs were not reported in detail in the NICE 2010 document. They were extracted by NICE from this systematic review:

Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. Health technology assessment. 2005;9(49):iii-iv, ix-x, 1-78.

Roderick et al., 2005 8 RCT studies included (o.a. Fitzgerald 2001, Heit 1997, Leclerc 1996); and all of them included in the guideline review Study type: SR	7260	Type of surgery: Orthopaedic: 9	Between day 1 to day 14.	**OAC-adjusted Warfarin** adjusted (5 studies), warfarin fixed (3 studies) and Acenocoumarin adjusted International Normalised Ratio 2-3 (1 study) Timing: Ranged from time admitted to 14 days postoperatively/discharge Additional noncomparative prophylaxis: NR Vs. **LMWH** Timing: Ranged from time admitted to 14 days postoperatively/discharge Additional noncomparative prophylaxis: NR	DVT: confirmed by fibrinogen uptake, venograph or doppler US PE by scan, angiogram, X-ray or post-mortem	ALLOCATION CONC: NR RANDO: NR BLINDING : NR FOLLOW-UP: NR ITT: NR Not reported: LoS, QoL, PTS.

6.3.2 Summary and conclusions. Vitamin K antagonists versus LMWH in elective knee replacement

VKA versus LMWH for 14 days or until discharge for thromboprophylaxis in elective knee replacement			
Bibliography: Meta-analysis NICE 2010(54), included these RCTs: Fitzgerald 2001(106), Heit 1997(107), Leclerc 1996(108)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
DVT (symptomatic and asymptomatic)	1220 (3 studies) treatment 14 d or until discharge	**45.0% vs 29.8%** **RR: 1.50 (95% CI 1.29 to 1.74)** **SS in favour of LMWH** Absolute effect: 15% (95% CI 10% to 20%)	⊕⊕⊕⊖ **MODERATE** Study quality:-1 no ITT and <80% patients considered Consistency:OK Directness:OK; but consider dosage Imprecision:OK
Pulmonary Embolism	1220 (3 studies) treatment 14 d or until discharge	0.5% vs 0.3% RR: 1.39 (0.19 to 10.16) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 no ITT and <80% patients considered Consistency:OK Directness:OK, but consider dosage LMWH Imprecision:-1
Major bleeding	1575 (3 studies) treatment 14 d or until discharge	**2.8% vs 4.8%** **RR: 0.58 (95% CI 0.34 to 0.97)** **SS in favour of VKA** Absolute effect: -2% (95% CI -4% to 1%)	⊕⊕⊕⊖ **MODERATE** Study quality:-1 no ITT+directness Consistency:OK Directness:dosages LMWH? Imprecision:OK

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

In this meta-analysis by NICE 2010, vitamin K antagonists are compared to LMWH in elective knee replacement. 3 RCTs were included. LMWH dosages in these trials were higher than the recommended prophylactic dose in Belgium.

The outcome DVT was checked for in all patients using imaging techniques, so the reported rate of DVT consists of both symptomatic and asymptomatic DVT.

There is a lower rate of DVT with LMWH compared to VKA.
GRADE: MODERATE quality of evidence

No statistically significant difference in pulmonary embolism rates is found between both treatments.
GRADE: LOW quality of evidence

There is a higher rate of major bleeding with LMWH compared to VKA.
GRADE: MODERATE quality of evidence

Nice 2010 found 3 old trials (Friedman 1994(109); Hamulyak 1995(110); Hull 1993(111)) that compare adjusted dose VKA to LMWH in a population of elective hip OR knee replacement. The results are not published in the full NICE document. A forest plot, published in the appendices, finds a significant difference for DVT (RR= 1.26; 95%CI 1.11 to 1.43) in favour of LMWH. There were no significant differences for pulmonary embolism and major bleeding

6.3.3 Dabigatran versus enoxaparin in elective knee replacement

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: G008 Eriksson 2007 RE-MODEL(112) Design: non-inferiority trial RCT (DB) (PG) Setting: 105 centers in Europe, Australia, and South Africa Duration of follow-up: 3 months	n= 2101 Mean age: 68y Previous VTE(DVT/PE): NR Current malignancy: NR Recent surgery: NR Recent trauma: NR Immobilized:NR <u>Inclusion</u> ≥18 years and >40 kg, scheduled for primary elective unilateral total knee replacement who provided signed informed consent <u>Exclusion</u> -Any bleeding diathesis; -History of acute intracranial disease or hemorrhagic stroke; -Major surgery, trauma, uncontrolled hypertension or myocardial infarction	Dabigatran etexilate, 150 mg or 220 mg once-daily, starting with a half-dose 1–4 h after surgery vs subcutaneous enoxaparin 40 mg once-daily, starting the evening before surgery Both for 6–10 days.	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes (double-dummy) Personnel: yes Assessors: yes FOLLOW-UP: 98.8% in safety analysis *("safety population consisted of all randomized patients who received at least one dose of study treatment (either subcutaneous injection or oral drug)")* 73.3% in efficacy analysis (all patients who had evaluable venography) Drop-outs and Exclusions: • Described: not fully • Balanced across groups: yes ITT: no Power: probably adequate SELECTIVE REPORTING: no Other important methodological remarks: *Elastic compression stockings*
			Composite of total VTE (venographic or symptomatic deep vein thrombosis (DVT) and/or symptomatic pulmonary embolism (PE)) and all-cause mortality during treatment (PO) (Bilateral venography was performed within 24 h of the last oral dose, according to a standardized technique described previously. Diagnosis of DVT was established as a consistent intraluminal filling defect on at least two venogram images. PE was established by ventilation/ perfusion scintigraphy, pulmonary angiography, spiral computed tomography, or autopsy. Symptomatic DVT during treatment and follow-up was confirmed by compression ultrasound or venography.	**Dabigatran 220: 183/503 (36.4%)** **Enoxaparin: 193/512 (37.7%)** **Absolute risk difference (ARD): -1.3% (95% CI -7.3 to 4.6)** **P-value for non-inferiority: 0.0003** **SS** Dabigatran 150: 213/526 (40.5%) Enoxaparin: 193/512 (37.7%) ARD: 2.8% (95% CI -3.1 to 8.7) P-value for non-inferiority: 0.017 NS
			Major VTE and VTE-related mortality	Dabigatran 220: 13/506 (2.6%) Enoxaparin: 18/511 (3.5%) ARD: -1.0 (95% CI -3.1 to 1.2) P-value: 0.38	

	within the past 3 months; -Gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; -Severe liver disease; -Aspartate aminotransferase or alanine aminotransferase (ALT) levels more than two times the upper limit of the normal range (ULN) within the past month; -Severe renal insufficiency (creatinine clearance <30 mL min)1); -Concomitant long-acting non-steroidal anti-inflammatory drug therapy (also contraindicated during study treatment); -Active malignant disease; -Being female and of childbearing potential			NS Dabigatran 150: 20/527 (3.8%) Enoxaparin: 18/511 (3.5%) ARD: 0.3 (95% CI-2.0 to 2.6) P-value:0.82 NS	*were permitted, but intermittent pneumatic compression devices were prohibited."* *-"On the basis of prior findings, we chose a non-inferiority margin of 9.2%; this minimum difference preserves two-thirds of the 95% confidence interval (CI) difference between enoxaparin and placebo."* Sponsor: Boehringer Ingelheim, Copenhagen, Denmark
			Safety		
			Major bleeding	Dabigatran 220: 10/679 (1.5%) Enoxaparin: 9/694 (1.3%) p =0.82 NS Dabigatran 150: 9/703 (1.3%) Enoxaparin: 9/694 (1.3%) p =1.0 NS	
			Clinically relevant non-major bleeding	Dabigatran 220: 40/679 (5.9%) Dabigatran 150: 48/703 (6.8%) Enoxaparin: 37/694 (5.3%) "NS"	
			Minor bleeding	Dabigatran 220: 60/679 (8.8%) Dabigatran 150: 59/703 (8.4%) Enoxaparin: 69/694 (9.9%) "NS"	
			Liver enzyme elevation	"NS"	
			Acute coronary events	"NS"	

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: G009 Re-Mobilize Writing Committee 2009(113) Design: Double-blind, active controlled, noninferiority randomized trial RCT (DB) (PG) Setting: 58 centers in the United States, 30 in Canada, 8 in Mexico, and 1 in the United Kingdom Duration of	n= 2615 Mean age: 66y Previous VTE(DVT/PE): NR Current malignancy: NR Recent surgery:NR Recent trauma: NR Immobilized:NR <u>Inclusion</u> -18 years or older -Weighing more than 40 kg -Had undergone primary elective unilateral total knee arthroplasty <u>Exclusion</u> -A known inherited or acquired clinically significant bleeding disorder;	Oral dabigatran etexilate 220 or 150 mg once daily vs Enoxaparin 30 mg SC BID After surgery, continued for 12-15 days	Efficacy		RANDO: Adequate ALLOCATION CONC:unclear BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: double-dummy FOLLOW-UP: 99.3% in safety analysis 73.0% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes (806 vs 823 vs 819) ITT: no (efficacy analysis on all patients with evaluable venography) Power: probably inadequate (lower than predicted event rates and slightly lower number of
			Total VTE events (symptomatic or venographic deep vein thrombosis [DVT] and/or symptomatic pulmonary embolism [PE]) and all cause mortality during treatment. (PO) *"Diagnosis of DVT was considered established if there was a consistent intraluminal filling defect on at least 2 venogram images. Pulmonary embolism was diagnosed by a high-probability result on ventilation-perfusion scintigraphy, pulmonary angiography, spiral computed tomography, or autopsy. Symptomatic DVT during treatment and follow-up was confirmed by compression ultrasound or venography.*	Dabigatran 220mg: 188/604 (31.1%) Dabigatran 150mg: 219/649 (33.7%) Enoxaparin: 163/643 (25.3%) Dabigatran 220 vs enoxaparin Risk difference: 5.8% (95% CI 0.8 to 10.8) **Dabigatran is not non-inferior vs enoxaparin** p=0.0234 NS **Dabigatran 150 vs enoxaparin** **Risk difference: 8.4% (95% CI 3.4 to 13.3)** **Dabigatran is not non-inferior vs enoxaparin** **p =0.0009** **SS in favour of Enoxaparin**	

follow-up: 3 months after surgery	-Major surgery, trauma, uncontrolled hypertension, or myocardial infarction within the last 3 months -History of acute intracranial disease or hemorrhagic stroke -Gastrointestinal or urogenital bleeding or ulcer disease within the last 6 months -Severe liver disease - AST, ALT > 2× the upper limit of the normal range -Severe renal insufficiency (creatinine clearance<30 mL/min) -Need for concomitant longacting NSAID or treatment with an anticoagulant during study drug treatment -Active malignant disease -Platelet count < 100 × 109/L -Pregnant, nursing, or child-bearing potential without effective birth		**Major VTE (proximal DVT, PE and VTE related mortality)**	DABIGATRAN 220: 3.4% (21/618) DABIGATRAN 150: 3.0% (20/656) Enoxaparin: 2.2% (15/668) DABIGATRAN 220 vs Enoxaparin: Risk difference: 1.2% (95% CI −0.7 to 3.0) p =0.21 NS DABIGATRAN 150 vs Enoxaparin: risk difference: 0.8% (95% CI −0.9 to 2.5). p =0 36 NS	patients than needed) SELECTIVE REPORTING: unclear reporting and lack of statistical testing in several secondary outcomes Other important methodological remarks: *Elastic compression stockings were permitted, but intermittent pneumatic compression devices were prohibited."* "N*on-inferiority margin of 9.2%" An upper limit of 9.2% for the 95% confidence interval (CI) for the risk difference found between dabigatran and enoxaparin treatments for the primary efficacy outcome was chosen as the margin for noninferiority. If this margin were not exceeded, dabigatran would have preserved at least two thirds of the superiority of enoxaparin over placebo demonstrated in a previous study.* Sponsor: Boehringer Ingelheim
			Symptomatic DVT, PE or death during follow-up	Dabigatran 220: 5/604 Dabigatran 150: 6/649 Enoxaparin: 6/643	
			Safety		
			Major bleeding during treatment (defined according to accepted guidelines)	DABIGATRAN 220: 5/857 (0.6%) DABIGATRAN 150: 5/871 (0.6%) Enoxaparin: 12/868 (1.4%) "NS"	

	control		Clinically relevant nonmajor bleeding during treatment (defined according to accepted guidelines)	DABIGATRAN 220: 23/857 (2.7%) DABIGATRAN 150: 22/871 (2.5%) Enoxaparin: 21/868 (2.4%) “similar”	
			Major bleeding posttreatment	DABIGATRAN 220: 1/857 (0.1%) DABIGATRAN 150: 2/871 (0.2%) Enoxaparin: 0/868 NT	
			Clinically relevant nonmajor bleeding posttreatment	DABIGATRAN 220: 6/857 (0.7%) DABIGATRAN 150: 5/871 (0.5%) Enoxaparin: 3/868 (0.3%) NT	

6.3.4 Summary and conclusions. Dabigatran versus enoxaparin in elective knee replacement

Dabigatran 220mg qd versus enoxaparin 40mg qd or 30mg bid in the prevention of venous thromboembolism in patients undergoing knee arthroplasty			
Bibliography: Eriksson 2007 RE-MODEL(112), Re-Mobilize Writing Committee 2009(113)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Total VTE events (symptomatic or venographic DVT or symptomatic PE or all-cause mortality) during treatment (PO)	4716 (2 studies) FU: 6-15d	**RE-MODEL trial** vs enoxaparin 40mg 36.4% vs 37.7% ARD=-1.3% (95%CI -7.3 to 4.6) dabigatran 220mg is non-inferior to enoxaparin 40mg **RE-MOBILIZE trial** vs enoxaparin 2x30mg 31.1% vs 25.3% **ARD= 5.8%(95%CI 0.8 to 10.8)** **SS in favour of enoxaparin** dabigatran 220mg is inferior to enoxaparin 2x30mg	⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 73% in efficacy analysis and no ITT Consistency: NA Directness: -1 asymptomatic VTE in composite outcome Imprecision: OK ⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 73% in efficacy analysis and no ITT Consistency: NA Directness: -1 asymptomatic VTE in composite outcome Imprecision: OK
Major VTE and VTE-related mortality	4716 (2 studies) FU 3 months	**RE-MODEL trial** vs enoxaparin 40mg 2.6% vs 3.5% ARD=-1.0 (95%CI -3.1 to 1.2) NS **RE-MOBILIZE trial** vs enoxaparin 2x30mg 3.4% vs 2.2% ARD=1.2% (95%CI -0.7 to 3.0) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 73% in efficacy analysis and no ITT Consistency: NA Directness: -1 asymptomatic VTE in composite outcome Imprecision: OK ⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 73% in efficacy analysis and no ITT Consistency: NA Directness: -1 asymptomatic VTE in composite outcome Imprecision: OK
Major bleeding	4716 (2 studies) FU 3 months	**RE-MODEL trial** vs enoxaparin 40mg 1.5% vs 1.3%, NS **RE-MOBILIZE trial** vs enoxaparin 2x30mg 0.7% vs 1.4%, NT	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1, no CI reported Not applicable
Clinically relevant non-major bleeding	4716 (2 studies) FU 3 months	**RE-MODEL trial** vs enoxaparin 40mg 5.9% vs 5.3%, NT **RE-MOBILIZE trial** vs enoxaparin 2x30mg 3.4% vs 2.7%, NT	Not applicable

Two non-inferiority trials compared oral dabigatran in a daily dose of 220 mg to subcutaneous enoxaparin 40 mg once daily (Eriksson 2007 RE-MODEL) or 30mg twice daily (RE-MOBILIZE 2009) for the prevention of venous thromboembolism (VTE) after total knee arthroplasty. Treatment duration varied between 6 and 15 days. Follow-up of the primary outcome was during treatment only; follow-up for the secondary outcomes was 3 months. Mortality was not reported as a separate outcome.

There was conflicting evidence on the difference between dabigatran and enoxaparin for the prevention of the composite of total VTE and mortality during treatment (primary outcome). Dabigatran 220 mg was non-inferior to enoxaparin 40mg for the prevention of this composite outcome
GRADE: LOW quality of evidence
Dabigatran 220 mg was inferior to enoxaparin 2x30mg for the prevention of this composite outcome.
GRADE: LOW quality of evidence

There was no statistically significant difference between dabigatran 220mg and both dosages of enoxaparin for the composite of major VTE and VTE-related mortality.
GRADE: LOW quality of evidence

No conclusions can be drawn on the difference between dabigatran and enoxaparin for the rate of major bleeding or clinically relevant minor bleeding, because of insufficient statistical information.
GRADE: not applicable

Dabigatran 150mg qd versus enoxaparin 40mg qd or 30mg bid in the prevention of venous thromboembolism in patients undergoing knee arthroplasty			
Bibliography: Eriksson 2007 RE-MODEL(112), Re-Mobilize Writing Committee 2009(113)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Total VTE events (symptomatic or venographic DVT or symptomatic PE or all-cause mortality) during treatment (PO)	4716 (2 studies) FU: 6-15d	**RE-MODEL trial** vs enoxaparin 40mg 40.5% vs 37.7% ARD: 2.8% (95% CI -3.1 to 8.7), dabigatran 220 is non-inferior to enoxaparin 40mg **RE-MOBILIZE trial** vs enoxaparin 2x30mg 33.7% vs 25.3% **ARD=8.4% (95%CI 3.4 to 13.3)** **SS in favour of enoxaparin** dabigatran is inferior to enoxaparin 2x30mg	⊕⊕⊖⊖ **VERY LOW** Study quality: -1 noninferiority trial, 73% in efficacy analysis and no ITT Consistency: OK when considered separately Directness: -1 asymptomatic VTE in composite outcome Imprecision: OK ⊕⊕⊖⊖ **VERY LOW** Study quality: -1 noninferiority trial, 73% in efficacy analysis and no ITT Consistency: OK when considered separately Directness: -1 asymptomatic VTE in composite outcome Imprecision: OK
Major VTE and VTE-related mortality	4716 (2 studies) FU 3 months	**RE-MODEL trial** vs enoxaparin 40mg 3.8% vs 3.5% ARD=0.3 (95%CI-2.0 to 2.6) NS **RE-MOBILIZE trial** vs enoxaparin 2x30mg 3.0% vs 2.2% ARD=0.8% (95%CI−0.9 to 2.5) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 73% in efficacy analysis and no ITT Consistency:NA Directness: -1 asymptomatic VTE in composite outcome Imprecision: OK ⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 73% in efficacy analysis and no ITT Consistency: NA Directness: -1 asymptomatic VTE in composite outcome Imprecision: OK
Major bleeding	4716 (2 studies) FU 3 months	**RE-MODEL trial** vs enoxaparin 40mg 1.3% vs 1.3%, NS **RE-MOBILIZE trial** vs enoxaparin 2x30mg 0.8% vs 1.4%, NT	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1, no CI reported in both studies, Not applicable
Clinically relevant non-major bleeding	4716 (2 studies) FU 3 months	**RE-MODEL trial** vs enoxaparin 40mg 6.8% vs 5.3%, NT **RE-MOBILIZE trial** vs enoxaparin 2x30mg 3% vs 2.7%, NT	Not applicable

Two non-inferiority trials compared oral dabigatran in a daily dose of 150 mg to subcutaneous enoxaparin 40 mg once daily (Eriksson 2007 RE-MODEL) or 30mg twice daily (RE-MOBILIZE 2009) for the prevention of venous thromboembolism (VTE) after total knee arthroplasty. Treatment duration varied between 6 and 15 days. Follow-up of the primary outcome was during treatment only; follow-up for the secondary outcomes was 3 months. Mortality was not reported as a separate outcome.

There was conflicting evidence on the difference between dabigatran 150mg and enoxaparin for the prevention of the composite of total VTE and mortality during treatment (primary outcome).
Dabigatran 150 mg was non-inferior to enoxaparin 40mg for the prevention of this composite outcome;
GRADE: LOW quality of evidence
Dabigatran 220 mg was inferior to enoxaparin 2x30mg for the prevention of this composite outcome.
GRADE: LOW quality of evidence

There was no statistically significant difference between dabigatran 150 mg and enoxaparin in both dosages for the composite of major VTE and VTE-related mortality.
GRADE: LOW quality of evidence

No conclusions can be drawn on the difference between dabigatran and enoxaparin for the rate of major bleeding or clinically relevant minor bleeding, because of insufficient statistical information.
GRADE: not applicable

6.3.5 Apixaban versus enoxaparin in elective knee replacement

Study details	n/Population	Comparison	Outcomes		Methodological
664_Lassen-2010-ADVANCE-2(114) Design: DB PG Non inferiority trial Setting: Multicentre (73% European patients) Duration of follow-up: Patients had follow-up assessments 30 and 60 days after last	n= 3057 Mean age: 67 Women: 72% Previous VTE(DVT/PE): DVT: 2% PE: <1% Current malignancy: NR Previous orthopaedic surgery: -18% (knee replacement) -5.5% (hip replacement) -3.5% (hip or knee fracture surgery) Recent trauma: NR Immobilized:NR <u>Inclusion</u> Patients were eligible for the study if they were scheduled to have	apixaban 2·5 mg orally twice daily and enoxaparin-matching placebo injections vs enoxaparin 40 mg subcutaneously once daily and apixaban-matching placebo tablets. For 10-14 days	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: (1501+1508/3057) 98.4% in safety analysis (976+997/3057) 65% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT:no The authors report having done an ITT for the non-inferiority testing, but this is not apparent Power: adequate SELECTIVE REPORTING: no Other important methodological remarks :
			All venous thromboembolism and all-cause death (composite of adjudicated asymptomatic or symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and all-cause death with onset during the intended treatment period of 12 days (within 2 days) or within 2 days of last dose of study drug) (PO) The presence or absence of asymptomatic deep vein thrombosis at the end of the intended treatment period was assessed with bilateral venography done between day 10 and day 14 (day 1 was the day of surgery). Clinically suspected deep vein thrombosis was confi rmed or excluded with ultrasonography or venography, and suspected pulmonary embolism with ventilation-perfusion lung scanning, spiral computed tomography, or pulmonary angiography	Apixaban: 147/976 (15.06%) Enoxaparin: 243/997 (24.37%) RR : 0.62 (0.51 to 0.74) SS; one sided p <0.0001when tested for non-inferiority and for superiority	

dose of study drug.	unilateral elective total knee replacement or same-day bilateral knee replacement, including revision…. <u>Exclusion</u> Patients were excluded if they had active bleeding or a contraindication to anticoagulant prophylaxis, or needed continuing anticoagulant or antiplatelet treatment. Additional exclusion criteria were uncontrolled hypertension, active hepatobiliary disease, impaired renal function, thrombocytopenia, anaemia, heparin allergy, allergy to radiographic contrast dye, or other disorders preventing bilateral venography.		**Major venous thromboembolism (composite of adjudicated symptomatic or asymptomatic proximal deep vein thrombosis, non-fatal pulmonary embolism, and venous thrombo embolism-related death)**	Apixaban: 13/1195(1.09%) Enoxaparin: 26/1199 (2.17%) RR : 0.50 (0.26 to 0.97) SS; one sided p for superiority =0.0186	apixaban was non-inferior to enoxaparin for the primary effi cacy outcome using prespecifi ed non-inferiority margins in which the upper limit of the 95% CI of the RR should not exceed 1·25, and for absolute risk diff erence the upper limit of the 95% CI should not exceed 5·6%. If both these criteria were met, then we planned a priori to test for superiority. If superiority was established for the primary effi cacy outcome, then we planned a priori to test the secondary effi cacy outcome for non-inferiority using a prespecifi ed margin in which the upper limit of the 95% CI for RR should not exceed 1·5, and if this occurred to then test for superiority Sponsor: Bristol-Myers Squibb and Pfi zer.
			Symptomatic venous thromboembolism or venous thromboembolism-related death	Apixaban: 7/1528(0.46%) Enoxaparin: 7/1529 (0.46%) RR : 1 (0.35 to 2.85) NT	
			All deep vein thrombosis	Apixaban: 142/971(14.6%) Enoxaparin: 243/997 (24.4%) NT	
			Symptomatic deep vein thrombosis	Apixaban: 3/1528(0.20%) Enoxaparin: 7/1529 (0.46%) NT	
			Proximal deep vein thrombosis, symptomatic or asymptomatic¶	Apixaban: 9/1192(0.76%) Enoxaparin: 26/1199 (2.17%) NT	
			Pulmonary embolism, fatal or non-fatal‡	Apixaban: 4/1528(0.26%) Enoxaparin: 0/1529 (0.00%) NT	
			Death	Apixaban: 2/1528(0.13%) Enoxaparin: 0/1529 (0.00%) NT	
			Safety (number of events)		

			Adjudicated major bleeding events* The definition of major bleeding was adapted from the criteria for bleeding in non-surgical patients of the International Society of Thrombosis and Haemostasis. Major bleeding was defined as acute clinically overt bleeding accompanied by one or more of the following: a decrease in blood haemoglobin concentration of 20 g/L or more during 24 h; transfusion of two or more units of packed red blood cells; critical site bleeding (including intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding); bleeding into the operated joint needing reoperation or intervention; intramuscular bleeding with compartment syndrome; or fatal bleeding.	Apixaban: 9/1501(0.6%) Enoxaparin: 14/1508 (0.9%) ARR : -0.33% (-0.95 to 0.29), NS p =0.3014	
			Adjudicated clinically relevant non-major bleeding included acute clinically overt episodes such as wound haematoma, bruising or ecchymosis, gastrointestinal bleeding, haemoptysis, haematuria, or epistaxis that did not meet criteria for major bleeding.	Apixaban: 44/1501(2.9%) Enoxaparin: 58/1508 (3.8%) ARR : -0.91% (-2.20 to 0.38) p =0.1668 (two sided)	
			Adjudicated major or clinically relevant non-major bleeding events	Apixaban: 53/1501(3.5%) Enoxaparin: 72/1508 (4.8%) ARR : -1.24% (-2.66 to -0.18) p =0.0881 (two sided)	

			Minor bleeding events Bleeding was regarded as minor if clinically overt but not adjudicated as major or clinically relevant nonmajor bleeding.	Apixaban: 51/1501(3.4%) Enoxaparin: 54/1508 (3.6%) NT	
			All bleeding events	Apixaban: 104/1501(6.9%) Enoxaparin: 126/1508 (8.4%) ARR : -1.39% (-3.29 to -0.51) p =0.1412 (two sisded)	
			AT more than three times ULN (treatment + follow-up)	Apixaban: 25/1501(2%) Enoxaparin: 23/1508 (2%) NT	
			Total serum bilirubin more than two times ULN (treatment + follow-up)	Apixaban: 15/1501(>1%) Enoxaparin: 8/1508 (>1%) NT	
			Number of patients with at least one serious adverse event. (treatment)	Apixaban: 72/1501(5%) Enoxaparin: 88/1508 (6%) NT	

Study details	n/Population	Comparison	Outcomes		Methodological
702_Lassen 2009 ADVANCE-1(115) Design: DB PG Non inferiority trial Setting: 129 sites in 14 countries Duration of follow-up: patients were followed for 60 days after anticoagulation therapy was stopped.	n= 3195 Mean age: 65y 62% women Previous VTE: DVT: 3.3% PE: 0.5% Current malignancy: NR Previous orthopaedic surgery: -22.5% (knee replacement) -5.1% (hip replacement) -4% (hip or knee fracture surgery) Recent trauma: NR Immobilized:NR <u>Inclusion</u> scheduled to undergo total knee replacement surgery for one or both knees, including revision of a previously inserted artificial joint.	2.5 mg of apixaban orally twice daily as well as an injection of placebo vs 30 mg of enoxaparin subcutaneously every 12 hours along with placebo tablets for 10-14 days	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 99.6% in safety analysis 71.6 % in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: no For primary efficacy analysis, were included patients who underwent randomization and who had an efficacy outcome that could be evaluated. - Efficacy outcomes were also analyzed according to a prespecified per-protocol definition; the results of this analysis are included in the Supplementary Appendix Power: unclear (event rates 55% of predicted rate) SELECTIVE REPORTING: no
			All VTE (asymptomatic and symptomatic DVT, nonfatal PE)and death from any cause (PO) The presence or absence of deep-vein thrombosis was assessed with the use of bilateral venography between day 10 and day 14. When deep-vein thrombosis was suspected on the basis of clinical information, ultrasonography or venography was used for confirmation. For suspected pulmonary embolism, the diagnosis was confirmed or ruled out with the use of ventilation–perfusion lung scanning, spiral computed tomography, or pulmonary angiography.	**Intended treatment period** Apixaban: 104/1157 (9.0%) Enoxaparin:100/1130(8.8%) RR : 1.02 (95%CI 0.78 to 1.32) ARR: 0.11 (95%CI -2.22 to 2.44) p=0.06 for non-inferiority (non-inferiority criterion not met)	
			Major VTE and death from any cause	**Intended treatment period** Apixaban: 26/1269 (2.1%) Enoxaparin: 20/1216(1.6%) RR : 1.25 (95% CI 0.70 to 2.23) ARR: 0.36 (95%CI -0.30 to 1.06) NS, p value not reported	
			Symptomatic VTE and VTE related death	**Intended treatment period** Apixaban: 19/1599(1.2%) Enoxaparin: 13/1596(0.8%) RR : 1.46 (95%CI 0.72 to 2.95) ARR: 0.38 (95%CI -0.30 to 1.06) NS, p value not reported	

	<u>Exclusion</u> Active bleeding or a contraindication to anticoagulant prophylaxis, or if they required ongoing anticoagulant or antiplatelet treatment. Additional exclusion criteria were uncontrolled hypertension, active hepatobiliary disease, clinically significant impairment of renal function, thrombocytopenia, anemia, allergy to heparin, and allergy to radiographic contrast dye or another contraindication to bilateral venography.		**All DVT**	**Intended treatment period** Apixaban: 89/1142(7.8%) Enoxaparin: 92/1122(8.2%) NT	Other important methodological remarks: -The study plan was based on the hypothesis that apixaban would be noninferior to enoxaparin with respect to the primary efficacy outcome, with the use of a prespecified noninferiority margin in which the upper limit of the 95% confidence interval for relative risk did not exceed 1.25 and the upper limit of the 95% confidence interval for the difference in risk did not exceed 5.6 percentage points. Both criteria had to be met to establish noninferiority. Authors also planned to test for superiority if apixaban met the prespecified criteria for noninferiority All P values reported for the noninferiority analysis of the primary outcome and its components are onesided, and all P values reported for bleeding are two-sided. Sponsor: Bristol-Myers Squibb and Pfizer
			Symptomatic DVT	**Intended treatment period** Apixaban: 3/1599(0.2%) Enoxaparin: 7/1596(0.4%) NT **Intended Follow-up period** Apixaban: 3/1562 (0.2%) Enoxaparin: 2/1554 (0.1%) NT	
			Proximal DVT	**Intended treatment period** Apixaban: 9/1254(0.2%) Enoxaparin: 11/1207(0.4%) **NT**	
			All pulmonary emboli	**Intended treatment period** Apixaban: 16/1599(1.0%) Enoxaparin: 7/1596(0.4%) **NT** **Intended Follow-up period** Apixaban: 3/1562 (0.2%) Enoxaparin: 2/1554 (0.1%) **NT**	
			Death	**Intended treatment period** Apixaban: 3/1599(0.2%) Enoxaparin: 3/1596 (0.2%) NT **Intended Follow-up period** Apixaban: 0 Enoxaparin: 3/1554 (0.2%) NT	

			Safety (n patients with events)		
			All bleeding events (PO)	**Intended treatment period** Apixaban: 85/1596 (5.3%) Enoxaparin: 108/1588 (6.8%) ARR: -1.52 (-3.18 to 0.13) P=0.08	
			Adjudicated major bleeding events Major bleeding was defined as acute, clinically overt bleeding accompanied by one or more of the following events: a decrease in the hemoglobin level of 2 g per deciliter or more within a 24-hour period; a transfusion of 2 or more units of packed red cells; bleeding at a critical site (i.e., intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding); bleeding into the operated joint, requiring an additional operation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding.	**Intended treatment period** Apixaban: 11/1596 (0.7%) Enoxaparin: 22/1588 (1.4%) ARR: -0.81 (-1.49 to 0.14) P=0.053	
			Adjudicated clinically relevant nonmajor bleeding events such bleeding included acute, clinically overt bleeding, such as wound hematoma, bruising or ecchymosis, gastrointestinal bleeding, hemoptysis, hematuria, or epistaxis that did	**Intended treatment period** Apixaban: 35/1596 (2.2%) Enoxaparin: 47/1588 (3.0%) ARR: -0.77 (-1.87 to 0.33) P=0.05	

			not meet the other criteria for major bleeding.		
			Adjudicated major or clinically relevant nonmajor bleeding events	**Intended treatment period** **Apixaban: 46/1596 (2.9%)** **Enoxaparin: 68/1588 (4.3%)** **ARR: -1.46 (-2.75 to 0.17)** **P=0.03** **SS in favour of apixaban**	
			Minor bleeding events Bleeding was defined as minor if it was clinically overt but did not meet the criteria for either major or clinically relevant nonmajor bleeding.	**Intended treatment period** Apixaban: 39/1596 (2.4%) Enoxaparin: 40/1588 (2.5%)	

6.3.6 Summary and conclusions. Apixaban versus enoxaparin in elective knee replacement

Apixaban 2.5 mg bid versus subcutaneous enoxaparin 30 mg bid or 40mg qd for the prevention of venous thromboembolism after total knee arthroplasty			
Bibliography: Lassen 2009 ADVANCE-1(115), Lassen 2010 ADVANCE-2(114)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	6252 (2 studies) 10-14d	**Lassen 2010** vs enoxaparin 40 mg 0.13% vs 0%, NT **Lassen 2009** vs enoxaparin 2x30mg 0.2% vs 0.2%, NT	Not applicable Not applicable
Composite of any DVT, non-fatal PE, or death from any cause (PO)	6252 10-14d	**Lassen 2010** vs enoxaparin 40 mg 15.06% vs 24.37% **RR=0.62 (95% CI 0.51 to 0.74), SS, one-sided p<0.0001 for non-inferiority and for superiority in favour of apixaban** **Lassen 2009** vs enoxaparin 2x30mg 9.0% vs 8.8% RR=1.02 (95% CI 0.78 to 1.32) ARR=0.11 (95% CI -2.22 to 2.44) **P=0.06 for non-inferiority (non-inferiority criterion not met)**	⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 65% in efficacy analysis and ITT not clear Consistency: NA Directness: -1 asymptomatic DVT in composite outcome Imprecision: OK ⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 72% in efficacy analysis and no ITT Consistency: NA Directness: -1 asymptomatic DVT in composite outcome Imprecision: OK
Major VTE (proximal symptomatic or asymptomatic DVT, nonfatal PE, or death related to VTE)	6252 (2 studies) 10-14d	**Lassen 2010** vs enoxaparin 40 mg 1.09% vs 2.17% **RR=0.50 (95% CI 0.26 to 0.97), SS, one-sided p for superiority=0.0186 in favour of apixaban** **Lassen 2009** vs enoxaparin 2x30mg not reported	⊕⊕⊕ ⊖ **MODERATE** Study quality: OK Consistency: NA Directness: -1 asymptomatic DVT in composite outcome Imprecision: OK Not applicable
Symptomatic DVT	6252 (2 studies) 10-14d	**Lassen 2010** vs enoxaparin 40 mg during treatment 0.20% vs 0.46%, NT **Lassen 2009**	Not applicable Not applicable

		<u>vs enoxaparin 2x30mg</u> 0.2% vs 0.4%, NT	
Major bleeding	6252 (2 studies) 10-14d	**<u>Lassen 2010</u>** <u>vs enoxaparin 40 mg</u> 0.6% vs 0.9% ARR=-0.33% (95% CI -0.95 to 0.29), NS, p=0.301 **<u>Lassen 2009</u>** <u>vs enoxaparin 2x30mg</u> 0.7% vs 1.4% ARR=-0.81 (-1.49 to 0.14), NS, p=0.053	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK ⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Clinically relevant non-major bleeding	6252 (2 studies) 10-14d	**<u>Lassen 2010</u>** <u>vs enoxaparin 40 mg</u> 2.9% vs 3.8% ARR=-0.91 (95% CI -2.20 to 0.38), NS, p=0.1668 **<u>Lassen 2009</u>** <u>vs enoxaparin 2x30mg</u> 2.2% vs 3.0% **ARR=-0.77 (95% CI -1.87 to 0.33), p=0.05**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK ⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

Two non-inferiority trials compared oral apixaban 2x2.5mg daily to subcutaneous enoxaparin 40 mg once daily (Lassen 2010) or 30 mg bid (Lassen 2009) for the prevention of venous thromboembolism (VTE) after total knee arthroplasty. Treatment duration varied between 10 and 14 days.

No conclusions can be drawn on the difference between apixaban 2x2.5mg and subcutaneous enoxaparin 40 mg daily in mortality rate or symptomatic DVT during treatment, because there was insufficient statistical information for this outcome.
GRADE: not applicable

No conclusion can be drawn for the difference between apixaban 2x2.5mg and subcutaneous enoxaparin 2x30mg daily in the rate of mortality or symptomatic DVT during treatment. There was insufficient statistical information for these outcomes.
GRADE: not applicable

Apixaban 2x2.5mg was superior to enoxaparin 40 mg for the composite outcome of any deep venous thrombosis (DVT), non-fatal pulmonary embolism (PE), or death from any cause during treatment.
GRADE: LOW quality of evidence

For the composite outcome of any deep venous thrombosis (DVT), non-fatal pulmonary embolism (PE), or death from any cause during treatment, the criterion for non-inferiority of apixaban 2x2.5mg compared to enoxaparin 2x30 mg was not met.
GRADE: LOW quality of evidence

Apixaban 2x2.5mg was superior to enoxaparin 40 mg for the composite outcome of proximal symptomatic or asymptomatic DVT, non-fatal PE, or death related to VTE.
GRADE: MODERATE quality of evidence

No conclusion can be drawn for the difference between apixaban 2x2.5mg and subcutaneous enoxaparin 2x30mg in the composite outcome of proximal symptomatic or asymptomatic DVT, non-fatal PE, or death related to VTE. The outcome was not reported.
GRADE: not applicable

There was no statistically significant difference between apixaban 2x2.5 mg daily and subcutaneous enoxaparin 40 mg daily in the rate of major bleedings during treatment.
GRADE: HIGH quality of evidence

There was no statistically significant difference between apixaban 2x2.5 mg daily and subcutaneous enoxaparin 2x30 mg daily in the rate of major bleedings during treatment.
GRADE: HIGH quality of evidence

There was no statistically significant difference between apixaban 2x2.5 mg daily and subcutaneous enoxaparin 40 mg daily in the rate of clinically relevant non-major bleedings during treatment.
GRADE: HIGH quality of evidence

There was a borderline statistically significant difference between apixaban 2x2.5 mg daily and subcutaneous enoxaparin 2x30 mg daily in the rate of clinically relevant non-major bleedings during treatment, in favour of apixaban.
GRADE: HIGH quality of evidence

6.3.7 Rivaroxaban versus enoxaparin in elective knee replacement

Study details	n/Population	Comparison	Outcomes		Methodological
756_Lassen 2008 RECORD 3(116) Design: RCT DB PG Non-inferiority study Setting: 147 centers in 19 countries Duration of follow-up: Treatment period between 10 and 14 days Then, patients were followed up for 30–35 days after the last dose The mean	n= 2531 Mean age: 67.6y Previous VTE(DVT/PE): 3.7% Current malignancy: NR Previous orthopaedic surgery: 28.9% Recent trauma: NR Immobilized:NR <u>Inclusion</u> Patients were eligible for the study if they were 18 years of age or older and were scheduled for total knee arthroplasty <u>Exclusion</u> We excluded patients with active bleeding or a high risk of bleeding that contraindicated the use of low-molecular-weight heparin and patients with any	Oral rivaroxaban, 10 mg once daily, beginning 6 to 8 hours after surgery vs subcutaneous enoxaparin, 40 mg once daily, beginning 12 hours before surgery. (double dummy)	Efficacy (n patients with events)		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 97.2% in safety analysis 67 % in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: No -modified intention-to-treat population (for superiority efficacy analysis): the modified intention-to-treat population included all patients who had undergone surgery, who took a study medication, and who had an adequate assessment for thromboembolism. -modified intention-to-treat
			Composite of any deep vein thrombosis, nonfatal pulmonary embolism, or death from any cause within 13 to 17 days after surgery (PO) (Deep-vein thrombosis was assessed between day 11 and day 15, or earlier if symptoms were present, by means of ascending, bilateral venography. In cases of suspected deep-vein thrombosis, ultrasonography or venography was used to confirm the diagnosis. In cases of suspected pulmonary embolism, ventilation–perfusion scintigraphy of the lung and chest radiography or spiral computed tomography were performed, or pulmonary angiography was performed.)	(P<0.001 for the noninferiority analysis (per-protocol analysis); Margin 4% points; data not shown) <u>Modified intention to treat population</u> **Rivaroxaban: 79/824 (9.6%)** **Enoxaparin: 166/878 (18.9%)** **ARR : -9.2% (-12.4 to -5.9)** **SS; p for superiority <0.001**
			Major venous thromboembolism (i.e., proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death related to venous thromboembolism) up to day 17 after surgery	<u>Modified intention to treat population for major VTE</u> **Rivaroxaban: 9/908 (1.0%)** **Enoxaparin: 24/925 (2.6%)** **ARR : -1.6% (-2.8 to -0.4)** **P for superiority =0.01**
			Death	**Up to day 17** <u>Modified intention to treat population (67% FU)</u> Rivaroxaban: 0/824 (0.0%)

duration of therapy was 11.9 days with rivaroxaban and 12.5 days with enoxaparin	contraindication to the use of enoxaparin or with any contraindication necessitating adjustment of its dose. Other exclusion criteria included conditions preventing bilateral venography, clinically significant liver disease, concomitant use of protease inhibitors of HIV or fibrinolytic agents, planned intermittent pneumatic compression, requirement of ongoing anticoagulant therapy, and pregnancy or breast-feeding.			Enoxaparin: 2/878 (0.2%) ARR : -0.2% (-0.8 to 0.2) P=0.23 <u>Safety population who underwent surgery</u> Rivaroxaban: 0/1201 (0.0%) Enoxaparin: 2/1217 (0.2%) ARR : -0.2% (-0.6 to 0.2) P=0.21 **During follow-up** <u>Safety population who underwent surgery</u> **Rivaroxaban: 0/1201 (0.0%)** **Enoxaparin: 4/1217 (0.3%)** **ARR : -0.3% (-0.8 to 0.0)** **P=0.05**	population for major VTE analysis: Patients were eligible for this analysis if only proximal veins were assessed by means of venography. -Safety population who underwent surgery: all patients who received at least one dose of a study medication and who also underwent surgery. non-inferiority margin: "Given the efficacy data from the phase 2 studies of rivaroxaban and the contemporary data on the comparison group, we found that a margin of 4 percentage points was acceptable"; "and an absolute margin of 1.5% for major venous thromboembolism" Power: adequate SELECTIVE REPORTING: no Sponsor: Bayer HealthCare and Johnson & Johnson
			Pulmonary embolism	**Up to day 17** <u>Modified intention to treat population</u> Rivaroxaban: 0/824 (0.0%) Enoxaparin: 4/878 (0.5%) ARR : -0.5% (-1.2 to 0.0) P=0.06 <u>Safety population who underwent surgery</u> **Rivaroxaban: 0/1201 (0.0%)** **Enoxaparin: 4/1217 (0.3%)** **ARR : -0.3% (-0.8 to 0.0)** **P=0.05**	
			Deep vein thrombosis	**Up to day 17**	

				<u>Modified intention to treat population</u> **Rivaroxaban: 79/824 (9.6%)** **Enoxaparin: 160/878 (18.2%)** **ARR : -8.4% (-11.7to -5.2)** **P<0.001**	Pharmaceutical Research & Development.
			Symptomatic venous thromboembolism (Symptomatic venous thromboembolism was defined as any symptomatic deep-vein thrombosis (proximal or distal) or symptomatic nonfatal or fatal pulmonary embolism)	**Up to day 17** <u>Safety population who underwent surgery</u> **Rivaroxaban: 8/1201 (0.7%)** **Enoxaparin: 24/1217 (2.0%)** **ARR : -1.3% (-2.2 to -0.4)** **P=0.005** **During follow-up** <u>Safety population who underwent surgery</u> Rivaroxaban: 5/1201 (0.4%) Enoxaparin: 3/1217 (0.2%) ARR : 0.2% (-0.3 to 0.6) P=0.44	
			Safety (n patients with events) (Safety population)		
			Major bleeding between intake of the first dose of study medication and 2 days after the last dose (Major bleeding was defined as bleeding that was fatal, that involved a critical organ, or that required reoperation or clinically overt bleeding outside the surgical site that was associated with a decrease in the Hb level of 2 g or more per deciliter or requiring infusion of 2 or more	**Up to day 17** Rivaroxaban: 7/1220(0.6%) Enoxaparin: 6/1239 (0.5%) P=0.77	

			units of blood.)		
			Any bleeding	**Up to day 17** Rivaroxaban: 60/1220(4.9%) Enoxaparin: 60/1239 (4.8%) P=0.93	
			Non major bleeding	**Up to day 17** Rivaroxaban: 53/1220(4.3%) Enoxaparin: 54/1239 (4.4%) NT	
			Clinically relevant nonmajor bleeding	**Up to day 17** Rivaroxaban: 33/1220(2.7%) Enoxaparin: 28/1239 (2.3%) NT	
			Any adverse event	**Up to day 17** Rivaroxaban: 776/1220(63.6%) Enoxaparin: 844/1239 (68.1%) NT	
			Cardiovascular adverse event	**Up to day 17** Rivaroxaban: 4/1220(0.3%) Enoxaparin: 3/1239 (0.2%) NT **During follow-up** Rivaroxaban: 0/1220(0.0%) Enoxaparin: 6/1239 (0.5%) NT	

Study details	n/Population	Comparison	Outcomes		Methodological
Ref 714 Turpie2009 RECORD 4(117) Design: non-inferiority (and superiority) RCT DB PG Setting: 131 centres in 12 countries Duration of follow-up: Treatment period between 10 and 14 days Then, patients were followed up for 30–35 days after the last dose	n= 3148 Mean age: 64 Previous VTE(DVT/PE): 2.2% Current malignancy: NR Previous orthopaedic surgery: 32% Recent trauma: NR Immobilized:NR <u>Inclusion</u> Patients were eligible for the study if they were aged 18 years or older and were scheduled for total knee arthroplasty <u>Exclusion</u> Patients were excluded if they had active bleeding or a high risk of bleeding, or any disorder contraindicating the use of enoxaparin or that might necessitate enoxaparin dose adjustment. Other	Rivaroxaban 10 mg orally daily and enoxaparin-matching placebo injections vs enoxaparin 30 mg subcutaneously every 12h and rivaroxaban-matching placebo tablets for 10-14 days	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 96.3 % in safety analysis 55.3 % in efficacy analysis for primary outcome Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: No Efficacy was assessed as non-inferiority of rivaroxaban compared with enoxaparin in the per-protocol population (absolute non-inferiority limit –4%); if non-inferiority was shown, authors assessed whether rivaroxaban had superior effi cacy in the modified intention-to-treat population (<u>Modified ITT population:</u> included all patients who had taken at least one dose of study medication (<u>safety</u>
			Composite of any deep-vein thrombosis, non-fatal pulmonary embolism, or death from any cause up to day 17 after surgery. (PO) Deep-vein thrombosis was assessed between days 11 and 15 by systematic, ascending, bilateral veno graphy with a standardized technique.Suspected symptom matic deep vein thrombosis was assessed by ultrasound and, if positive, was to be confi rmed with venography. Susp ected pulmonary embolism was confi rmed by pulmonary angiography, by ventilation-perfusion lung scintigraphy with chest radiography, or by contrast-enhanced spiral CT	<u>Treatment period</u> **<u>Per protocol population (55% FU)</u>** **Rivaroxaban: 58/864 (6.7%)** **Enoxaparin: 82/878 (9.3%)** **ARR : -2.71% (-5.25 to -0.17)** **SS; p for non -inferiority <0.0001 (non-inferiority limit :–4%)** **SS; p for superiority =0.0362** **<u>Modified intention to treat population (61% FU)</u>** **Rivaroxaban: 67/965(6.9%)** **Enoxaparin: 97/959 (10.1%)** **ARR : -3.19% (-5.67 to -0.71)** **SS; p for superiority=0.0118 in favour of rivaroxaban**
			Major venous thromboembolism (ie, proximal deep-vein thrombosis, non-fatal pulmonary embolism, or death related to venous thromboembolism).	<u>Treatment period</u> <u>Per protocol population (68% FU)</u> Rivaroxaban: 111/1011 (1.1%) Enoxaparin: 13/1122 (1.5%) ARR : -0.37% (-1.34 to 0.60) **SS; p for non -inferiority <0.0001** (non-inferiority limit –1·5%) NS; p for superiority=0.4556 <u>Modified intention to treat population (71% FU)</u>	

	exclusion criteria included disorders preventing bilateral venography,clinically significant liver disease, severe renal impairment (creatinine clearance <30 mL per min), concomitant use of drugs that strongly inhibit cytochrome P450, such as protease inhibitors or ketoconazole, pregnancy or breastfeeding, planned intermittent pneumatic compression, or the requirement for ongoing anticoagulant therapy.			Rivaroxaban: 13/1122(1.2%) Enoxaparin: 22/1112 (2.0%) ARR : -0.80% (-1.82 to 0.22) NS; p for superiority =0.1237	<u>population</u>), had also undergone the planned surgery, and had an adequate assessment for thromboembolism. These patients were included <u>in the per-protocol</u> population if, in addition, adequate assessment of thromboembolism was done no later than 36 h (if positive) or 72 h (if negative) after the last dose of study drug and they had no major protocol deviations.) Power: unclear (changed parameters during study, but higher number of unassessable venograms and lower than expected event rates) SELECTIVE REPORTING: unclear Other important methodological remarks : -During the study, sample size
			Death	<u>Treatment period</u> Rivaroxaban: 2/1526(0.1%) Enoxaparin: 3/1508 (0.2%) ARR : -0.07% (-0.46 to 0.30) NS; p =0.7449 <u>During follow-up</u> Rivaroxaban: 4/1526(0.3%) Enoxaparin: 3/1508 (0.2%) ARR : -0.06% (-0.35 to 0.50) NS; p =0.8044	
			Non-fatal pulmonary embolism	<u>Treatment period</u> Rivaroxaban: 4/1526(0.3%) Enoxaparin: 8/1508 (0.5%) ARR : -0.27% (-0.80 to 0.21) NS; p =0.2531	
			Pulmonary embolism	<u>Treatment period</u> Rivaroxaban: 5/1526(0.3%) Enoxaparin: 8/1508 (0.5%) ARR : -0.20% (-0.80 to 0.21) NS; p =0.5250	

			Symptomatic venous thromboembolism	Treatment period Rivaroxaban: 11/1526(0.7%) Enoxaparin: 18/1508 (1.2%) ARR : -0.47% (-1.16 to 0.23) NS; p =0.1868 During follow-up Rivaroxaban: 3/1526(0.2%) Enoxaparin: 3/1508 (0.2%) ARR : 0.00% (-0.32 to 0.32) NS; p =0.9979	was increased from the planned 2300 participants, primarily because preliminary blinded study data indicated a lower overall blinded event rate for the primary effi cacy endpoint and a higher number of venograms inadequate for assessment than originally assumed. The authors state: 'The low incidence of major bleeding events in this study compared with other similar studies could, in part, be attributed to the definition of bleeding used. In this study, major bleeding did not include bleeding leading to treatment cessation or surgical-site bleeding events unless they were fatal or required reoperation.' Sponsor: Bayer Schering Pharma AG, Johnson & Johnson Pharmaceutical Research & Development.
			Safety (number of patients)		
			Major bleeding Major bleeding was defi ned as clinically overt bleeding that was fatal, occurred in a critical organ (eg, retroperitoneal, intracranial, intraocular, or intraspinal), necessitated operation, was outside of the surgical site and associated with a fall in haemoglobin of 2 g/dL or more (calculated from the postoperative haemoglobin baseline value before the event), or required an infusion of two or more units of blood.	Treatment period Rivaroxaban: 10/1526(0.7%) Enoxaparin: 4/1508 (0.3%) NS; p =0.1096	
			Clinically relevant non-major bleeding Clinically relevant non-major bleeding, was defi ned as multiple-source bleeding, unexpected haematoma (>25 cm^2), excessive wound haematoma, nose bleeding	Treatment period Rivaroxaban: 39/1526(2.6%) Enoxaparin: 30/1508 (2.0%) NT	

			(>5 min), gingival bleeding (>5 min), macroscopic haematuria, rectal bleeding, coughing or vomiting blood, vaginal bleeding, blood in semen, intra-articular bleeding with trauma, or surgical-site bleeding		
			Non-major bleeding	<u>Treatment period</u> Rivaroxaban: 155/1526(10.2%) Enoxaparin: 138/1508 (9.2%) NT	
			Any bleeding	<u>Treatment period</u> Rivaroxaban: 160/1526(10.5%) Enoxaparin: 142/1508 (9.4%) NS; p =0.3287	
			Major bleeding plus clinically relevant non-major bleeding	<u>Treatment period</u> Rivaroxaban: 46/1526 (3%) Enoxaparin: 34/1508 (2.3%) NS; p =0.1790	

6.3.8 Summary and conclusions. Rivaroxaban versus enoxaparin in elective knee replacement

Rivaroxaban 10 mg/d versus enoxaparin 30 mg bid or 40mg qd for the prevention of venous thromboembolism after total knee arthroplasty			
Bibliography: Turpie2009 RECORD 4(117), Lassen 2008 RECORD 3(116)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	5679 (2 studies) up to day 17 + 30-35d follow-up after treatment	**Turpie 2009** vs enoxaparin 2x30 mg during treatment: 0.3% vs 0.2% ARR=-0.06% (95% CI -0.35 to 0.50), NS, p=0.745 **Lassen 2008** vs enoxaparin 40mg up to day 17: 0% vs 0.2% ARR=-0.2% (95% CI -0.6 to 0.2), NS, p=0.21 During follow-up after treatment: 0% vs 0.3% **ARR=-0.3% (95% CI -0.8 to 0), p=0.05**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: NA Directness: OK Imprecision: OK ⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: NA Directness: OK Imprecision: OK
Composite of any DVT, non-fatal PE, or death from any cause (PO)	5679 (2 studies) up to day 17	**Turpie 2009** vs enoxaparin 2x30 mg up to day 17: 6.9% vs 10.1% **ARR=-3.19% (95% CI -5.67 to -0.71), SS, p for superiority= 0.012 in favour of rivaroxaban** **Lassen 2008** vs enoxaparin 40mg up to day 17: 9.6% vs 18.9% **ARR=-9.2% (-12.4 to -5.9), SS, p<0.001 for noninferiority and p<0.001 for superiority in favour of rivaroxaban**	⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 55% in efficacy analysis and no ITT Consistency: NA Directness: -1 asymptomatic DVT in composite outcome Imprecision: OK ⊕⊕⊖⊖ **LOW** Study quality: -1 noninferiority trial, 67% in modified ITT analysis Consistency: NA Directness: -1 asymptomatic DVT in composite outcome Imprecision: OK
Major VTE (proximal DVT, nonfatal PE, or death related to VTE)	5679 (2 studies) up to day 17	**Turpie 2009** vs enoxaparin 2x30 mg during treatment: 1.2% vs 2.0% ARR=-0.80 (95% CI -1.82 to 2.0), NS, p for superiority=0.124 **Lassen 2008** vs enoxaparin 40mg up to day 17: 1% vs 2.6% **ARR=-1.6% (-2.8 to -0.4), SS, p**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 noninferiority trial, 71% in modified ITT analysis Consistency: NA Directness: OK Imprecision: OK ⊕⊕⊕⊖ **MODERATE** Study quality: -1 noninferiority trial, 67% in modified ITT analysis Consistency: NA

		for superiority=0.01 in favour of rivaroxaban	Directness: OK Imprecision: OK
Symptomatic VTE	5679 (2 studies) up to day 17 + follow-up after treatment up to 35d	**Turpie 2009** vs enoxaparin 2x30 mg during treatment: 0.7% vs 1.2% ARR=-0.47% (95% CI -1.16 to 0.23), NS, p=0.187 during follow-up after treatment: 0.2% vs 0.2%, NS **Lassen 2008** vs enoxaparin 40mg Up to day 17: 0.7% vs 2.0% **ARR=-1.3% (95% CI -2.2 to -0.4), SS, p=0.005 in favour of rivaroxaban** During follow-up after treatment: 0.4% vs 0.2% ARR=0.2% (95% CI -0.3 to 0.6), NS, p=0.44	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK ⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Major bleeding	5679 (2 studies) up to day 17	**Turpie 2009** vs enoxaparin 2x30 mg 0.7% vs 0.3% NS, p=0.11 **Lassen 2008** vs enoxaparin 40mg 0.6% vs 0.5% NS, p=0.77	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK ⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Clinically relevant non-major bleeding	5679 (2 studies) up to day 17	**Turpie 2009** vs enoxaparin 2x30 mg 2.6% vs. 2.0%, NS **Lassen 2008** vs enoxaparin 40mg 2.7% vs 2.3%, NT	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK ⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK

Two non-inferiority trials compared oral rivaroxaban 10mg daily to subcutaneous enoxaparin 2x30mg (Turpie 2009) or 40mg once daily (Lassen 2008) for the prevention of venous thromboembolism (VTE) after total knee arthroplasty. Treatment duration varied between 10 and 14 days; all outcomes except one were reported for this period only. The rate of symptomatic venous thromboembolism was also reported during follow-up in both studies. One study (Lassen 2008) also reported the mortality rate in the follow-up period. In the study comparing rivaroxaban with enoxaparin 2x30mg, only 55% of patients were included in the noninferiority analysis (per protocol) for the primary

outcome; in our table the results of the superiority analysis are reported (61% of patients included in the modified intention to treat analysis).

There was no statistically significant difference in mortality rate between rivaroxaban 10 mg daily and subcutaneous enoxaparin 2x30 mg daily during treatment.
GRADE: HIGH quality of evidence

There was no statistically significant difference in mortality rate between rivaroxaban 10 mg daily and subcutaneous enoxaparin 40 mg daily during treatment.
GRADE: HIGH quality of evidence

There was a borderline statistically significant difference in mortality rate between rivaroxaban 10 mg daily and subcutaneous enoxaparin 40 mg daily during follow-up.
GRADE: HIGH quality of evidence

Rivaroxaban 10 mg daily was superior to subcutaneous enoxaparin 2x30 mg daily for the composite primary outcome of any DVT, non-fatal PE, or death from any cause during treatment.
GRADE: LOW quality of evidence

Rivaroxaban 10 mg daily was superior to subcutaneous enoxaparin 40 mg daily for the composite primary outcome of any DVT, non-fatal PE, or death from any cause during treatment.
GRADE: LOW quality of evidence

There was no statistically significant difference between rivaroxaban 10 mg daily and subcutaneous enoxaparin 2x30 mg daily for the composite outcome of major VTE (proximal DVT, nonfatal PE, or death related to VTE) during treatment.
GRADE: MODERATE quality of evidence

Rivaroxaban 10 mg daily was superior to subcutaneous enoxaparin 40 mg daily for the composite outcome of major VTE (proximal DVT, nonfatal PE, or death related to VTE) during treatment.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in the rate of symptomatic VTE between rivaroxaban 10 mg daily and subcutaneous enoxaparin 2x30 mg daily during treatment or follow-up.
GRADE: HIGH quality of evidence

Rivaroxaban 10 mg daily was superior to subcutaneous enoxaparin 40 mg daily in the rate of symptomatic VTE during treatment but not during follow-up.
GRADE: HIGH quality of evidence

There was no statistically significant difference between rivaroxaban 10 mg daily and subcutaneous enoxaparin 2x30 mg daily for the rate of major bleeding during treatment.
GRADE: HIGH quality of evidence

There was no statistically significant difference between rivaroxaban 10 mg daily and subcutaneous enoxaparin 40 mg daily for the rate of major bleeding during treatment.
GRADE: HIGH quality of evidence

There was no statistically significant difference between rivaroxaban 10 mg daily and subcutaneous enoxaparin 2x30 mg daily for the rate of clinically relevant minor bleeding during treatment.
GRADE: HIGH quality of evidence

No conclusions can be drawn on the difference between rivaroxaban and enoxaparin 40mg for the rate of clinically relevant minor bleeding, because of insufficient statistical information.
GRADE: not applicable

6.4 Pharmacological treatment plus graduated compression stockings versus graduated compression stockings for thromboprophylaxis in elective knee replacement

6.4.1 Enoxaparin + graduated compression stockings versus graduated compression stockings in elective knee replacement

Ref	Comparison	N/n	Outcomes	Result**
ref* NICE 2010(54) Design: SR + MA Search date: dec 2008	LMWH (enoxaparin: group 1 20 mg, group 2 40mg, group 3 2x20mg) + GCS vs GCS (group 4: placebo injection)	N= 1 n= 396 (Fuji 2008)	**DVT**, **asymptomatic or symptomatic** (screened for by: Doppler ultrasound at 14 days)	**Enoxaparin 20mg +GCS:** 34/78 (43.6%) **Enoxaparin 40mg+GCS :** 26/74 (35.1%) **Enoxaparin 2x20mg+GCS:** 25/84 (30.0%) **GCS:** 48/79 (60.8%) **p value:** All groups receiving LMWH (gp 1,2 & 3) had significantly less DVT than the placebo group (gp 4). Enoxaparin 20mg +GCS vs. GCS = 0.038 Enoxaparin 40mg +GCS vs. GCS = 0.002 Enoxaparin 2x20mg +GCS vs. GCS = <0.001 No other significant differences between groups were found.
		N= 1 n=396 (Fuji 2008)	**Symptomatic pulmonary Embolism** (description: ventilation perfusion lung scans or pulmonary angiography at 90 days)	**Enoxaparin 20mg +GCS: 1/78 (1.2%)** **Enoxaparin 40mg +GCS: 1/74 (1.4%)** **Enoxaparin 2x20mg +GCS: 0/84** **GCS: 1/79 (1.2%)** **p value: Not significant**
		N= 1 n= 396 (Fuji 2008)	**Major bleeding** (description: bleeding episode that was retroperitoneal, intracranial, or intraocular o if it was associated with: death; transfusion of ≥2 units of packed red blood cells or whole blood (except autologous); a reduction of ≥2 g/d; or a serious or life threatening clinical events that required medical intervention.)	**Enoxaparin 20mg +GCS:** 0/89 **Enoxaparin 40mg +GCS:** 1/91 (1.1%) **Enoxaparin 2x20mg +GCS:** 3/95 (3.2%) **GCS:** 4/89 (4.5%) **p value:** Not significant
		N= 1 n= 396 (Fuji 2008)	**Minor bleeding** (description: at least one of the following features: epistaxis lasting >5 minutes or requiring intervention; ecchymosis or	**Enoxaparin 20mg +GCS:** 5/89 (5.6%) **Enoxaparin 40mg +GCS:** 6/91 (6.6%) **Enoxaparin 2x20mg +GCS:** 10/95 (10.5%)

			hematoma with a maximum size of >5 cm; haematuria not associated with urinary catheter trauma; gastrointestinal haemorrhage not related to intubation or a nasogastric tube; wound haematoma or haemorrhagic wound complications not associated with major haemorrhage; or subconjunctival haemorrhage requiring cessation of treatment	**GCS:** 4/89 (4.5%) **p value:** Not significant

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Note: NICE 2010 found another study with ardeparin, that was not included in our report.

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Fuji 2008(91) Country of study: Japan Setting: Department of Orthopaedic Surgery Study design: RCT	396	Patient group: Study 1: **Total knee replacement (TKR) (n=396)** Study 2: Total hip replacement (THR) Inclusion criteria: Patients aged ≥ 20 years (no upper age limit was applied) undergoing elective primary THR or TKR Age (mean): 69	Duration of follow-up: 90 days	**Study 1 (TKR)** **Group 1 (n= 93)** LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 20mg subcutaneous injection **Group 2(n= 94)** LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 40 mg subcutaneous injection **Group 3(n=99)** LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Twice daily 20mg subcutaneous injections **Group 4(n=96)** Placebo (saline) Start time: 24-36 hrs after surgery Duration: 14 days Subcutaneous injections (no frequency stated)	DVT, asymptomatic or symptomatic (screened for by: Doppler ultrasound at 14 days) Symptomatic pulmonary embolism (description: ventilation perfusion lung scans or pulmonary angiography at 90 days) Thigh DVT description: screened for by: Doppler ultrasound at 14 days Major bleeding: description: bleeding episode that was retroperitoneal, intracranial, or intraocular o if it was associated with: death; transfusion of ≥2 units of packed red blood cells or whole blood (except autologous); a reduction of ≥2 g/d; or a serious or life threatening clinical events that required medical intervention. Minor bleeding: description: at least one of the	ALLOCATION CONC: unclear (“*No details provided on allocation concealment”*) RANDO: unclear (“*Method of randomization not given”*) BLINDING : unclear *(“Study reports that it was blinded but no information provided and some of the injection regimens were once daily whilst others were twice daily* Outcomes not reported: All cause mortality, fatal bleeding, fatal PE, heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay FOLLOW-UP: drop-out 8.1% (32) FOLLOW-UP: 93% in safety analysis 77% in efficacy analysis ITT: no (‘modified’ ITT) Evidence level: 1+

				<u>Additional noncomparative prophylaxis:</u> More than 50% of patients received elastic stockings /bandages for part of the study. No other prophylaxis was used.	following features: epistaxis lasting >5 minutes or requiring intervention; ecchymosis or hematoma with a maximum size of >5 cm; haematuria not associated with urinary catheter trauma; gastrointestinal haemorrhage not related to intubation or a nasogastric tube; wound haematoma or haemorrhagic wound complications not associated with major haemorrhage; or subconjunctival haemorrhage requiring cessation of medication	Funding: Sanofi-Aventis

6.4.2 Summary and conclusions. Enoxaparin + graduated compression stockings versus graduated compression stockings in elective knee replacement

Enoxaparin 40mg qd + GCS versus GCS for thromboprophylaxis in total knee replacement surgery			
Bibliography: From meta-analysis NICE 2010(54), we selected 1 RCT: Fuji 2008(91)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
DVT (symptomatic or asymptomatic)	190 (1 study) treatment 14d FU 90d	35.1% vs 60.8% p=0.002 (no RR or CI reported)	⊕⊕⊕⊖ **MODERATE** Study quality:-1 no ITT and 77% in efficacy analysis Consistency:NA Directness:OK Imprecision:OK
Pulmonary embolism	190 (1 study) treatment 14d FU 90d	1.4% vs 1.2% NS (no RR or CI reported)	⊕⊕⊖⊖ **LOW** Study quality:-1 no ITT and 77% in efficacy analysis Consistency:NA Directness:OK Imprecision:-1 low rates
Major bleeding	190 (1 study) treatment 14d FU 90d	1.1% vs 4.5% NS (no RR or CI reported)	⊕⊕⊖⊖ **LOW** Study quality:-no ITT and 93% in analysis, only 1 trial Consistency:NA Directness:OK Imprecision:-1 low rates
Minor bleeding	190 (1 study) treatment 14d FU 90d	6.6% vs 4.5% NS (no RR or CI reported)	⊕⊕⊖⊖ **LOW** Study quality:-1 no ITT and 93% in efficacy analysis, only 1 trial Consistency:NA Directness:OK Imprecision:-1 low rates

We selected 1 RCT from the systematic review by NICE 2010, that compared LMWH + GCS to GCS in patients undergoing total knee replacement. This was a trial in Japanese patients, comparing 4 treatments (enoxaparin 20mg qd, enoxaparin 40mg qd or enoxaparin 20mg bid, all + GCS, versus GCS +placebo injection). We only report the comparison of enoxaparin 40mg qd + GCS to GCS.

The patients in this trial were screened for the outcome DVT using imaging techniques, so the reported rate of DVT consists of both symptomatic and asymptomatic DVT.
There is a lower rate of DVT with enoxaparin 40mg +GCS compared to GCS only.
GRADE: MODERATE quality of evidence

There is no statistically significant difference in the rates of pulmonary embolism.
GRADE: LOW quality of evidence

There is no statistically significant difference in the rates of major and minor bleeding.
GRADE: LOW quality of evidence

6.5 Duration of thromboprophylaxis in elective knee replacement

6.5.1 Post discharge LMWH or UFH versus no thromboprophylaxis in elective knee replacement

Ref	Comparison	N/n	Outcomes	Result
Sobieraj 2012(97) Design: SR Search date: dec 2008	Post discharge LMWH vs control	N= 1 n= 438 (Comp 2001)	**DVT (asymptomatic and symptomatic)**	LMWH: 38/217 (17.5%) Control: 46/221 (20.8%) RR=0.84 (95%CI 0.57 to 1.24) NS
		N= 1 n= 438 (Comp 2001)	**Pulmonary embolism**	LMWH: 0/217 (0.0%) Control: 2/221 (0.9%) OR: 0.14 (95%CI 0.01 to 2.2) NS
		N= 1 n= 438 (Comp 2001)	**Major bleeding**	LMWH: 0/217 (0.0%) Control: 1/221 (0.05%) OR: 0.14 (95%CI 0.003–6.95) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Comp 2001(98) PG RCT	438 (total knee replacement)	Patients with elective knee replacement Mean age: 64y Previous VTE: patients did not have clinical evidence of chronic or acute VTE in the past 12 months Cancer: NR	Duration of prophylaxis: in-hospital 8 days out-of hospital 19 days Duration of follow-up: 90d	Prolonged: In-hospital initiation of enoxaparin (30 mg twice daily during the in-hospital treatment period and starting 12-24h after surgery, then 40mg once daily during the out-of-hospital study interval) + postoperative initiation of extended therapy with enoxaparin Vs.	Patients were examined for clinical evidence of PE. At the end of the double-blind phase, all patients underwent bilateral venography and ultrasonography.	ALLOCATION CONC: adequate RANDO: adequate BLINDING : unclear FOLLOW-UP: 100%FU ITT: yes FUNDING: NR (another group of patients with total hip replacement

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
				Standard: In-hospital initiation of enoxaparin (30 mg twice daily, during the in-hospital treatment period and starting 12-24h after surgery, then 40mg once daily during the out-of-hospital study interval) + postoperative initiation of extended therapy with placebo		also included in this study, but not reported here)

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: 634 Barrellier 2010(118) Design: non-inferiority, RCT, OL, PG Setting: In a network of 17 public and private hospital centers in France Duration of follow-up: 3 months	n= 857 Mean age: 70 y <u>Inclusion</u> 45 years of age or older and scheduled for a first unilateral TKA. At Day 7±2, subjects were screened by ultrasonography for asymptomatic DVT and randomized. <u>Exclusion</u> Patients with asymptomatic proximal DVT not randomized and treated with anticoagulants. Patients also not randomized if they had one of the following events during the first treatment period: confirmed symptomatic DVT or PE, major bleeding, or confirmed HIT. Other exclusion criteria: History of confirmed symptomatic VTE; Stroke or MI <1 month; Current active bleeding; GI bleeding or hemorrhagic stroke < six months; major surgery <1 month; Active cancer; Renal impairment (creatinine	Short (10 days +/-2) vs Extended (35 days +/- 5) thromboprophylaxis Investigators' choice: unfractionated heparin (5000 U, two to three times per day), 4000 IU enoxaparin, 5000 IU dalteparin, 4500 IU tinzaparin, body-weight adjusted nadroparin, or 2.5 mg fondaparinux Graduated compression stockings were used in 62.6% (n=537).	Efficacy		RANDO: Adequate *(stratification by center and by the presence or absence of distal deep-vein thrombosis on whole-leg ultrasonography at Day 7±2)* ALLOCATION CONC: adequate BLINDING : Participants: No Personnel: No Assessors: Yes FOLLOW-UP: Lost-to follow-up: 2.3% Drop-out and Exclusions: 6.9% • Described: yes • Balanced across groups: yes Patients not treated with assigned treatment were more frequent in the short thromboprophylaxis group because investigators were reticent to stop prophylaxis in some patients who had been randomized in this group. ITT: No (analysis of all non-excluded patients per group) Per protocol: no Power: unclear
			Composite of proximal deep-vein thrombosis, any symptomatic deep-vein thrombosis, non-fatal symptomatic pulmonary embolism, major bleeding, heparin-induced thrombocytopenia, or all-cause death (PO) (confirmed by bilateral whole leg ultrasonography on Day 35±5,ventilation-perfusion pulmonary scintigraphy or spiral CT) Patients were systematically examined for deep-vein thrombosis by bilateral wholeleg ultrasonography on Day 35±5, or earlier if thrombosiswas clinically suspected.	Short: 17/420 (4.0%) Extended: 10/422 (2.4%) Absolute difference: 1.7% (90% CI -0.3 to 3.7) NS non-inferiority was not demonstrated
			Ultrasonographic (extension or new onset) distal deep-vein thrombosis at Day 35±5	Short: 62/420 (14.8%) Extended: 19/422 (4.5%) Absolute difference: 10.3% (90%CI 0.70 to 1.36) P<0.001 **SS in favour of extended treatment**	
			Safety		
			Major bleeding defined as fatal bleeding,	"The rate of major bleeding was less	

	clearance <30 mL/min); Hepatic impairment; A contraindication to anticoagulants; hypersensitivity to heparin; Patients who required therapeutic anticoagulation		bleeding that was intracranial, intraocular, retroperitoneal, gastrointestinal, or intra-articular, bleeding leading to re-operation, or bleeding requiring cessation of anticoagulant treatment	than 1% and similar in the two study groups."	Non-inferiority margin "On the basis of published data we hypothesized that the primary outcome rate in patients randomized to extended thromboprophylaxis would be 4%. Proposing a non-inferiority margin of 3% for the upper limit of the absolute difference in primary outcome rates" Sponsor: Caen University Hospital - French Health Ministry (Programme Hospitalier de Recherche Clinique).

6.5.2 Summary and conclusions. Post discharge LMWH or UFH versus no thromboprophylaxis in elective knee replacement

LMWH or unfractionated heparin post discharge (extended treatment) versus control (short treatment) after in-hospital thromboprophylaxis in total knee replacement			
Bibliography: systematic review Sobieraj 2012(97) selected 1 RCT: Comp 2001(98); 1 more recent RCT Barrellier 2010(118)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Composite of proximal and symptomatic DVT, non-fatal symptomatic PE, major bleeding, HIT or all-cause death	n= 857 (1 study) 35+/-5 days	Barrellier 2010 (LMWH or UFH) Short 4.0% vs Extended 2.4% ARD: 1.7% (90% CI -0.3 to 3.7) NS non-inferiority of short treatment was not demonstrated	⊕⊕⊖⊖ **LOW** Study quality: -1, non-inferiority and no ITT or PP analysis Consistency: NA Directness: -1, composite endpoint Imprecision: OK
DVT (asymptomatic and symptomatic)	n=1295 (2 studies) treat. 27d FU 3m 35+/-5d	Comp 2001 (LMWH) Extended 17.5% vs Short 20.8% RR=0.84 (95%CI 0.57 to 1.24) NS Barrellier 2010: Short 14.8% vs Extended 4.5% ARD: 10.3% (90%CI 0.70 to 1.36) **SS in favour of extended treatment**	⊕⊕⊕⊖ **MODERATE** Study quality: -1, non-inferiority, different randomization methods Consistency: OK Directness: OK Imprecision: OK
PE	n= 438 (1 study) treat. 27d FU 3m	Comp 2001 Extended 0 vs short (0.9%) OR: 0.14 (95%CI 0.01 to 2.2) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 wide CI
Major bleeding	n=1295 (2 studies) FU 3m	Comp 2001 Extended: 0 vs short (0.05%) OR: 0.14 (95%CI 0.003–6.95) NS Barrellier 2010: "The rate of major bleeding was less than 1% and similar in the two study groups."	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 wide CI

We selected 1 RCT (Comp 2001)from a systematic review (Sobieraj 2012) and 1 recent non-inferiority trial (Barrelier 2010) that compared extended duration LMWH or UFH (post discharge) to standard duration treatment (in-hospital thromboprophylaxis) in patients who had total knee replacement.

Both trials screened the patients for the outcome DVT at some point after surgery. The reported rate of DVT consists therefore of both symptomatic and asymptomatic DVT.

In one trial (Barrellier 2010) there was no statistically significant difference between both thromboprophylaxis regimens for the composite endpoint of proximal and symptomatic DVT, non-fatal symptomatic PE, major bleeding, heparin-induced thrombocytopenia or all-cause death; non-inferiority of the short treatment was not demonstrated.
GRADE: LOW quality of evidence

The larger trial (Barrelier 2010) found a statistically significant difference in deep vein thrombosis between the two treatment groups in favour of the extended LMWH/unfractionated heparin treatment. In the smaller trial (Comp 2001) this difference was not statistically significant
GRADE: MODERATE quality of evidence

No statistically significant difference in pulmonary embolism was observed between different treatment groups, but power was probably inadequate to detect a difference.
GRADE: MODERATE quality of evidence

Rates of major bleeding were low. The difference between treatment groups was not statistically significant.
GRADE: MODERATE quality of evidence

6.6 Meta-analyses comparing new anticoagulants to enoxaparin in hip or knee replacement

A large number of meta-analyses are being published, comparing newer anticoagulants to other therapies in the prevention of VTE. Methodological problems in these publications are the pooling of heterogenous trials: RCTs with different indications for thromboprophylaxis are pooled, different interventions or comparators are pooled, as are different treatment durations or different dosages. Included trials are mostly non-inferiority trials. Because of these methodological shortcomings, we do not report these in detail.
We will briefly report on 5 meta-analyses of recent date, that are based on an adequate systematic search, but still have a lot of these methodological shortcomings. The conclusions are:

- In hip or knee replacement surgery, there is no statistically significant difference between dabigatran and enoxaparin for (symptomatic) VTE and bleeding according to 3 meta-analyses.((119-121).
- In hip or knee replacement surgery, rivaroxaban is superior to enoxaparin in the prevention of symptomatic VTE according to 1 meta-analysis(119), and superior in the prevention of all VTE in 2 meta-analyses(121, 122). 2 meta-analyses(120, 123) found rivaroxaban to be superior to enoxaparin in the prevention of DVT.
  Most meta-analyses report a higher risk of certain bleeding outcomes with rivaroxaban (clinically relevant bleeding(119), clinically relevant+major bleeding(123), major bleeding(120)), while others do not find a significant difference(121, 122).
- In hip or knee replacement surgery, apixaban has a similar risk of symptomatic VTE compared to enoxaparin, and a lower risk of clinically relevant bleeding according to 1 meta-analysis(119). Another meta-analysis(123) finds a lower risk of DVT with apixaban, as well as and a lower risk of all bleeding events, when compared to enoxaparin.

Quality of evidence from these meta-analyses should be considered as low to very low.

7 Evidence tables and conclusions: Thromboprophylaxis in minor orthopedic surgery or plaster cast

7.1 Thromboprophylaxis in knee arthroscopy

7.1.1 LMWH versus no thromboprophylaxis in knee arthroscopy

Ref	Comparison	N/n	Outcomes	Result**
741 Ramos 2008(124) Design: SR + MA Search date: October 2006	LMWH treatment vs Control (no intervention)	N= 4 n= 527 (n=529 for clinical thrombotic events) Canata 2003 Michot 2002 Roth 1995 Wirth 2001	Thrombotic event (both clinical and through diagnostic procedure)	**LMWH: 3/262 (1.1%)** **Control: 20/265 (7.5%)** **RR: 0.16 (95%CI, 0.05 to 0.52)** **SS in favour of LMWH** **NNT: 17**
			Participant with clinical thrombotic event	1/262 (0.4%) vs 4/267 (1.5%) RR: 0.42 (95%CI, 0.06 to 3.14) NS
			All adverse events (including allergies, one patient with transient low levels of platelets,minor gastrointestinal bleeding, two episodes of hemarthrosis in the intervened knee)	25/262 (9.5%) vs 12/265 (4.5%) RR: 1.92 (95%CI, 0.97 to 3.80) NS
			Minor bleedings	19/262 (7.3%) vs 6/265 (3.0%) RR: 2.23 (95%CI, 0.99 to 4.99) NS

* Characteristics of included studies: see below

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Canata 2003(125) Design: RCT OL PG Hospital setting Italy	n = 36	Mean age: 31 years (age ≥ 16 and ≤ 59) <u>Inclusion criteria</u>: symptomatic ACL-deficient knees <u>Exclusion criteria:</u> None stated	6 days	LMWH treatment Vs Control (no intervention) <u>LMWH treatment:</u> enoxaparin sodium sc daily dose not specified	Compression color-coded sonography in case of clinically-suspected venous thrombosis	ALLOCATION CONC: unclear RANDO: unclear BLINDING : unclear FOLLOW-UP: not stated ITT: no POWER: not stated
Michot 2002(126) Design: RCT SB PG Prospective Hospital outpatient department Switzerland	N = 130	Mean age: 44 years (age ≥ 18 and < 80 years) Male: 84 (66%) Female: 44 (34%) <u>Inclusion criteria</u>: patients requiring diagnostic or therapeutic arthoscopic knee surgery as outpatients <u>Exclusion criteria:</u> - inability or unwillingness to give written informed consent; - past medical history of DVT or PE, - known deficiency of AT III, Protein C or Protein S; - ongoing anti-thrombotic therapy, - history of GI bleeding in the previous 2 weeks; - hypersensitivity to heparin; - history of CVA in the previous 6 months - severe renal or hepatic failure	30 days	LMWH treatment Vs Control (no treatment) <u>LMWH treatment:</u> 2,500 IU anti-FXa dalteparin; Low Liquemin, Roche, Basel, Switzerland) : - 60 to 120 minutes before starting the procedure - Six hours after the end of the operation Weight-adapted dose (2,500 IU if weight < 70 kg, 5,000 if > 70 kg): - daily up to 30 days postoperatively	Systematic questioning for symptoms of DVT and PE, or bleeding complications and bilateral compression ultrasonography (US). If US was not conclusive, venography was performed	ALLOCATION CONC: unclear RANDO: unclear BLINDING : unclear FOLLOW-UP: Lost-to follow-up: 5% ITT: yes <u>Remark:</u> Sample size was calculated at 400 patients but the trial was stopped at 130 because it was decided that withholding LMWH was unethical.

Roth 1995(127) Design: RCT PG Prospective Hospital outpatient department Germany	n = 144	Mean age: not mentioned <u>Inclusion criteria</u>: patients undergoing ambulatory arthroscopic meniscus intervention, sinovectomy, chondroplasty, loose-bodies resection Included patients with independent risk factors for thrombosis Included patients more than 60 years old. <u>Exclusion criteria:</u> Not stated	4 days	LMWH treatment Vs Control (no intervention) <u>LMWH treatment:</u> 0.3 ml sc fraxiparine 2 hours before the operation and self administered daily (except the first two doses) for 4 days after surgery	DVT was diagnosed, and venographically confirmed, all in the operated limb. Venography indication was established after clinical assessment or ultrasonography. No PE was detected (gammagraphy).	ALLOCATION CONC: unclear RANDO: unclear BLINDING : unclear FOLLOW-UP: Lost-to follow-up: not stated Excluded: 15% Described: Yes (22 were excluded due to non-compliance) ITT: no POWER: not stated
Wirth 2001(128) Design RCT SB PG Prospective Hospital Setting Germany	n = 239	Mean age: 38 years (age > 18 years) Male: 179 (75%) Female: 60 (25%) <u>Inclusion criteria</u>: elective knee arthroscopy <u>Exclusion criteria:</u> - pregnant; - history of DVT; - contraindication to contrast venography or trial medication - Patients also screened for additional risk factors (obesity, nicotine abuse, oral contraceptives and family history of thrombosis). If 3 or more present, patients were excluded	7 to 10 days	LMWH treatment Vs Control (no intervention) <u>LMWH treatment:</u> once daily injection of reviparin (1,750 anti Xa IU equivalent to 0.25 ml, sc) (Clivarin)	DVT diagnosed by compression color-coded ultrasonography or clinically symptomatic PE	ALLOCATION CONC: unclear RANDO: unclear BLINDING : unclear FOLLOW-UP: Lost-to follow-up: not stated Excluded: 7% Described: Yes Power: inadequate ITT: yes

Author's conclusions:

This meta-analysis suggests that LMWH reduces the incidence of distal DVT diagnosed by sonogram. The clinical benefit of this is uncertain. No strong evidence was found to conclude thromboprophylaxis is effective to prevent thromboembolic events and safe, in people with unknown risk factors for thrombosis, undergoing knee arthroscopy.

7.1.2 Summary and conclusions LMWH versus no thromboprophylaxis in knee arthroscopy

LMWH treatment versus no intervention for the prevention of VTE in adults undergoing knee arthroscopy			
Bibliography: meta-analysis Ramos 2008(124), selecting these RCTs: Canata 2003(125), Michot 2002(126), Roth 1995(127), Wirth 2001(128)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
VTE	527 (4 studies) 4-30d	**RR= 0.16 (95%CI 0.05 to 0.52)** **SS in favour of LMWH** **NNT= 17**	⊕⊕⊕⊖ **MODERATE** Study quality:-1 (not blind, no ITT + FU not reported in 2 studies) Consistency: OK (see forest plot) Directness: OK Imprecision: OK
Clinical VTE	529 (4 studies) 4-30d	RR= 0.42 (95%CI 0.06 to 3.14) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (not blind, no ITT + FU not reported in 2 studies) Consistency: OK Directness: OK Imprecision: -1 wide CI
Minor bleedings	527 (4 studies) 4-30d	RR= 2.23 (95%CI 0.99 to 4.99) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (not blind, no ITT + FU not reported in 2 studies) Consistency: OK Directness: OK Imprecision: -1 (small studies, not clear if power was adequate for this outcome)
Adverse events	527 (4 studies) 4-30d	RR= 1.92 (95%CI 0.97 to 3.80) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (not blind, no ITT + FU not reported in 2 studies) Consistency: OK Directness: OK Imprecision: -1 (small studies, not clear if power was adequate for this outcome)

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

In this meta-analysis of 4 studies, treatment with low molecular weight heparin (LMWH) was compared to no treatment for the prevention of venous thromboembolism in adults undergoing knee arthroscopy. The duration of follow-up in the studies varied from 4 to 30 days.
There was no information on the outcomes mortality, pulmonary embolism and major bleeding.

Treatment with LMWH resulted in a lower rate of venous thromboembolic events (VTE) than no treatment.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in the rate of clinical VTE between LMWH and no treatment.
GRADE: LOW quality of evidence

There was no statistically significant difference in the rate of minor bleedings between LMWH and no treatment.
GRADE: LOW quality of evidence

There was no statistically significant difference in the rate of adverse events between LMWH and no treatment.
GRADE: LOW quality of evidence

7.1.3 Graduated compression stockings versus LMWH in knee arthroscopy

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: Camporese 2008 (129) Design: RCT OL PG Setting: Italy, Department of knee surgery. Duration of follow-up: 3 months	n= 1317 (for this comparison) Mean age:42 Current malignancy: NR Recent trauma: NR Immobilized: NR <u>Inclusion</u> Knee arthroscopy patients, i.e.: consecutive outpatients scheduled for diagnostic arthroscopy or arthroscopy-assisted knee surgery for partial meniscectomy, cartilage shaving, cruciate ligament reconstruction, synovial resection, or combined surgical procedures. <u>Exclusion</u>	**GCS on operated leg** Start time: before weight bearing Duration: 7 days after operation Thigh lengths with pressure of 30-40 mmHg at the ankle vs **LMWH (Nadroparin)** Start time: 8 hours after operation Duration: 7 days after operation. 3800 anti-Xa IU daily subcutaneous injection. - Additional	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel (healthcare professionals): no Assessors: yes Remarks on blinding method: *"The study was not blinded to healthcare professionals or patients, although the assessors were blinded."* FOLLOW-UP: Lost-to follow-up: Drop-out and Exclusions: 63 drop-outs (9.6%) in GCS - 54 drop-outs (8.3%) in LMWH • Described: yes • Balanced across groups: no ITT: yes Power: inadequate for safety SELECTIVE REPORTING: no Sponsor: No external funding was received.
			Asymptomatic proximal DVT, symptomatic VTE and all cause mortality (PO) at 3 months	**GCS: 21/660 (3.2%)** **LMWH: 6/657 (0.9%)** **ARD: 2.3 (95%CI 0.7 to 4.0) percentage points** **P value: 0.005** **SS in favour of LMWH**	
			Asymptomatic proximal+distal VTE; symptomatic VTE and all cause mortality (SO)	**GCS: 31/660 (4.7%)** **LMWH: 12/657 (1.8%)** **ARD: 2.9 (95%CI 1.0 to 4.8) percentage points** **P value: 0.005** **SS in favour of LMWH**	
			All cause mortality at 3 months	GCS: 0/660 LMWH: 0/657 P value: N/A	
			Fatal pulmonary embolism (confirmed by: autopsy)	GCS: 0/660 LMWH: 0/657 P value: N/A	
			Symptomatic pulmonary embolism (confirmed by: ventilation perfusion scanning)	GCS: 2/660 (0.3%) LMWH: 2/657 (0.3%) P value: 1.00 NS	
			Symptomatic DVT (confirmed by: Doppler ultrasound)	**GCS: 12/660 (1.8%)** **LMWH: 2/657 (0.3%)** **P value: 0.012*** **SS in favour of LMWH**	
			DVT, asymptomatic or symptomatic	**GCS: 29/660 (4.4%)** **LMWH: 10/657 (1.5%)**	

	- Younger than 18 years of age - Pregnant - Previous VTE - Active cancer - Known thrombophilia - Receiving mandatory anticoagulation - Hypersensitive to LMWH - Recent major bleeding event - Severe renal or hepatic failure - Anticipated poor adherence - Geographic inaccessibility - Tourniquet thigh time greater than 1 hour.	noncomparative prophylaxis: None reported	(screened for by: Doppler ultrasound at 7 days)	**P value: 0.003*** **SS in favour of LMWH**	Other important methodological remarks: Notes: * Calculated by NCC using fisher‟s exact test. Three arms were originally planned. The 3rd arm (LMWH for 14 days) was stopped by the data monitoring committee after 444 patients had been recruited because of concerns about the potential safety issues related to a longer LMWH regimen. The data from this group are reported in the paper but not reported here. A subgroup analysis found that meniscectomy involved knee surgery was independently associated with the development of VTE.
			Thigh DVT (screened for by: Doppler ultrasound)	GCS: 8/660 (1.2%) LMWH: 2/657 (0.3%) P value: 0.108* NS	
			Calf DVT (screened for by: Doppler ultrasound)	**GCS: 21/660 (3.2%)** **LMWH: 8/657 (1.2%)** **P value: 0.023*** **SS in favour of LMWH**	
			Safety		
			Major and clinically relevant nonmajor bleeding events (PO)	GCS: 2/660 (0.0%) LMWH: 6/657 (0.9%) ARD: -0.6 (95%CI-1.5 to 0.2) percentage points P value: NR	
			Fatal bleeding	GCS: 0/660 LMWH: 0/657 P value: N/A	
			Major bleeding (description: clinically overt haemorrhage associated with a haemoglobin decrease of at least 20 g/L or requiring transfusion of 2 or more units of packed red blood cells, a retroperitoneal or intracranial event, a bleeding event requiring re intervention, or a hemarthrosis with joint drainage of more than 450mL)	GCS: 1/660 (0.2%) LMWH: 2/657 (0.3%) P value: 0.624* NS	
			Minor bleeding (description: not defined)	GCS: 20/660 (3.0%) LMWH: 23/657 (3.5%) P value: 0.646* NS	

*Information retrieved from NICE 2010(54)

7.1.4 Summary and conclusions. Graduated compression stockings versus LMWH in knee arthroscopy

Graduated compression stockings versus LMWH in patients undergoing knee arthroscopy			
Bibliography: Camporese 2008(129)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1317 (1 study) 3 months	0% vs 0% p-value not applicable	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: -1 not a primary outcome Imprecision: OK
Asymptomatic proximal DVT, symptomatic VTE and all cause mortality (PO) at 3 months	1317 (1 study) 3 months	3.2% vs 0.9% **ARD: 2.3 (95%CI 0.7 to 4.0) percentage points** **SS in favour of LMWH**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: -1 composite outcome includes asymptomatic DVT Imprecision: OK
Symptomatic DVT	1317 (1 study) 3 months	**1.8% vs 0.3%** **SS in favour of LMWH** **p=0.012**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: NA Directness: OK Imprecision: OK
Symptomatic PE	1317 (1 study) 3 months	0.3% vs 0.3% NS	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: NA Directness: OK Imprecision: OK
Major bleeding	1317 (1 study) 3 months	0.2% vs 0.3% NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 power inadequate
Minor bleeding	1317 (1 study) 3 months	3% vs 3.5% NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: -1 power inadequate

In this trial, graduated compression stockings were compared with nadroparin for a period of 7 days in patients undergoing knee artroscopy. Treatment lasted 7 days; follow-up was 3 months.

There was no statistically significant difference between graduated compression stockings and nadroparin in the mortality rate after three months.
GRADE: MODERATE quality of evidence

The rate of the composite outcome of asymptomatic proximal DVT, symptomatic VTE an all cause mortality was significantly lower with LMWH.
GRADE: MODERATE quality of evidence

Three months of treatment with nadroparin resulted in a lower rate of clinical venous thrombotic events than wearing graduated compression stockings during three months.
GRADE: HIGH quality of evidence

There was no statistically significant difference between graduated compression stockings and nadroparin in the rate of symptomatic pulmonary events after three months.
GRADE: HIGH quality of evidence

There was no statistically significant difference between graduated compression stockings and nadroparin in the rate of major bleedings after three months.
GRADE: MODERATE quality of evidence

There was no statistically significant difference between graduated compression stockings and nadroparin in the rate of minor bleedings after three months.
GRADE: MODERATE quality of evidence

7.1.5 Extended duration versus short duration thromboprophylaxis in knee arthroscopy

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: Marlovits 2007(130) Design: RCT: DB PG Setting: Austria, University Teaching Hospital Duration of follow-up: 23-28 days after surgery	n= 175 Mean age:30y Previous VTE(DVT/PE): NR Current malignancy: NR Recent surgery: NR Recent trauma: NR Immobilized: 37 (before surgery); 26 (>4days) <u>Inclusion</u> - Aged 19-55 years - Maximum weight of 100kg - Admitted to the hospital for arthroscopic ACL surgery <u>Exclusion</u> - Participated in another trial in the 4 weeks prior to this trial - Diagnosis of DVT confirmed by magnetic resonance	**Group 1: Extended LMWH (Enoxaparin)** Start time: 12-18 hrs pre-operatively End time: 3-8 days in hospital and then 20 days post discharge Duration: No average prophylaxis period provided in paper Dose, and frequency: 40mg subcutaneously once daily. Vs. **Group 2: short LMWH (Enoxaparin) and then placebo** Start time: 12-18 hrs pre-operatively End time: 3-8 days	Efficacy		RANDO: NR ALLOCATION CONC: NR BLINDING : Participants: unclear Personnel: unclear Assessors: unclear Remarks on blinding method: The operator conducting diagnosis was blinded to patient group. The paper states it was double blind and did use placebo as the control arm, however, no information about blinding was provided. FOLLOW-UP: Lost-to follow-up: 2 patients Drop-out and Exclusions: 15 (17%) in group 1, 20 (22%) in group 2. • Described: yes • Balanced across groups: yes ITT: No: Paper reports an intention to treat analysis but excludes patients who did not follow the study protocol
			All cause mortality	Extended LMWH: 0/87 Short LMWH: 0/88 P value: NS	
			Fatal pulmonary embolism (confirmed by: N/A)	Extended LMWH: 0/87 Short LMWH: 0/88 P value: NS	
			Symptomatic pulmonary embolism (confirmed by: lung scan)	Extended LMWH: 0/87 Short LMWH: 0/88 P value: NS	
			Symptomatic DVT (confirmed by: venography)	Extended LMWH: 0/87 Short LMWH: 3/88 (3.4%) P value: 0.246* NS	
			DVT, asymptomatic or symptomatic (confirmed by: Magnetic Resonance Venograpy at 23-28 days)	**Extended LMWH: 2/72 (2.8%)** **Short LMWH: 28/68 (41.2%)** **P value: <0.001** **SS in favour of Extended LMWH**	
			Thigh DVT (confirmed by: Magnetic Resonance Venograpy at 23-28 days)	**<u>Popliteal and Femoral</u>** **Extended LMWH: 3/72 (4.1%)** **Short LMWH: 18/68 (26.5%)** **P value: <0.001*** **SS in favour of extended LMWH** **<u>Popliteal</u>** **Extended LMWH: 2/72 (2.8%)** **Short LMWH: 12/68 (17.6%)**	

	venography on admission - Were receiving oral anticoagulant therapy (not including NSAID) or were allergic to heparin - Presence of haemophilia or other blood disorders - Presence of bleeding disorders (e.g. haemorrhagic injury, acute intracranial bleeding, peptic ulcer, gastrointestinal tract bleeding, and lung bleeding) - Pregnancy - Presence of other serious illness such as proliferative diabetic retinopathy, liver or pancreatic illness, multiple trauma, uncontrollable hypertension or endocarditis lenta.	in hospital after surgery And then placebo for 20 days post discharge Dose and frequency: 40mg subcutaneously once daily whilst in hospital And then placebo injections once daily post discharge. **Additional noncomparative prophylaxis:** None stated in paper		**P value: 0.003** **SS in favour of extended LMWH** **<u>Femoral</u>** **Extended LMWH: 1/72 (1.4%)** **Short LMWH: 6/68 (8.8%)** **P value: 0.044** **SS in favour of extended LMWH**	Power: adequate/inadequate SELECTIVE REPORTING: probable *("Outcomes not reported: Asymptomatic and symptomatic PE, Heparin induced thrombocytopaenia, pulmonary hypertension, post thrombotic syndrome quality of life, length of stay." – "Additional outcomes reported: Adverse events – no information.")* Other important methodological remarks: - Differences in reasons for drop outs between the two groups are not discussed. -- Inconsistency within paper of the number of patients randomised (87and 88 in text; 79 and 80 in figure 1). Difference due to those who did not undergo ACL operations. Sponsor: Supported by an unrestricted grant from Sanofi-Aventis. Notes: * calculated by Fisher‟s Exact Test
			Safety		
			Fatal bleeding	Extended LMWH: 0/ 87 Short LMWH: 0/ 88 P value: NS	
			Major bleeding (description: bleeding that was retroperitoneal, intracranial, intraspinal, or involving any other critical organ; bleedingleading to reoperation; transfusion of 2 units of packed red blood cells or whole blood; or overt bleeding with a bleeding index of two or more.)	Extended LMWH: 0/87 Short LMWH: 0/88 P value: NS	
			Minor bleeding (description: All other bleeding not defined in fatal or major bleeding)	Extended LMWH: 13/87 (15.0%) Short LMWH: 10/88 (11.4%) P value: 0.595 NS	

Study information retrieved from NICE 2010(54)

7.1.6 Summary and conclusions. Extended duration versus short duration thromboprophylaxis in knee arthroscopy

Extended (23-28d) versus short treatment (3-8 d in-hospital) with enoxaparin 40mg in patients with arthroscopic anterior cruciate ligament (ACL) surgery			
Bibliography: Marlovits 2007(130)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	175 (1 study) 23-28d	0 vs 0 NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: NA Imprecision: -1, small study, power for this outcome probably inadequate
Symptomatic DVT	175 (1 study) 23-28d	0 vs 3.4% NS, p=0.246	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: NA Imprecision: -1, small study, power for this outcome probably inadequate
Symptomatic PE	175 (1 study) 23-28d	0 vs 0 NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: NA Imprecision: -1, small study, power for this outcome probably inadequate
Asymptomatic or symptomatic DVT	175 (1 study) 23-28d	**2.8% vs 41.2%** **SS in favour of extended enoxaparin, p<0.001**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 FU 20%, no ITT Consistency: NA Directness: NA Imprecision: OK
Major bleeding	175 (1 study) 23-28d	0 vs 0 NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: NA Imprecision: -1, small study, power for this outcome probably inadequate
Minor bleeding	175 (1 study) 23-28d	15.0% vs 11.4% NS, p=0.595	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: NA Imprecision: -1, small study, power for this outcome probably inadequate

In this trial, extended treatment with enoxaparin (40 mg subcutaneously) for 23-28 days after surgery was compared to short treatment with enoxaparin for 3-8 days after surgery in patients undergoing arthroscopic anterior cruciate ligament (ACL) surgery.

There was no statistically significant difference in mortality rate between extended and short term treatment with enoxaparin.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in symptomatic DVT between extended and short term treatment with enoxaparin.
GRADE: MODERATE quality of evidence

Extended treatment with enoxaparin resulted in a lower rate of asymptomatic or symptomatic DVT's than short treatment with enoxaparin.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in symptomatic pulmonary embolism between extended and short term treatment with enoxaparin.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in major bleedings between extended and short term treatment with enoxaparin.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in minor bleedings between extended and short term treatment with enoxaparin.
GRADE: MODERATE quality of evidence

7.2 Thromboprophylaxis in plaster cast or orthosis

7.2.1 LMWH versus no thromboprophylaxis in plaster cast immobilization of the lower limb

Ref	Comparison	N/n	Outcomes	Result**
ref* NICE 2010(54) Design: SR+MA Search date: dec 2008	LMWH vs nil	N= 5 n= 1264 (Jorgensen 2002, Kock 1995, Kujath 1993, Lapidus 2007, Lassen 2002)	**DVT**	**LMWH: 51/633 (8%)** **Nil: 100/631 (16%)** **RR: 0.52 (95% CI 0.32 to 0.87) (a)** **SS in favour of LMWH** **Absolute effect: -7% (95% CI -11% to -3%)** *(a) There is substantial statistical heterogeneity between studies for this population (I2 =54.5 %, 2 on 4 df = 8.80, p= 0.07)*
		N= 3 n= 748 (Jorgensen 2002, Lapidus 2007, Lassen 2002)	**Symptomatic pulmonary embolism**	LMWH: 0/368 (0%) Nil: 2/380 (0.5%) RR: 0.20 (95% CI 0.01 to 4.22) NS Absolute effect: -1% (95% CI -2% to 1%)
		N= 3 n= 882 (Kock 1995, Lapidus 2007, Lassen 2002)	**Major bleeding**	LMWH: 2/445 (0.45%) Nil: 1/437 (0.23%) RR: 2.04 (95% CI 0.19 to 22.30) NS Absolute effect: 0% (95%CI -1% to 1%)
		N= 2 n=543 (Lapidus 2007, Lassen 2002)	**All cause mortality**	LMWH: 0/269 (0%) Nil: 0/274 (0%) RR not estimable Absolute effect: 0% (95% CI -1% to 1%)

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Jorgensen 2002(131) Country of study: Denmark Setting: Outpatients Study design: RCT	300	Patients wearing below knee plaster casts on lower extremity (reasons for plaster cast: fracture (n=220); tendon ruptures (n=61); other (n=19) Inclusion criteria: Age >18 Planned lower limb plaster cast of at least 3 weeks Exclusion criteria: Uncontrolled hypertension	While wearing plaster cast (mean duration 5.5 weeks)	**Group I: LMWH** tinzaparin (Innohep) 3500 IU self injected into abdominal wall once daily until plaster cast removed Vs. **Group II: no LMWH** Additional noncomparative prophylaxis: None	DVT, asymptomatic or symptomatic: diagnosed by ascending unilateral venography when plaster cast removed) DVT, asymptomatic or symptomatic: diagnosed by ascending unilateral venography when plaster cast removed Above knee DVT: diagnosed by ascending unilateral venography when plaster cast removed Symptomatic DVT: confirmed by ascending unilateral venography when plaster cast removed	**Limitations** Only assess one leg for DVT; patients and clinicians not masked to treatment; the reasons for two thirds of patients not reaching an endpoint are not clear for all patients **Outcomes not reported:** major and minor bleeding, heparin induced thrombocytopenia, postthrombotic syndrome, quality of life **Notes:** Bleeding data – excluded due to ambiguity in reporting and definition after discussions between reviewers. Evidence level: 1+ Funding: not reported List who was masked to interventions: assessors of venograms
Kock 1995(132) Country of study: Germany	428	Patients with leg injury for which conservative treatment without admission to hospital was indicated.	Until plaster cast removed	**Group I:** LMWH (Mono-Embolex NM (Sandoz) 0.3ml per syringe with an activated partial thrombo-	DVT, asymptomatic or symptomatic (* confirmed by venography when plaster cast removed)	List who was masked to interventions: nobody Evidence level:

Setting: Outpatients Study design: RCT		Below knee cast (n=366) or above knee casts (n=62). Reasons for plaster cast: Grade II sprains and bruises (n=122); Grade III sprains (n=130); fractures (n=72); other (n=15) Inclusion criteria: age 18-65 Exclusion criteria: Previous DVT Clotting disorders or anticoagulant medication Chronic venous insufficiency Plaster cast after surgery		plastin time activity of 1500 units & anit-Xa activity of 3000 units. Not reported when started, self injected until plaster cast removed Vs. **Group II:** no LMWH **Additional noncomparative prophylaxis:** None	Proximal DVT (as above) Calf DVT (as above)	1+ No. of dropouts: 89 Funding: not reported Limitations: Nobody masked to treatment. Does not report initial numbers randomised to each group Outcomes not reported: mortality, pulmonary embolism, minor bleeding, heparin induced thrombocytopenia, postthrombotic syndrome, quality of life Notes: * DVT checked by clinical examination, measurement of leg circumference, venous occlusion plethysmography, Bmode compression ultrasonography and duplex scanning and confirmed by venography
Kujath 1993(133) Country of study: Germany Study design: RCT Setting: Outpatients	306	Outpatients with leg injury treated conservatively and immobilisation by plaster cast. Type of injury: soft tissue (n=176); fractures (n=77) Inclusion criteria: Age >16 Immobilisation by plaster cast for at	Until plaster cast removed	**Group I:** LMWH (Fraxiparin) 0.3ml daily [36mg heparin fraction calcium, molecular mass 4000-5000. Started on first day of treatment, continued until plaster cast removed	**DVT, asymptomatic or symptomatic**: diagnosed by ultrasound confirmed by venography	List who was masked to interventions: no one Evidence level: 1+ No. of dropouts: 53 Funding: not reported Limitations: Nobody masked to

		least 7 days Exclusion criteria: Known thrombopathy		Vs. **Group II:** no LMWH **Additional noncomparative prophylaxis:** None		treatment. Outcomes not reported: mortality, pulmonary embolism, minor bleeding, heparin induced thrombocytopenia, postthrombotic syndrome, quality of life
Lapidus 2007(134) Country of study: Sweden Setting: Stockholm Soder Hospital (Nov2001-May2004) Study design: Single centre, double blinded RCT	105	Achilles tendon rupture, all received surgery. Inclusion criteria: - Consecutive patients - 18-75 years old - Admitted because of Achilles tendon rupture (0- 72h) and accepted for surgery Exclusion criteria: - Recent surgery or thromboembolic event (during the proceeding 3 months) - Known malignancy	Up to 6 weeks	**Group 1**: LMWH Dalteparin 5000U Vs. **Group 2:** Placebo (9%w/v sodium chloride), 0.2 ml in identical syringes to dalteparin. Frequency: once daily Route: subcutaneous injection Start time: Within hours post surgery End time: up to 6th week, or mobilisation Duration: up to 6 weeks after surgery All patients given 45 syringes. **Additional noncomparative prophylaxis**:	All cause mortality confirmed by: No death was reported Fatal pulmonary embolism confirmed by: None reported Symptomatic pulmonary embolism confirmed by: ventilation perfusion scan or spiral CT if suspected) **DVT, asymptomatic or symptomatic** screened for by: unilateral ascending phlebography of the affected legs, or colour duplex sonography (CDS) when phlebography fails at the 3rd week and 6th week, on the last day of the dose (or a day after), and when thrombosis is suspected, whichever earlier. Thigh DVT screened for	Evidence level: 1+ List who was masked to interventions: Investigators, patients, radiologist who carried out standardised final evaluation Funding: Pfizer/Pharmacia and Karolinska Institute provided grants. Dalteparin provided by Pharmacia/ Pfizer Limitations: - Positive events detected by CDS, but not confirmed by phlebography (either not performed or not interpretable) had not been included in the primary and secondary analysis of efficacy - Only the affected leg was scanned routine scanning Outcomes not reported: Symptomatic DVT, Thigh DVT; Fatal or neurological or upper GI bleeding, Heparin induced

				Not mentioned	by: as above, defined as affecting popliteal vein or any other more proximal vein, with or without involvement of the calf veins Fatal bleeding description: no death or major bleeding reported Major bleeding description: requiring blood transfusion/surgery, or at a critical site such as intracranial, intraocular, intraspinal, or retroperitoneal) Minor bleeding description: A nose bleed	thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay Notes: - All admitted Achilles tendon rupture patients l who required surgery was assessed for eligibility (n=285), and 257 fulfilled criteria. - Patients with asymptomatic DVT detected by CDS but not verified by phlebography were excluded (n=5, 4 in placebo) - Subjects were trained in selfinjection by study nurse in hospital. - Patients were followed up at 3 weeks after surgery, where plaster casts were changed and screening for DVT was done, and screened again at the end of study
Lassen 2002(135) RCT	440	Outpatients with fracture of the leg or rupture of the Achilles tendon requiring at least five weeks immobilisation in plaster cast or brace within 4 days of injury.	49 days Study period 11 days	**Group I** LMWH (Reviparin, 1750 anti-Xa units self injected daily Started not more than more 4 days after fractures and continued throughout immobilisation. **Group II** Placebo **Additional**	**DVT**, **asymptomatic or symptomatic** (diagnosed by unilateral venography within a week of plaster cast removal) **Symptomatic pulmonary embolism** (confirmed by ventilation perfusion scanning) **Major bleeding** (defined	Evidence level: 1+ Dropouts (not treated): Int: 15 Comp: 21 Dropouts 69/440 Denominator for Group 1 set as 217 – the number randomised to be consistent as ITT. Paper reported safety population based on 438, but unclear which

				noncomparative prophylaxis: Patients who underwent surgery were permitted to have had heparin treatment lasting up to 4 days **before** randomisation. Numbers treated .	as clinically apparent bleeding associated with a decrease of at least 2.0g per deciliter in the hemoglobin level, requirement for transfusion of at least 2 units of packed red cells, or retroperitoneal or intracranial bleeding or other bleeding that investigators decided required permanent discontinuation of treatment)	were the patients excluded. **Funding:** supported by grant from Knoll.

Low Molecular Weight Heparine versus Placebo in patients with fracture below the knee(followed by surgery)

Study details	n/Population	Comparison	Outcomes		Methodological
727 Goel(136) Design: RCT DB PG Setting: Hospital Duration of follow-up: 12 weeks (follow –up at 2, 6, 8 and 12 weeks) (or until fracture had united)	n= 305 Mean age: 41 years (Age > 18 and < 75 years) Male: 61.9% Female: 38.1% Previous VTE : none <u>Inclusion:</u> - Patients with unilateral displaced, fractures below the knee requiring operation - Patients with simultaneous injury of a minor nature (eg. conservatively managed wrist, scapula, clavicular fracture not inhibiting patient mobilisation) <u>Exclusion:</u> - Non-surgical treatment - Fractures above the knee - Polytrauma patients - Fractures not treated within 48 hours - Patients with history of DVT or PE - Patients limited from early mobilisation - Patients with foot fractures	Low Molecular Weight Heparine (Dalteparin (Fragmin) - 2h pre-operatively and 8h post operatively: 2500 IU - each morning until day 14: 5000 IU) Vs Placebo (Saline injection) For 14 days	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions: 22% Described: yes Balanced across groups: no Lost to follow-up 19% in LMWH group 25% in placebo group ITT: not mentioned Power: inadequate (218 patients necessary in each study arm but because of withdrawal of funding, the researchers were unable to recruit sufficient numbers of patients) SELECTIVE REPORTING: no Other important methodological remarks:
			Incidence of DVT (PO) (bilateral venography at day 14) (remark: all DVTs were asymptomatic)	Dalteparin: 11/126 (8.73%) Placebo: 14/111 (12.6%) RR: not mentioned NS (p = 0.22)	
			Safety		
			Major bleeding	Dalteparin: 0 Placebo: 0	
			Minor bleeding	Dalteparin: 0 Placebo: 0	
			Mortality	Dalteparin: 1/126 (0.79%) (but cause was unrelated to thrombosis or its sequelae) Placebo: 0	

	- Medical contraindications to surgery - Patients receiving anticoagulation - Inability to provide consent -Patients with platelet counts less than 100 - Patients with elevated serum creatinine > 200 µmol/L				- Patient compliance with injections and follow-up > 95% in both groups - Smokers in LMWH group: 29% Smokers in placebo group: 34.2% (but trial included smoking as a confounding factor) Sponsor: funding not mentioned 'No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.'

7.2.2 Summary and conclusions. LMWH versus no thromboprophylaxis in plaster cast immobilization of the lower limb

LMWH versus no treatment for thromboprophylaxis with lower limb plaster cast or brace			
Bibliography: meta-analysis NICE 2010(54), included following RCTs: Jorgensen 2002(131), Kock 1995(132), Kujath 1993(133), Lapidus 2007(134), Lassen 2002(135). 1 more recent RCT found:Goel 2009(136)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Mortality	n=848 (3 studies) 6-7 w	NICE 2010 0% vs 0% RR not estimable Goel 2009 0.8% vs 0% NT	Not applicable
DVT (symptomatic or asymptomatic)	n= 1569 (6 studies) 1-7 w	NICE 2010 8% vs 16% **RR: 0.52 (95%CI 0.32 to 0.87)** **SS in favour of LMWH** Absolute effect: -7% (95% CI -11% to -3%) *There is substantial statistical heterogeneity between studies for this population* Goel 2009 8.7% vs 12.6% RR: not mentioned NS (p = 0.22)	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: -1 conflicting results Directness: -1 heterogeneous study populations Imprecision: OK
PE	n= 748 (3 studies) 5.5-7 w	NICE 2010 0% vs 0.5% RR: 0.20 (95% CI 0.01 to 4.22) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 heterogeneous study populations Imprecision: -1 wide CI
Major bleeding	n= 1187 (4 studies) 6-7 w	NICE 2010 0.45% vs 0.23% RR: 2.04 (95%CI 0.19 to 22.30) NS Goel 2009 0% vs 0%	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -1 heterogeneous study populations Imprecision: -1 wide CI

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

We selected 1 meta-analysis (NICE 2010) of 3 RCTs and one more recent RCT (Goel 2009) that compared low molecular weight heparins with no prophylaxis in patients with lower limb plaster casts or braces (duration: up to 7 weeks). The populations were clinically heterogeneous: One RCT (Kock 1995) in the meta-analysis included both below and above knee immobilization whereas the others all studied only below-knee plaster casts. In the meta-analysis, injuries included fracture,

Achilles tendon rupture or soft tissue trauma, treated surgically or conservatively. In the more recent RCT (Goel 2009) all patients had below-knee fracture that was treated surgically.

Only one death was reported in the LMWH group of one study (Goel 2009); no deaths were reported in the other studies. Statistical significance was not tested.
GRADE: NA

In the NICE 2010 meta-analysis there is a statistical significant difference between treatment groups for all DVT (symptomatic and asymptomatic) in favour of low molecular weight heparins. In one smaller study (Goel 2009) no statistically significant difference was observed.
GRADE: LOW quality of evidence

Three pooled RCTs reported the outcome “pulmonary embolism” but did not observe any statistically significant difference between treatment groups.
GRADE: LOW quality of evidence

There is no statistically significant difference between treatment groups in major bleeding outcomes.
GRADE: LOW quality of evidence

7.2.3 Extended duration versus short duration thromboprophylaxis in plaster cast immobilization of the lower limb

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: Lapidus 2007(137) (source: NICE 2010(54)) Design: RCT DB PG Setting: Sweden, Stockholm Soder Hospital (May2000-March2004) Duration of follow-up: Up to 6 weeks	n= 272 Mean age: 48 (18-76) years <u>Inclusion</u> - 18-75 years old - Admitted because of acute ankle (0-72h) fracture accepted for surgery <u>Exclusion</u> - Inability or refusal to sign informed consent form - Ongoing treatment with anticoagulant therapy - Known allergy to contrast media - Planned follow up at another hospital - Recent surgery - Known malignancy - Current bleeding disorder - Pregnancy - Treatment with high	**Group 1** **LMWH: Dalteparin 5000U**, once daily until removal of plaster cast Subcutaneous injection Vs. **Group 2** **Placebo** (9%w/v sodium chloride), 0.2 ml in identical syringes to dalteparin. -- Start time: 7 days post surgery End time: until plaster cast removed (mean 44 days±2) Duration: up to 6	Efficacy		RANDO: NR ALLOCATION CONC: *("not specifically reported but states identical syringes were prefilled with either dalteparin or sodium chloride")* BLINDING : *("List who was masked to interventions: All")* Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 75 patients: 28% Drop-out and Exclusions: 75 patients: 28% ITT: No Power: NR Other important methodological remarks: Evidence level: 1+ **Limitations:**
			All cause mortality	Group1: 0/136 (0%) Group 2: 0/136 (0%) P value: 1.0 NS	
			Fatal pulmonary embolism	Group1: 0/136 (0%) Group 2: 0/136 (0%) P value: 1.0 NS	
			Symptomatic pulmonary embolism (confirmed by: ventilation perfusion scan or spiral CT if suspected)	Group1: 0/136 (0%) Group 2: 0/136 (0%) P value: 1.0 NS	
			Symptomatic DVT (confirmed by: phlebography or CDS whenever indicated) One of the 8 events is a calf muscle vein thrombosis, not specified which group	Group1: 2/136 (1,5%) Group 2: 6/136 (4,4%) P value: 0.28 NS <u>Plaster cast subgroup:</u> Group 1: 2/114 (1,8%) Group 2: 6/108 (5,6%) P value: 0.16 NS *[value calculated by NCC-AC team using Fishers' exact test]*	
			DVT, asymptomatic or symptomatic (screened for by: unilateral ascending	<u>Up to Week 6 (by phlebography) "ITT analysis"</u> Group1: 21/101 (21%)	

	doses of acetyl salicylic acid (≥325 mg) or other platelet inhibitors - Multi-trauma (injuries involving >1 organ system in addition to the musculoskeletal system or multiple fractures)	weeks after surgery **Additional noncomparative prophylaxis:** <u>Both groups received 5000Uof s/c dalteparin</u> once daily for 7 days, starting on evening after surgery. All received 1000mL Dextran 60 on admission	phlebography of the affected legs, or colour duplex sonography (CDS) when phlebography fails at 2nd and 6th week, on the last day of the dose (or a day after), and when thrombosis is suspected, whichever earlier.	Group 2: 27/96 (28%) P value:0.2 NS <u>Up to Week 6 (by phlebography), per protocol</u> Group1: 13/75 (17%) Group 2: 17/65 (26%) P value:0.2 NS <u>Up to Week 6 (by phlebography or CDS, "ITT analysis")</u> Group1: 24/117 (20%) Group 2:34/109 (31%) P value:0.07 NS **<u>Plaster cast subgroup</u>** <u>Up to Week 6 (by phlebography)" ITT analysis"</u> **Group1: 18/86 (21%)** **Group 2: 27/75 (36%)** **P value: 0.04** **SS in favour of group 1** <u>Up to Week 6 (by phlebography), per protocol</u> **Group1: 21/99 (21%)** **Group 2: 33/86 (38%)** **P value: 0.02** **SS in favour of group 1**	Only the affected leg was scanned. Baseline risk factors and comorbidities not reported **Outcomes not reported:** Calf DVT, minor bleeding, heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay **Additional outcomes reported:** - Details/reasons for patients to be non-evaluable - Compliance, duration of immobilisation, subgroup analysis of orthosis and casts - Average age of patients who used an orthosis was 45 years p=0.03 compared to plaster cast patients **Notes:** - All subjects were trained in self-injection by as study nurse before leaving hospital. - All ankle fracture patients admitted to hospital who required surgery was assessed for eligibility (n=1072). Details of reason for exclusion provided
			Thigh DVT (screened for by: as above, defined as affecting popliteal vein or any other more proximal vein, with or	Group1: 4/101 (4,0%) Group 2: 3/96 (3,1%) P value: 0.2	

			without involvement of the calf veins)	NS	**Sponsor:** Pfizer/Pharmacia and Karolinska Institute provided grants
			Safety		
			Fatal bleeding	Group1: 0/136 (0%) Group 2: 0/136 (0%) P value: 1.0 NS	
			Major bleeding (description: requiring blood transfusion/ surgery, or at a critical site such as intracranial, intraocular, intraspinal, or retroperitoneal)	Group1: 0/136 (0%) Group 2: 0/ 136 (0%) P value: 1.0 NS <u>Plaster cast subgroup:</u> Group 1: 0/114 (0%) Group 2: 0/108 (0%) NS	
			Minor bleeding (description: All local bleedings not classified as "major bleeding")	Group1: 1/ 136 (0.7%) Group 2: 1/136 (0.7%) P value: 1.0 NS	

7.2.4 Summary and conclusions. Extended duration versus short duration thromboprophylaxis in plaster cast immobilization of the lower limb

LMWH post discharge(mean 44 days) versus placebo, after initial 7 day LMWH for thromboprophylaxis in lower limb plaster casts or orthosis after ankle fracture surgery			
Bibliography: Lapidus 2007(137) (source: NICE 2010(54))			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	n= 272 (1 study) up to 6 w	0% vs 0% NS	⊕⊕⊖⊖ **LOW** Study quality: -1 only 1 trial, no ITT, considerable loss to FU Consistency: NA Directness: OK Imprecision: -1 power NR
DVT (asymptomatic + symptomatic)	n= 272 (1 study) up to 6 w	21% vs 28% NS **<u>Plaster cast subgroup</u>** 21% vs 36% **P value: 0.04** **SS in favour of post discharge LMWH tromboprophylaxis**	⊕⊕⊖⊖ **LOW** Study quality: -1 only 1 trial, unclear definition ITT Consistency: NA Directness: OK Imprecision: -1 power NR
PE (symptomatic)	n= 272 (1 study) up to 6 w	0 vs 0% NS	⊕⊕⊖⊖ **LOW** Study quality: -1 only 1 trial Consistency: NA Directness: OK Imprecision: -1 power NR
Major bleeding	n= 272 (1 study) up to 6 w	0 vs 0% NS	⊕⊕⊖⊖ **LOW** Study quality: -1 only 1 trial Consistency: NA Directness: OK Imprecision: -1 power NR

In this trial LMWH was compared to placebo in patients who had surgery for acute ankle fracture and received a plaster cast or orthosis after surgery. Both study groups received 5000 units of dalteparin s.c. daily during the first week after surgery and after that were either treated with prolonged LMWH or placebo until cast or orthosis removal.

No deaths were reported.
GRADE: LOW quality of evidence

In the entire study population no statistically significant difference in total events of deep vein thrombosis was observed. However, there were significantly less events of DVT in the dalteparin group compared to the placebo group in the plaster cast subanalysis.
GRADE: LOW quality of evidence

No cases of symptomatic pulmonary embolism were reported.
GRADE: LOW quality of evidence

No cases of major bleeding were reported.
GRADE: LOW quality of evidence

8 Evidence tables and conclusions: Thromboprophylaxis in general surgery

8.1 Pharmacological treatment versus placebo for thromboprophylaxis in general surgery

8.1.1 UFH versus placebo in general surgery

Ref	Comparison	N/n	Outcomes	Result**
ref*NICE 2010(54) Design: SR+MA Search date: dec 2008	UFH Vs No prophylaxis	N= 21 n= 3315 (Abernethy 1974, Ballard 1973, Bergqvist 1980, Clarke-Pearson 1983, Clarke-Pearson 1990, Coe 1978, Gallus 1973, Gordon-Smith 1972, Anon 1979, Hedlund 1979, Lahnborg 1975, Lawrence 1977, MacIntyre 1974, Marchetti 1983, Plante 1979, Ribaudo 1975, Sasahara 1984, Strand 1975, Taberner 1978, Törngren1979, Wu 1977)	**DVT**	**UFH: 170 /1729 (9.8%)** **No prophylaxis: 342 /1586 (21.6%)** **RR: 0.45 (95% CI 0.36 to 0.56)** **SS in favour of UFH** **Absolute effect: -21% (95% CI -31% to -11%)**
		N= 10 n= 1275 (Abernethy 1974, Bejjani 1983, Clarke-Pearson 1983, Coe 1978, Anon 1979, Lahnborg 1975, Lahnborg 1976, Marchetti 1983, Osman 2007, Ribaudo 1975)	**Pulmonary embolism**	**UFH: 26/645 (4.0%)** **No prophylaxis: 48/630 (7.6%)** **RR: 0.52 (95% CI 0.30 to 0.90)** **SS in favour of UFH** Absolute effect: -3% (95% CI -8% to 1%)
		N= 21 n= 3542 (Abernethy 1974, Allen 1978, Bejjani 1983, Bergqvist 1980, Clarke-Pearson 1983, Gordon-Smith 1972, Anon 1979, Hedlund 1979, Jourdan 1984, Kruse-Blinkenberg 1980, Lahnborg 1975, Lawrence 1977, MacIntyre 1974, Marchetti 1983, Osman 2007, Ribaudo 1975, Sagar 1975, Sasahara 1984, Taberner 1978, Törngren1979, Wu 1977)	**Major bleeding**	UFH: 97 /1878 (5.2%) No prophylaxis: 58 /1664 (3.5%) RR: 1.38 (95% CI 0.98 to 1.96) NS Absolute effect:1% (95% CI 0% to 2%)

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Osman 2007(138) Country of study: Egypt Setting: Dec 2003 to March 2005. Urology and Nephrology Centre, Mansoura University Study design: Prospective randomised open label study List who was masked to interventions: Open label?	75	Inclusion criteria: Consecutive, isolated, live-donor renal transplantation operated by the same surgical team Exclusion criteria: Categorised as "risky " because - a history of thromboembolic disease - artheromatous arteries - collagen vascular disease Note: The groups were comparable, in the menthioned variables. However, there was a trend to significance for pretransplant haemoglobin levels, p=0.07	2 weeks? Not clearly stated	LMWH Dose: 3500anti-Xa IU in 0.35 ml once daily Duration: 1week Vs. UFH Dose: 5000IU, twice daily Duration: 1 week Vs. Control: did not receive heparinisation **Additional noncomparative prophylaxis:** Not reported Note: All patients discharged 2 weeks post operatively if no post-operative complications were found	All cause mortality confirmed by: no mortality reported Fatal pulmonary embolism confirmed by: screening method and frequency not specified Symptomatic DVT confirmed by: screening method and frequency not specified Major bleeding description: Reoperated. Found to be due to slipped ligature	**Evidence level:** 1- **Funding**: None stated **Limitations:** - Open label study - No indication that patients or investigators were blinded – very likely open label study - Method of DVT screening not clearly specified, and frequency of screening not reported. - Duration of follow up not clearly stated **Outcomes not reported:** PE asymptomatic or symptomatic, DVT, asymptomatic or symptomatic, Thigh DVT, Calf DVT, Fatal bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay **Additional outcomes reported:** - Graft thrombosis - Number receiving transfusion - Mean transfused units - Haemoglobin drop in non transfused patients - Other transplant related

						parameters
Ballard 1973(139) Design: RCT	110	Elective major gynaecological surgery (& Duration of surgery)	7 days postoperatively	5000 units of Calciparine (Laboratoire Choay, Pairs) or sodium heparin by deep subcutaneous injection vs No heparin	DVT Confirmed by 125I-labelled fibrinogen Distal DVT: Confirmed by 125I-labelled fibrinogen	Evidence level: 1+ Not reported: PE PTS bleeding QoL Funding: not reported
Clarke- Pearson 1990(140) Design: RCT	324	Major abdominal or pelvic surgical procedure for gynaecological malignancy (radical vulvectomy or pelvic exenteration). Patients stratified by risk factor. Excluded: thromboembolism within previous 3 months; warfarin or heparin treatment within previous 6 weeks	7 postoperative days for intervention, followed clinically for 30 postoperative days	UFH (Calciparine) 5000 units in 1mL volume every 8 hours vs No treatment	DVT: Confirmed by FUT. Bilateral DVT: Confirmed by FUT. Symptomatic PE: Confirmed by pulmonary arteriography	Evidence level: 1+ Comments: 20 patients dropped out after randomization mainly due to operation cancellation. None developed evidence of DVT or PE No additional prophylaxis used. Other outcomes reported: Retroperitoneal suction output; no. with postoperative haematocrit <30%; wound separation; lymphocyst. Not reported: PTS, QoL, survival. length of hospital stay, funding.

The other included RCTs were not individually reported in NICE 2010. They were extracted (by NICE) from this systematic review.

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Collins 1988(56) 74 studies included (includes Abernethy 1974(141), Allen 1978(142), Bejjani 1983(143), Bergqvist 1980(144), Clarke-Pearson 1983(145), Coe 1978(146), Gallus 1973(59), Gordon-Smith 1972(147), Anon 1979(148), Hedlund 1979(149), Jourdan 1984(150), Kruse-Blinkenberg 1980(151), Lahnborg 1975(152), Lahnborg 1976(153), Lawrence 1977(154), MacIntyre 1974(155), Marchetti 1983(156), Plante 1979(157), Ribaudo 1975(158), Sagar 1975(159), Sasahara 1984(160), Strand 1975(161), Taberner 1978(162), Törngren 1979(163), Wu 1977(164); all were included in the guideline review) 63 of these studies were included in the guideline review Design: SR	15598	Type of surgery: General (7 studies) Urology (1 study) Not all studies reported on all outcomes.	7 days-9 months	UFH Dose: Subcutaneous and given perioperatively. Given for 2–16 days or until ambulatory or discharged. vs no prophylaxis	DVT: confirmed by radiolabelled fibrinogen or scanning	Also reported, wound haematoma, death, but data not given for patient numbers by control/intervention group. Event rates reported here are for all studies as published in the systematic review.

The SR by Collins 1988 was discussed in the literature review that was undertaken for the consensus conference venous thromboembolism 2002. It was given a quality score of 6.5/12.
Here is the detailed appraisal:

		Reference + scoring date
	Quality criterium	COLLINS
	N° of studies examined	74
	N° of patients examined	15.598
	Duration of outcome measurement	1 w
	Design of studies (CO/RCT/CT)	RCT
	Journal of publication	N Engl J Med
	Year of publication	1988
	Financial support	British Heart Research
	Setting in general practice	hospital
1	Effect clinically relevant	1
2	Clinical question clear	1
3	Effect measure given (OR/RR/...)	1
4	Confidence interval of effect/difference reported	0.5
5	Adequate search strategy	0.5
6	Publication bias examined	0
7	Inclusion/exclusion criteria for studies	1
8	Quality of studies examined	0
9	Statistical method described	1
10	Variability of studies examined	0.5
11	Quality score in analysis	0
12	Assessor blinded or double-blind RCTs	0
SCORE TOTAL 1 to 12		**6.5**

Remarks:
NICE 2010 states:
“All cause mortality was not identified as a key outcome during the development of the surgical guideline. Much of the data were identified from systematic reviews where all cause mortality was not reported. There was not time during the development of this guideline to review all cause mortality for this population.”

8.1.2 Summary and conclusions. UFH versus placebo in general surgery

UFH versus no thromboprophylaxis in general surgery (gastrointestinal, gynaecological, laparoscopic, thoracic and urological surgery)			
Bibliography: meta-analysis NICE 2010(54) included these RCTs: Osman 2007(138), Ballard 1973(139), Clarke- Pearson 1990(140), Abernethy 1974(141), Allen 1978(142), Bejjani 1983(143), Bergqvist 1980(144), Clarke-Pearson 1983(145), Coe 1978(146), Gallus 1973(59), Gordon- Smith 1972(147), Anon 1979(148), Hedlund 1979(149), Jourdan 1984(150), Kruse-Blinkenberg 1980(151), Lahnborg 1975(152), Lahnborg 1976(153), Lawrence 1977(154), MacIntyre 1974(155), Marchetti 1983(156), Plante 1979(157), Ribaudo 1975(158), Sagar 1975(159), Sasahara 1984(160), Strand 1975(161), Taberner 1978(162), Törngren 1979(163), Wu 1977(164)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
DVT (symptomatic and asymptomatic)	n= 3315 (21 studies) 7d-9m	9.8% vs 21.6% **RR: 0.45 (95% CI 0.36 to 0.56)** **SS in favour of UFH** Absolute effect: -21% (95% CI -31% to -11%)	Not applied
Pulmonary embolism	n= 1275 (10 studies) 7d-9m	4.0% vs 7.6% **RR: 0.52 (95% CI 0.30 to 0.90)** **SS in favour of UFH** Absolute effect: -3% (95% CI -8% to 1%)	Not applied
Major bleeding	n= 3542 (21 studies) 7d-9m	5.2% vs 3.5% RR: 1.38 (95% CI 0.98 to 1.96) NS	Not applied

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

This meta-analysis included 21 RCTs that compared unfractionated heparin with no thromboprophylaxis in patients who underwent general surgery. All trials but one predate 1990. Most studies were extracted from an old SR (Collins 1988), already discussed in the previous literature search for the consensus conference on VTE in 2002.

We have insufficient information whether all trials screened the patients for the outcome DVT at some point after surgery. This does seem to be the case for many of the trials. The reported rate of DVT consists therefore of both symptomatic and asymptomatic DVT.

No mortality rates were reported.

There were statistically significantly less events of deep vein thrombosis and pulmonary embolism in the patient group treated with unfractionated heparin compared to those who did not receive thromboprophylaxis.

There was no statistically significant difference between the groups in major bleeding outcomes.

We did not score this comparison using GRADE because insufficient data on the included RCTs could be obtained.

Nice states that all included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). They remark, however, that many of the trials are old and surgical practice may have changed since these trials were published.

8.1.3 LMWH versus placebo in general surgery

Ref	Comparison	N/n	Outcomes	Result**
ref*NICE 2010(54) Design: SR+MA Search date: DEC 2008	LMWH Vs. No prophylaxis	N= 4 n= 433 (Le Gagneux 1987, Marassi 1993, Ockelford 1989, Valle 1988)	**DVT**	**LMWH: 6/219 (2.7%)** **No prophylaxis: 28/214 (13.1%)** **RR: 0.22 (95% CI 0.10 to 0.51)** **SS in favour of LMWH** **Absolute effect: -10% (95%CI -22% to 3%)**
		N= 5 n= 5134 (Ockelford 1989, Valle 1988, Ho 1999, Osman 2007, Pezzuoli 1989)	**Pulmonary embolism**	**LMWH: 2/2551 (0.078%)** **No prophylaxis: 13/2583 (0.5%)** **RR: 0.22 (95% CI 0.06 to 0.78)** **SS in favour of LMWH** **Absolute effect: 0% (95% CI -1% to 0%)**
		N= 7 n= 5426 (Balas 1992, Le Gagneux 1987, Ockelford 1989, Valle 1988, Ho 1999, Osman 2007, Pezzuoli 1989)	**Major bleeding**	**LMWH: 75 /2696 (2.8%)** **No prophylaxis: 37 /2730 (1.4%)** **RR: 2.01 (95% CI 1.31 to 3.07)** **SS in favour of no prophylaxis** **Absolute effect: 1% (95% CI 1% to 2%)**

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Balas 1992(165) Country of study: Setting: hospital Study design: DB RCT	189 (no. of patients for whom the group distributio n was available)	General surgery % cancer surgery NR	Treatment duration: 5-8d Duration of follow-up: NR	Nadroparin 2850 vs placebo Time of first administration: preop. 12h	Diagnosis DVT: venography but data not available	NR not available in pubmed
Marassi 1993(166) Country of study: Setting: hospital Study design: OL RCT	64	Abdominal surgery % cancer surgery NR	Treatment duration: 7d Duration of follow-up: 7d	Nadroparin 2850 Vs. No treatment Time of first administration: preop. 2h	Diagnosis DVT at the end of treatment: fibrinogen uptake test + venography	Allocation concealment: unclear Unclear randomization procedure. Open study
Le Gagneux 1987(167) Country of study: Setting: Study design: DB RCT	89	Prostatectomy % cancer surgery NR	Treatment duration NR Duration of follow-up: NR	Enoxaparin 6000 Vs. Placebo Time of first administration: preop. 12h	Diagnosis DVT at the end of treatment: fibrinogen uptake test + venography	NR not available in pubmed
Ockelford 1989(168) Country of study: Setting: Study design: DB RCT	197	Abdominal surgery 43% cancer surgery	Treatment duration: 5-9d Duration of follow-up: 6 weeks	Dalteparin 2500 Vs. Placebo Time of first administration: preop. 1-2h	Diagnosis DVT at the end of treatment: fibrinogen uptake test	NR only abstract available

Ho 1999(169) Country of study: Singapore, asian patients Setting: Study design: OL RCT	303 (no. of patients for whom the group distributio n was available)	Colorectal surgery 94% cancer surgery	Treatment duration: >4d Duration of follow-up: 9 months	Enoxaparin 4000 Vs. No treatment Time of first administration: preop 12h	Screening: daily clinical assessments and Doppler studies (day 3 and 5 postop) Diagnosis DVT: confirmed by duplex ultrasound PE confirmed by lung scans or postmortem examinations	ALLOCATION CONCEALMENT probably adequate RANDO: unclear BLINDING: open label; blinded assessments FU: >10% exclusions in enoxaparin group (erroneous administration)
Pezzuoli 1989(170) Country of study: Setting: Study design: DB RCT	4.498	General surgery 33% cancer surgery	Treatment duration: >7d Duration of follow-up: 3 weeks	Nadroparin 2850 Vs. Placebo Time of first administration: preop. 2h	Diagnosis DVT at the end of treatment: not evaluated Post mortem on every patient who died	NR only abstract available
Valle 1988(171) Country of study: Setting: Study design: DB RCT	100	Abdominal and breast surgery % cancer surgery NR	Treatment duration: 7d Duration of follow-up: NR	Pamaparin 3200 Vs. Placebo Time of first administration: preop. 2h	Diagnosis DVT at the end of treatment: ultrasound + venography	ALLOCATION CONCEALMENT: unclear RANDO: unclear BLINDING: double blind, assessor blinded ITT: yes
Osman 2007(138) Country of study: Egypt Setting: Dec 2003 to March	75	Inclusion criteria: Consecutive, isolated, live-donor renal transplantation operated by the same surgical team Exclusion criteria:	2 weeks? Not clearly stated	LMWH Dose: 3500anti-Xa IU in 0.35 ml once daily Duration: 1week Vs.	All cause mortality confirmed by: no mortality reported Fatal pulmonary embolism confirmed by: screening method and	**Evidence level (NICE 2010)** 1- **Funding**: None stated **Limitations:** - Open label study

2005. Urology and Nephrology Centre, Mansoura University Study design: Prospective randomised open label study List who was masked to interventions: Open label?		Categorised as "risky " because - a history of thromboembolic disease - artheromatous arteries - collagen vascular disease Note: The groups were comparable, in the menthioned variables. However, there was a trend to significance for pretransplant haemoglobin levels, p=0.07		UFH Dose: 5000IU, twice daily Duration: 1 week Vs. Control: did not receive heparinisation **Additional noncomparative prophylaxis:** Not reported Note: All patients discharged 2 weeks post operatively if no post-operative complications were found	frequency not specified Symptomatic DVT confirmed by: screening method and frequency not specified Major bleeding description: Reoperated. Found to be due to slipped ligature	- No indication that patients or investigators were blinded – very likely open label study - Method of DVT screening not clearly specified, and frequency of screening not reported. - Duration of follow up not clearly stated **Outcomes not reported:** PE asymptomatic or symptomatic, DVT, asymptomatic or symptomatic, Thigh DVT, Calf DVT, Fatal bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay **Additional outcomes reported:** - Graft thrombosis - Number receiving transfusion - Mean transfused units - Haemoglobin drop in non transfused patients - Other transplant related parameters

Only Osman 2007 was reported in detail in NICE 2010.
The other RCTs were not reported in detail in the NICE 2010 document. They were extracted by NICE from this systematic review:
Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. The British journal of surgery. 2001;88(7):913-30.

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Mismetti et al., 2001 9 studies included, of which Balas 1992, Marassi 1993, Le Gagneux 1987, Ockelford 1989, Valle 1988, Ho 1999, Pezzuoli 1989 (all of them included in guideline review) 8 of these studies were included in the guideline review Design: SR	5520	General (7 studies) Urology (1 study) Not all studies reported on all outcomes.	LMWH during 4-9 days. Length of follow up: 7 days-9 months	LMWH (preoperative 7 studies, post operative 1 study) Vs. Nil or Placebo	DVT: Clinical, confirmed by US or veno/FUT	Also reported, wound haematoma, death, but data not given for patient numbers by control/intervention group. Evidence level: 1+

Remarks:
NICE 2010 states:
"All cause mortality was not identified as a key outcome during the development of the surgical guideline. Much of the data were identified from systematic reviews where all cause mortality was not reported. There was not time during the development of this guideline to review all cause mortality for this population.

8.1.4 Summary and conclusions. LMWH versus placebo in general surgery

LMWH versus no thromboprophylaxis in general surgery (gastrointestinal, gynaecological, laparoscopic, thoracic and urological surgery)			
Bibliography: meta-analysis NICE 2010(54) included 7 RCTs: Balas 1992(165), Marassi 1993(166), Le Gagneux 1987(167), Ockelford 1989(168),			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
DVT (symptomatic and asymptomatic)	n= 433 (4 studies) 5-9d	2.7% vs 13.1% **RR: 0.22 (95% CI 0.10 to 0.51**) **SS in favour of LMWH** Absolute effect: -10% (95%CI -22% to 3%)	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 small trials, limited data available Consistency: OK Directness: -1 heterogenous population Imprecision: OK
PE	n= 5134 (5 studies) 5d-2w	0.1% vs 0.5% **RR: 0.22 (95% CI 0.06 to 0.78**) **SS in favour of LMWH** Absolute effect: 0% (95% CI -1% to 0%)	⨁⊖⊖⊖ **VERY LOW** Study quality: small trials, 2 OL with unclear randomization, 3 limited data Consistency:OK Directness: -1 heterogenous population Imprecision:OK
Major bleeding	n= 5426 (7 studies) 5d-2w	2.8% vs 1.4% **RR: 2.01 (95%CI 1.31 to 3.07)** **SS in favour of no prophylaxis** Absolute effect: 1% (95% CI 1% to 2%)	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 limited data for 3/7, 2 OL Consistency:OK Directness: -1 heterogenous population Imprecision:OK

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

This meta-analysis included 7 RCTs that compared LMWH with no thromboprophylaxis in patients who underwent general surgery. General surgery was defined as gastrointestinal, gynaecological, laparoscopic, thoracic and urological surgery. Some trials also included cancer patients. This is a clinically heterogeneous population.

No mortality rates were reported.

There were statistically significantly less events of deep vein thrombosis and pulmonary embolism in the patient group treated with LMWH compared to to those who did not receive thromboprophylaxis.
GRADE: VERY LOW quality of evidence (quality estimate based on limited data)

However, the number of major bleeding events was twice as high in the LMWH group compared to the no treatment group. This difference was statistically significant.
GRADE: VERY LOW quality of evidence (quality estimate based on limited data)

8.2 Duration of thromboprophylaxis in general surgery

8.2.1 Extended duration thromboprophylaxis versus short duration in abdominal or pelvic surgery

Ref	Comparison	N/n	Outcomes	Result**
732 Rasmussen 2009(172) Design: SR + MA Search date: January 2008	LMWH vs placebo	N= 4 n= 901 Bergqvist 2002 Jorgensen 2002 Lausen 1998 Rasmussen 2006	All VTE	**LMWH: 6.1% (95%CI, 4.0% to 8.7%)** **Placebo: 14.3% (95%CI, 11.2% to 17.8%)** **OR = 0.41 (95%CI, 0.26 to 0.63)** **SS, in favour of LMWH** **NNT = 13 (95%CI, 9 to 24)**
			All DVT	**OR = 0.43 (95%CI, 0.27 to 0.66)** **SS, in favour of LMWH** **NNT = 26 (95%CI, 17 to 59)**
			Proximal DVT	**OR = 0.27 (95%CI, 0.13 to 0.57)** **SS, in favour of LMWH**
			Symptomatic VTE	**LMWH: 0.2% (95%CI, 0.0% to 1.2%)** **Placebo: 1.7% (95%CI, 0.8% to 3.4%)** **OR = 0.22 (95%CI, 0.06 to 0.80)** **SS, in favour of LMWH** **NNT = 66 (95% CI 36 - 400),**
			Bleeding complications	LMWH: 3.7% (95%CI, 2.4% to 5.5%) Placebo: 4.1% (95%CI, 2.7% to 6.0%) OR = 1.11 (95%CI, 0.62 to 1.97) NS
			Mortality	LMWH: 5.8% (95%CI, 3.9 to 8.3) Placebo: 5.35% (95%CI, 3.6 to 7.6) OR = 1.12 (95%CI, 0.65 to 1.93) NS

* Characteristics of included studies: see below

** as calculated from meta-analysis by authors

Ref + design	n	Population	Duration	Comparison	Definiton of outcomes	Methodology
Bergqvist 2002(173) Design: RCT DB Venography	501	Patient characteristics: Patients undergoing surgery for abdominal or pelvic cancer	3 months	Enoxaparin 40 mg until day 6-10. Randomization at day 6-10: LMWH (Enoxaparin 40 mg) 25-31d Vs Placebo	All patients were scheduled for bilateral venography. Adequate definitions of VTE and bleeding complications were described in the paper.	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Double = patient, healthcare providers, data collectors, outcome assessors and data analysts FOLLOW-UP: <80% for DVT ITT: no Patients were included in the final analysis if they have reached a evaluable VTE end point (venogram or objective verification of symptomatic VTE
Lausen 1998(174) Design: RCT Assessor-blinded venography	118	Patient characteristics: Patients undergoing major abdominal surgery or non cardiac thoracic surgery for either benign or malignant disease	Not defined	LMWH (tinzaparin 3500 IE) Vs Placebo	All patients were scheduled for bilateral venography. An adequate definition of VTE was described int he paper. No definition of bleeding complications was given in the paper, but bleeding episodes were described.	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Open label = Assessor-blinded evaluation of the venograms, but patients, healthcare providers and data-analyst were not blinded FOLLOW-UP: not reported Compliance > 97% ITT: no Patients were included in the final analysis if they have reached an evaluable VTE end point (venogram or objective verification of symptomatic VTE The study was terminated prematurely due to lack of funding.
Rasmussen 2006(175) Design: RCT OL Assessor-blinded venography	427 (n= 248 cancer patients)	Patient characteristics: Patients undergoing major abdominal surgery for either benign or malignant disease	3 months	Dalteparin for 7 days, randomization at day 7: LMWH (dalteparin 5000 IE) for another 3	All patients were scheduled for bilateral venography. Adequate definitions of VTE and bleeding complications were described in the paper.	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : open label = Open-label study with assessor-blinded evaluation of the venograms. Patients, healthcare providers and data-analyst were not blinded.

				week Vs No treatment		FOLLOW-UP: >80% for DVT Compliance > 97% ITT: no Patients were included in the final analysis if they have reached an evaluable VTE end point (venogram, autopsy or objective verification of symptomatic VTE).
Jorgensen 2002(176) Design: RCT DB Venography	108	<u>Patient characteristics:</u> Patients undergoing curative surgery for abdominal or pelvic cancer	90 d	In-hospital tinzaparin. Randomisation at discharge: LMWH (tinzaparin 3500 IE) 4weeks Vs Placebo	All patients were scheduled for bilateral venography. Adequate definitions of VTE and bleeding complications were described. However, the planned interim analysis per-formed with the 328 patients included in the study did not reveal any significant difference between the two treatment groups.	<u>Not included in meta-analysis because data not extracatble</u> ALLOCATION CONC: Unclear RANDO: Adequate BLINDING : Double blind =Patients, healthcare provides, data collectors, outcome assessors and data analysts were blinded FOLLOW-UP: not reported The study was terminated prematurely due to lack of funding. This study was terminated prematurely by the sponsors due to an unexpected high withdrawal rate of patients. ITT: no The authors defined the ITT-population as patients with an evaluable efficacy end point. Patients were included inthe final analysis if they reached an evaluable VTE end point (venogram or objective verification of symptomatic VTE).

<u>Remarks:</u>

Patients were included in the final analysis if they reached an evaluable VTE end point (venogram or objectiveverification of symptomatic VTE).

Rasmussen is a member the advisory board of Pfizer, Denmark. All three authors were investigators on three of the randomised trials included in this review

<u>Author's conclusions:</u>

Prolonged thromboprophylaxis with LMWH significantly reduces the risk of VTE compared to thromboprophylaxis during hospital admittance only, without increasing bleeding complications after major abdominal or pelvic surgery.

8.2.2 Summary and conclusions. Extended duration thromboprophylaxis versus short duration in abdominal or pelvic surgery

Prolonged LMWH (31-31d) versus placebo after hospital discharge for thromboprophylaxis in abdominal or pelvic surgery			
Bibliography: meta-analysis Rasmussen 2009(172) included 4 RCTs: Bergqvist 2002(173), Lausen 1998(174), Rasmussen 2006(175), Jorgensen 2002(176)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Mortality	n=901 (4 studies) 3 m	LMWH: 5.8% (95%CI 3.9 to 8.3) Pla: 5.35% (95%CI 3.6 to 7.6) OR = 1.12 (95%CI, 0.65 to 1.93) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 FU NR, no ITT Consistency: OK Directness: OK Imprecision: OK
All VTE	n=901 (4 studies) 3 m	6.1% (95%CI 4.0% to 8.7%) vs 14.3% (95%CI 11.2% to 17.8%) **OR = 0.41 (95%CI, 0.26 to 0.63)** **SS in favour of LMWH** NNT = 13 (95% CI 9 to 24)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 FU NR, no ITT Consistency: OK Directness: OK Imprecision: OK
Symptomatic VTE	n=901 (4 studies) 3 m	0.2% (95%CI 0.0% to 1.2%) vs 1.7% (95%CI, 0.8% to 3.4%) **OR = 0.22 (95%CI, 0.06 to 0.80)** **SS, in favour of LMWH** NNT = 66 (95% CI 36 - 400)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 FU NR, no ITT Consistency: OK Directness: OK Imprecision: OK
DVT (symptomatic + asymptomatic)	n=901 (4 studies) 3 m	**OR = 0.43 (95%CI, 0.27 to 0.66)** **SS, in favour of LMWH** NNT = 26 (95%CI 17 to 59)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 FU NR, no ITT Consistency: OK Directness: OK Imprecision: OK
Bleeding	n=901 (4 studies) 3 m	3.7% (95%CI, 2.4% to 5.5%) vs 4.1% (95%CI, 2.7% to 6.0%) OR = 1.11 (95%CI, 0.62 to 1.97) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 FU NR, no ITT Consistency: OK Directness: OK Imprecision: OK

* As calculated from meta-analysis by authors

A meta-analysis of four RCTs compared prolonged LMWH thromboprophylaxis with standard thromboprophylaxis during hospital stay in abdominal or pelvic surgery patients. Patients were randomized after an initial in-hospital treatment, to receive either tinzaparin, dalteparin or enoxaparin for about three months after hospital discharge, whereas the control groups received placebo. The populations included both cancer patients and non-cancer patients.

No statistically significant difference was observed in mortality between LMWH and placebo groups.
GRADE: MODERATE quality of evidence

Prolonged thromboprophylaxis with LMWH significantly reduces the risk of VTE and DVT after major abdominal or pelvic surgery compared to shorter duration in-hospital prophylaxis.
GRADE: MODERATE quality of evidence

There is no statistically significant difference in bleeding complications between the treatment groups.
GRADE: MODERATE quality of evidence

8.2.3 Extended duration thromboprophylaxis versus short duration in cancer patients undergoing surgery

Ref	Comparison	N/n	Outcomes	Result
Akl 2008(177) Design: SR + MA Search date: January 2007	LMWH extended (beyond hospital stay) vs LMWH limited (during hospital stay)	N= 1 n= 248 Rasmussen 2006	**All DVT (symptomatic and asymptomatic)**	**At 4 weeks post surgery** **RR= 0.21 (95% CI 0.05 to 0.94)** **SS in favour of extended thromboprophylaxis**
		N=1 n=501 Bergqvist 2002	**Major bleeding**	At 4 weeks post surgery RR= 2.94 (95% CI 0.12 to 71.85) NS At 3 months post surgery RR=2.94 (95%CI 0.31–28.08) NS
		N=1 n=501 Bergqvist 2002	**Minor bleeding**	At 4 weeks and at 3 months post surgery RR= 1.31 (95% CI 0.56 to 3.05) NS
		N=1 n=501 Bergqvist 2002	**Mortality**	at 3 months RR= 0.49 (95% CI 0.12 to 1.94) NS at one year RR=1.23 (95% CI 0.70–2.15) NS

Illustrative comparative risks reported but calculation method unclear and not stated.

'Crude' absolute risks not reported

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Bergqvist 2002(173) (ENOXACAN II) Design: RCT DB Venography	501	Patient characteristics: Patients undergoing surgery for abdominal or pelvic cancer	3 months	Enoxaparin 40 mg until day 6-10. Randomization at day 6-10: LMWH (Enoxaparin 40 mg) 25-31d Vs Placebo	All patients were scheduled for bilateral venography. Adequate definitions of VTE and bleeding complications were described in the paper.	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Double = patient, healthcare providers, data collectors, outcome assessors and data analysts FOLLOW-UP: <80% for DVT ITT: no Patients were included in the final analysis if they have reached a evaluable VTE end point (venogram or objective verification of symptomatic VTE
Rasmussen 2006(175) (FAME) Design: RCT OL Assessor-blinded venography	427 (n= 248 cancer patients)	Patient characteristics: Patients undergoing major abdominal surgery for either benign or malignant disease	3 months	Dalteparin for 7 days, randomization at day 7: LMWH (dalteparin 5000 IE) for another 3 week Vs No treatment	All patients were scheduled for bilateral venography. Adequate definitions of VTE and bleeding complications were described in the paper.	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : open label = Open-label study with assessor-blinded evaluation of the venograms. Patients, healthcare providers and data-analyst were not blinded. FOLLOW-UP: >80% for DVT Compliance > 97% ITT: no Patients were included in the final analysis if they have reached an evaluable VTE end point (venogram, autopsy or objective verification of symptomatic VTE).
Jorgensen 2002(176)	108	Patient characteristics: Patients	90 d	In-hospital tinzaparin. Randomisation at	All patients were scheduled for bilateral venography. Adequate	Not included in meta-analysis because data not extracatble

Design: RCT DB Venography		undergoing curative surgery for abdominal or pelvic cancer		discharge: LMWH (tinzaparin 3500 IE) 4weeks Vs Placebo	definitions of VTE and bleeding complications were described. However, the planned interim analysis per- formed with the 328 patients included in the study did not reveal any significant difference between the two treatment groups.	ALLOCATION CONC: Unclear RANDO: Adequate BLINDING : Double blind =Patients, healthcare provides, data collectors, outcome assessors and data analysts were blinded FOLLOW-UP: not reported The study was terminated prematurely due to lack of funding. This study was terminated prematurely by the sponsors due to an unexpected high withdrawal rate of patients. ITT: no The authors defined the ITT-population as patients with an evaluable efficacy end point. Patients were included in the final analysis if they reached an evaluable VTE end point (venogram or objective verification of symptomatic VTE).

8.2.4 Summary and conclusions. Extended duration thromboprophylaxis versus short duration in cancer patients undergoing surgery

Prolonged LMWH (21-35d)versus short duration (6-10d) thromboprophylaxis in cancer patients undergoing surgery			
Bibliography: systematic review Akl 2008(177) reported Bergqvist 2002(173) and Rasmussen 2006(175), Jorgensen 2002(176)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	n= 501 (1 study) 3m	RR= 0.49 (95% CI 0.12 to 1.94) NS	⊕⊕⊖⊖ **LOW** Study quality: -1, low FU, no ITT Consistency: NA Directness: -1 Imprecision: -1 wide CI
DVT (symptomatic and asymptomatic)	n= 248 (1 study) 4w	RR= 0.21 (95% CI 0.05 to 0.94) **SS in favour of extended thromboprophylaxis**	⊕⊕⊖⊖ **LOW** Study quality: -1, low FU, no ITT Consistency: NA Directness: -1, asymptomatic DVT Imprecision: OK
Major bleeding	n= 501 (1 study) 4w	RR= 2.94 (95% CI 0.12 to 71.85) NS	⊕⊕⊖⊖ **LOW** Study quality: -1, not reported in 2/3 trials Consistency: NA Directness: Imprecision: -1, wide CI
Minor bleeding	n= 501 (1 study) 4w	RR= 1.31 (95% CI 0.56 to 3.05) NS	⊕⊕⊖⊖ **LOW** Study quality: -1, not reported in 2/3 trials Consistency: NA Directness: Imprecision: -1, wide CI

A systematic review found three RCTs that compared prolonged LMWH thromboprophylaxis with limited duration (in-hospital) thromboprophylaxis during hospital stay in cancer patients undergoing major abdominal or pelvic surgery. Patients were randomized after an initial in-hospital treatment (6-10 days) of LMWH, to receive either LMWH or placebo for another 21-35 days. All patients were scheduled for bilateral venography at the end of treatment.
Only 2 trials had data that could be extracted and reported.

No statistically significant difference was observed in mortality rates between extended and limited duration LMWH thromboprophylaxis.
GRADE: LOW quality of evidence

Prolonged thromboprophylaxis with LMWH significantly reduces the risk of all DVT (symptomatic and asymptomatic) after major abdominal or pelvic surgery.
GRADE: LOW quality of evidence

There is no statistically significant difference in minor or major bleeding complications between the treatment groups.
GRADE: LOW quality of evidence

9 Evidence tables and conclusions: Thromboprophylaxis in medical patients / immobilisation

9.1 Pharmacological treatment versus placebo for thromboprophylaxis in medical patients

9.1.1 Heparin versus no heparin in general medical patients

Ref	Comparison	N/n	Outcomes	Result**
400 Lederle 2011(178) Design: SR + MA Search date: April 2011 <u>Remark:</u> All events after randomization according to ITT, even if the original authors had excluded them <u>Funding source:</u> The American College of Physicians Clinical Guidelines Committee supported this	Heparin (LMWH – UFH or fondaparinux in 1 study) vs no heparin	**All Patients:**		
		N = 18 n = 36122	**Mortality**	OR = 0.93 (95%CI, 0.86 to 1.00) Absolute effect per 1000 patients: -6 (95%CI, -11 to 0) NS
		N = 6 n = 6163	**Sympomatic DVT**	OR = 0.75 (95%CI, 0.43 to 1.30) Absolute effect per 1000 patients: -2 (95%CI, -6 to 3) NS
		N = 15 n = 35579	**PE**	**OR = 0.70 (95% CI, 0.56 to 0.87)** **Absolute effect per 1000 patients: -3 (95%CI, -5 to -1)** **SS in favour of active treatment**
		N = 8 n = 34977	**PE associated with death**	OR = 0.81 (95%CI, 0.61 to 1.08) Absolute effect per 1000 patients: -1 (95%CI, -2 to 0) NS
		N = 7 n = 32301	**Fatal PE**	OR = 1.01 (95%CI, 0.68 to 1.48) Absolute effect per 1000 patients: -0 (95%CI, -1 to 2) NS
		N = 14 n = 9266	**All bleeding events**	OR = 1.28 (95%CI, 1.05 to 1.56) Absolute effect per 1000 patients: 9 (95%CI, 2 to 18) NS
		N = 17 n = 35852	**Major bleeding events**	**OR = 1.61 (95%CI, 1.23 to 2.10)** **Absolute effect per 1000 patients: 4 (95%CI, 1 to 7)** **SS in favour of no heparin**
		Medical patients (no stroke):		
		N = 10 n = 20717 Belch 1981 Dahan 1986 Gärdlund 1996 Samama 1999 Fraisse 2000 Leizorovicz 2004	**Mortality**	Heparin: 679/10466 (6.5%) No heparin: 679/10 251 (6.6%) OR = 0.94 (95%CI, 0.84 to 1.04) Absolute effect per 1000 patients: -4 (95%CI, -11 to 3) NS

project.		Mahé 2005 Cohen 2006 Lederle 2006 Weber 2008		
		N = 5 n = 5957	**Symptomatic DVT**	Heparin: 25/3166 (0.79%) No heparin: 27/2791 (0.96%) OR = 0.78 (95%CI, 0.45 to 1.35) Absolute effect per 1000 patients: -2 (95%CI, -6 to 4) NS
		N = 10 n = 20717 Belch 1981 Dahan 1986 Gärdlund 1996 Samama 1999 Fraisse 2000 Leizorovicz 2004 Mahé 2005 Cohen 2006 Lederle 2006 Weber 2008	**PE**	Heparin: 88/10 466 (0.84%) No heparin: 127/10 251 (1.2%) **OR = 0.69 (95%CI, 0.52 to 0.90)** **Absolute effect per 1000 patients: -4 (95%CI, -6 to -1)** **SS in favour of heparin**
		N = 6 n = 20094	**PE associated with death**	Heparin: 50/10 157 (0.49%) No heparin: 53/9937 (0.53%) OR = 0.93 (95%CI, 0.63 to 1.38) Absolute effect per 1000 patients: 0 (95%CI, -2 to 2) NS
		N = 5 n = 17620	**Fatal PE**	Heparin: 21/8927 (0.24%) No heparin: 26/8693 (0.30%) OR = 0.77 (95%CI, 0.43 to 1.37) Absolute effect per 1000 patients: -1 (95%CI, -2 to 1) NS
		N = 8 n = 8744	**All bleeding events**	Heparin: 216/4550 (4.7%) No heparin: 115/4194 (2.7%) OR = 1.34 (95%CI, 1.08 to 1.66) Absolute effect per 1000 patients: 9 (95%CI, 2 to 18)
		N = 9 n = 20447 Belch 1981 Gärdlund 1996	**Major bleeding events**	Heparin: 41/10 331 (0.40%) No heparin:25/10116 (0.25%) OR = 1.49 (95%CI, 0.91 to 2.43)

		Samama 1999 Fraisse 2000 Leizorovicz 2004 Mahé 2005 Cohen 2006 Lederle 2006 Weber 2008		Absolute effect per 1000 patients: 1 (95%CI, 0 to 3) NS
		Patients with stroke:		
		N = 8 n = 15405 McCarthy 1977 McCarthy 1986 Turpie 1987 Dickmann 1988 Prins 1989 Sandset 1990 Kay 1995 International Stroke Trial Collaborative group 1997	**Mortality**	Heparin: 496/5276 (9.4%) No heparin: 990/10 129 (9.8%) OR = 0.91 (95%CI, 0.70 to 1.18) Absolute effect per 1000 patients: -9 (95%CI, -29 to 18) NS
		N = 1 n = 206	**Sympomatic DVT**	Heparin: 0/101 No heparin: 1/105 (0.95%) OR = 0.14 (95%CI, 0.00 to 7.09) Absolute effect per 1000 patients: -9 (95%CI, -10 to 57) NS
		N = 5 n = 14862 Turpie 1987 Dickmann 1988 Prins 1989 Sandset 1990 International Stroke Trial Collaborative group 1997	**PE**	Heparin: 39/5015 (0.78%) No heparin: 95/9847 (0.96%) OR = 0.72 (95%CI, 0.50 to 1.04) Absolute effect per 1000 patients: -3 (95%CI, -5 to 0) NS
		N = 2 n = 14883	**PE associated with death**	Heparin: 32/5004 (0.64%) No heparin: 72/9879 (0.73%) OR = 0.70 (95%CI, 0.46 to 1.05) Absolute effect per 1000 patients: -2 (95%CI, -4 to 0) NS
		N = 2 n = 14861	**Fatal PE**	Heparin: 25/4912 (0.51%) No heparin: 40/9769 (0.41%) OR = 1.25 (95%CI, 0.74 to 2.09) Absolute effect per 1000 patients: 1 (95%CI, -1 to 4)

				NS
		N = 6 n = 522	**All bleeding events**	Heparin: 24/272 (8.8%) No heparin: 25/250 (10%) OR = 0.95 (95%CI, 0.55 to 1.63) Absolute effect per 1000 patients: -5 (95%CI, -45 to 53) NS
		N = 8 n = 15405 McCarthy 1977 McCarthy 1986 Turpie 1987 Dickmann 1988 Prins 1989 Sandset 1990 Kay 1995 International Stroke Trial Collaborative group 1997	**Major bleeding events**	Heparin: 79/5276 (1.5%) No heparin:89/10129 (0.88%) **OR = 1.66 (95%CI, 1.20 to 2.28)** **Absolute effect per 1000 patients: 6 (95%CI, 2 to 12)** **SS in favour of no heparin**

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Methodology
Weber 2008(179) Design: RCT OL Region: Switzerland	20	Mean age: 70 y (range: 55–88 y) <u>Indication for PA (= Prophylactic anticoagulation):</u> Cancer <u>Inclusion</u>: admitted to center of continuous care with an estimated life expectancy ≥ 6 mo <u>Exclusion</u>: VTE within 6 mo, active bleeding, creatinine clearance <20 mL/min per 1.73 m^2, thrombocytopenia, history of heparin thrombocytopenia, PTT >45 s, or PT <35% and concomitant anticoagulation on admission	90d (treatment + follow up)	Heparin (Nadroparin, 2850 U/d (weight < 70 kg) or 3800 U/d (weight > 70 kg) vs Usual care <u>Duration</u>: Not reported	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : none FOLLOW-UP: Not reported ITT: yes Funding: Not stated
Cohen 2006(180) Design: RCT DB Region: Multinational	849	Mean age: 75 y (range, 53–96 y) Men: 42% <u>Indication for PA:</u> CHF (NYHA class III or IV) or acute respiratory, inflammatory, or infectious disease <u>Inclusion</u>: indications as listed, aged ≥ 60 y, and expected to remain in bed for ≥ 4 d <u>Exclusion</u>: endocarditis; cerebral metastasis; recent hemorrhagic or ischemic stroke; brain, spinal, or ophthalmologic surgery; indwelling intrathecal or epidural catheter; serum creatinine level >180 µmol/L (>2.04 mg/dL) in a well-hydrated patient; documented hypersensitivity to contrast media; anticipated intubation for > 24 h; use of	32d	Heparin (Fondaparinux, 2.5 mg/d) vs No Heparin <u>Duration</u>: 6 – 14 d (median: 7 d)	ALLOCATION CONC:Adequate RANDO: Adequate BLINDING : Double FOLLOW-UP: not adequatly described ITT: no Funding: Industry

		antithrombotics ≤ 48 h before random assignment; indication for anticoagulant prophylaxis or therapy; or life expectancy < 1 mo			
Lederle 2006(181) Design: RCT DB Region: USA	280	Mean age: 72 y Men: 99% <u>Indication for PA:</u> Hospitalization in general medical unit <u>Inclusion</u>: admitted or transferred to medical service of VA medical center on day of random assignment or the previous day; aged ≥ 60 y; and remaining under care of VA medical service ≥3 d from random assignment <u>Exclusion</u>: receiving or requiring anticoagulation for reasons other than VTE prophylaxis; known thrombocytopenia; hypertension; other contraindication to low-dose heparin, in the opinion of the patient's physicians; "supportive or palliative care only" status; or occurrence of myocardial infarction, stroke, major surgery (defined as requiring general, spinal, or epidural anesthesia and lasting >30 min), or any eye surgery within the past 30 d	90 d	Heparin (Enoxaparin, 40 mg/d) vs Placebo <u>Duration</u>: until discharge (mean: 12 d)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Double FOLLOW-UP: adequately described ITT: yes Funding: Nonindustry
Mahé 2005(182) Design: RCT DB Region: Multinational	2474	Mean age: 76 y Men: 41% <u>Indication for PA:</u> CHF or acute or respiratory disease <u>Inclusion</u>: age ≥ 40 y, hospitalized <24 h because of acute medical	21d	Heparin (Nadroparin, 7500 U/d) Vs Placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Double FOLLOW-UP: Not reported ITT: yes

		illness, and immobilization Exclusion: conditions that could increase the risk for hemorrhage (hypertension, active gastroduodenal ulcer, renal failure, PT <50%, or platelet count <50 X 10^9 cells/L), conditions that required full-dose anticoagulation, stroke or major surgery ≤30 d and anticoagulant or antiplatelet therapy ≤7 d, or pregnancy		Duration: 21 d or until discharge (mean: 13 d)	Funding: Industry
Leizorovicz 2004(183) and Kucher 2005(184) Design: RCT DB Region: Multinational	3706	Mean age: 69 y Indication for PA: Acute CHF, acute respiratory failure, infectious disease, acute rheumatologic disorders, or inflammatory bowel disease Inclusion: age ≥40 y, acute medical condition that required hospitalization ≥ 4 d, and ≤3 d of previous immobilization Exclusion: acute coronary syndrome within the previous month, a major surgical or invasive procedure in the previous month or to be done within the next 2 wk, bacterial endocarditis, immobilized lower limb because of a cast or fracture, stroke ≤ 3 mo, high risk for bleeding, platelet count <100 X 10^9 cells/L, heparin or LMWH prophylaxis > 48 h before random assignment, contraindication to heparin anticoagulation, creatinine level >176.8 µmol/L (>2.0 mg/dL), hepatic insufficiency or active hepatitis, pregnancy or breastfeeding, or life expectancy <1 mo	90d	Heparin (Dalteparin, 5000 U/d) Vs Placebo Duration: 14 d	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Double FOLLOW-UP: : not adequately described ITT: no Funding: Industry
Fraisse 2000(185)	223	Mean age: 68 y	11d	Heparin	ALLOCATION CONC: Adequate

Design: RCT DB Region: France		Men: 78% <u>Indication for PA:</u> Acute decompensated COPD on mechanical ventilation <u>Inclusion</u>: age 40–80 y and weight 45–110 kg <u>Exclusion</u>: confirmed DVT within 6 mo or signs of DVT on Doppler ultrasonography at inclusion; an organic lesion that could bleed (active gastroduodenal ulcer or recent hemorrhagic CVA); severe liver failure leading to a decrease of PT to < 50%; severe renal impairment; confirmed or uncontrolled hypertension; congenital or acquired coagulation disorder; history of hypersensitivity or thrombocytopenia to heparins of any type; contraindication to anticoagulation, venography, or angiography; or receiving acetylsalicylic acid, ticlopidine, or oral anticoagulants		(Naddroparin, 3800 - 5700 U/d) vs Placebo <u>Duration</u>: 21 d or until weaned from mechanical ventilation (mean: 11 d)	RANDO: Adequate BLINDING : Double FOLLOW-UP: adequately described ITT: no Funding: Industry
Samama 1999(186) and Alikhan 2003(187) (subgroup) Design: RCT Region: Multinational	1102	Mean age: 73 y <u>Indication for PA:</u> CHF (NYHA class III or IV), acute or chronic respiratory disease, infectious disease, or acute rheumatologic disorders <u>Inclusion</u>: age ≥ 40 y, hospitalized ≥6 d, and not immobilized ≤ 3 d <u>Exclusion</u>: stroke or major surgery within 3 mo; contraindications to the use of iodinated contrast medium; known thrombophilia; creatinine level > 150.20 µmol/L (>1.7 mg/dL); HIV infection; uncontrolled arterial	110 d	Heparin (Enoxaparin, 20 mg/d; enoxaparin, 40 mg/d) Vs Placebo <u>Duration</u>: 6 – 14 d (mean: 7 d)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Double FOLLOW-UP: adequately described ITT: yes Funding: Industry

		hypertension, active peptic ulcer, bacterial endocarditis, or other conditions that could increase risk for hemorrhage; hypersensitivity to heparin or heparin-induced thrombocytopenia; platelet count < 100 X 10^9 cells/L, prolonged aPTT, PT <50%, or an international normalized ratio >1.2; required anticoagulation or received any type of anticoagulation for >48 h; and pregnancy or women of childbearing years			
Gärdlund 1996(188) Design: RCT OL Region: Sweden	11693	Mean age: 76 y <u>Indication for PA:</u> Infectious disease <u>Inclusion</u>: Age ≥55 y <u>Exclusion</u>: ongoing anticoagulation, readmission 60 d from random assignment, active bleeding, coagulation disorder, dialysis, liver failure, HIV infection, or terminal disease	60 d	Heparin (UFH, 5000 U twice daily) Vs Usual care <u>Duration</u>:21 d or until discharge (mean: 7 d)	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : None FOLLOW-UP: adequately described ITT: yes Funding: Mainly non-industry
Dahan 1986(189) Design: RCT DB Region: France	270	Mean age: 80 y Men: 62% <u>Indication for PA:</u> Heart failure, respiratory diseases, malignant disease, infectious disease, or other <u>Inclusion</u>: age ≥ 65 y and nonsurgical inpatient <u>Exclusion</u>: ongoing anticoagulant or platelet inhibitor therapy; active bleeding, including cerebral hemorrhage; coagulation disorders; short-term hospitalization (<7 d); thyroid diseases; or iodine allergy	10 d	Heparin (Enoxaparin, 60 mg/d) Vs Placebo <u>Duration</u>: 10 d or until discharge	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : double FOLLOW-UP: adequately described ITT: no Funding: None stated

Belch 1981(190) Design: RCT Region: Scotland	100	Mean age: 66 y Men: 69% Indication for PA: Heart failure or chest infection Inclusion: age ≥ 40–80 y Exclusion: definite risk for bleeding, DVT or PE on admission, iodine allergy, or confined to bed >2 d before admission	14 d	Heparin (UFH, 5000 U, 3 times daily) Vs Usual care Duration: 14 d or until discharge (mean: 9 d)	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : DVT diagnosed by person unaware of treatment assignment FOLLOW-UP: Not reported ITT: yes Funding: None stated
International Stroke Trial Collaboration Group 1997(191) Design: RCT OL Region: International	14578	Age ranges: < 50 y : 5% 50–59 y : 11% 60–69 y : 23% 70–79 y: 35% > 80 y: 26% Inclusion: evidence of acute stroke within 48 h, no evidence of ICH, and no clear indications for or contraindications to aspirin or heparin Exclusion: ongoing anticoagulation, small likelihood of worthwhile benefit (symptoms likely to resolve in a few hours or patient severely disabled before the stroke), or high risk for adverse effects (hypersensitivity to aspirin, active peptic ulcer, or recent GI bleeding)	6 mo	Heparin (UFH, 5000 U twice daily) Vs Avoid heparin Duration: 14 d or until discharge (mean: 11 d)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Open label FOLLOW-UP: adequately described ITT: modified ITT (> 99%) Funding: Multiple sources, mainly non-industry
Kay 1995(192) Design: RCT DB Region:	312	Mean age: 67 y Asian (Chinese): 100% Inclusion: diagnosis of acute stroke within the previous 48 h and aged <80 y	90 d	Heparin (Nadroparin, 4100 U/d) Vs Placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Double FOLLOW-UP: adequately described

Hong Kong		Exclusion: CT evidence of ICH, transient neurologic deficits, sustained hypertension, major confounding neurologic or systemic illness (including a previous disabling stroke), recent major operation or known tendency toward bleeding, current anticoagulation or valvular heart disease necessitating such therapy, known hypersensitivity or any other adverse reaction to heparin, stroke but no motor deficit, or death considered to be imminent		Duration: 10 d	ITT: no Funding: Industry and non-industry
Sandset 1990(193) Design: RCT DB Region: Norway	103	Mean age: 75 y Inclusion: diagnosis of acute stroke within 72 h Exclusion: comatose, hemorrhagic stroke on CT scan, stroke onset >72 h before inclusion, strokes qualifying for heparin therapy (mostly progressive or of embolic origin), bleeding diathesis, severe hypertension, severe renal failure, severe liver failure, severe anemia, thrombocytopenia, or cancer	14 d (mortality: 28 d)	Heparin (Dalteparin, 3000–5500 U/d (based on body weight), VS Placebo Duration: 14 d or until discharge	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Double FOLLOW-UP: adequately described ITT: no Funding: Industry and non-industry
Prins 1989(194) Design: RCT DB Region: The Netherlands	60	Median age range: 71–80 y Inclusion: ischemic stroke within 72 h Exclusion: ongoing anticoagulation or comatose	28 d	Heparin (Dalteparin, 2500 U twice daily) VS Placebo Duration: 14 d or until discharge	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Double FOLLOW-UP: Not reported ITT: yes (for most outcomes) Funding: None stated
Dickmann 1988(195) Design:	46	Mean age: 61 y Inclusion: diagnosis of acute stroke within previous 24 h	10 d	Heparin (UFH, 5000 U, 3 times daily) Vs	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : None

RCT OL Region: Germany		<u>Exclusion</u>: bleeding diathesis, hypertension, or deep coma with signs of brain herniation		Usual care (these patients received heparin at day 10) <u>Duration</u>: 6 d (at day 4)	FOLLOW-UP: Not reported ITT: yes Funding: None stated
Turpie 1987(196) Design: RCT DB Region: Canada	75	Mean age: 69 y (range: 28–90 y) <u>Inclusion</u>: diagnosis of acute stroke <u>Exclusion</u>: ongoing anticoagulation; CT evidence of hemorrhagic stroke; nonparalytic stroke; assessment of qualifying stroke >7 d after onset; stroke thought to be embolic in origin, thus requiring anticoagulation; acute DVT; history of subarachnoid hemorrhage; bleeding disorder; sensitivity to iodine or contrast dye; severe liver or renal dysfunction; or GI bleeding or active peptic ulcer	90 d	Heparin (Danaparoid, 1000 U via IV load, then 750 U twice daily) VS Placebo <u>Duration</u>: 14 d or until discharge (mean: 12 d)	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : Double FOLLOW-UP: adequately described ITT: no Funding: : Industry and non-industry
McCarthy 1986(197) Design: RCT OL Region: UK	305	Mean age: 76 y Men: 43% <u>Inclusion</u>: diagnosis of stroke within previous 48 h <u>Exclusion</u>: bleeding diathesis, hypertension, grade 3 or 4 hypertensive retinopathy, history of subarachnoid hemorrhage, active peptic ulcer, allergy to iodine, goiter or thyrotoxicosis, recent myocardial infarction, or cancer	84 d	Heparin (UFH, 5000 U, 3 times daily) VS Usual care <u>Duration</u>: 14 d	ALLOCATION CONC: unclear RANDO: Adequate BLINDING : None FOLLOW-UP: Not reported ITT: yes Funding: Industry and non-industry
McCarthy 1977(198)	32	Mean age: 79 y Men: 34%	28 d	Heparin (UFH, 5000 U, 3 times daily)	ALLOCATION CONC: unclear RANDO: Adequate

Design: RCT OL Region: UK		Inclusion: diagnosis of stroke within previous 48 h Exclusion: blood in cerebrospinal fluid, bleeding diathesis, hypertension, grade 3 or 4 hypertensive retinopathy, history of subarachnoid hemorrhage, history of active peptic ulcer, allergy to iodine, goiter or thyrotoxicosis, or recent myocardial infarction		VS Usual care Duration: 14 d	BLINDING : None FOLLOW-UP: Not reported ITT: yes Funding: None stated

Remarks:
Non-English-language studies were not included, but these were few and small.
The studies that were included did not screen patients with computed tomography, so the findings presented herein should reflect clinical disease.
Randomisation was an inclusion criteria for the meta-analysis. Therefore, we assume that randomization was adequate for all the studies because it was never mentioned elsewhere.

Author's conclusions:
Heparin prophylaxis had no significant effect on mortality, may have reduced PE in medical patients and all patients combined, and led to more bleeding and major bleeding events, thus resulting in little or no net benefit.

Enoxaparin versus placebo in acutely ill medical patients wearing elastic compression stockings

Study details	n/Population	Comparison	Outcomes		Methodological
Ref 345 Kakkar 2011(199) Design: RCT DB PG Setting: international, multicenter study at 193 sites in China, India, Korea, Malaysia, Mexico, The Philippines, and Tunisia. Duration of follow-up: up to 90d	n= 8323 Mean age:65y Previous VTE: 0.5% Current malignancy: 5.9% <u>Inclusion</u> men and women, ≥40y, hospitalized within 48 hours before randomization for at least one of the following conditions: acute decompensation of heart failure; active cancer; or severe systemic infection in addition to at least one of the following conditions: chronic pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary fibrosis, or the pulmonary restrictive syndrome), obesity (BMI ≥30), a personal history of venous thromboembolism, or an age of 60 years or older. In addition, an anticipated duration of hospitalization ≥6 days and an American Society of Anesthesiologists health status score of≥ 3; or, for patients with cancer, an Eastern	Enoxaparin for 10+/-4days plus elastic stockings with graduated compression (4171 patients) Vs Placebo for 10+/-4days plus elastic stockings with graduated compression (4136 patients)	Efficacy		RANDO: adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0.5% at day 30 (0.9% at day 90 Drop-out and Exclusions: 0.2 % A total of 16 patients (0.2%) were subsequently excluded either because they had been given an erroneous randomization number (4 patients) or because they did not receive the study drug and had no follow-up data (12 patients). • Described: yes • Balanced across groups: yes
			Death from any cause at 30 days (PO)	Day 30: Enoxaparin: 205/4171 (4.9%) Placebo: 199 /4136 (4.8%) RR=1.0 (95%CI: 0.8 to 1.2) P=0.93; NS	
			Death from any cause at 14 and 90 days	Day 14: Enoxaparin: 121/4171 (2.9%) Placebo:119/4136 (2.9%) RR=1.0(95% CI 0.8 to 1.3); P = 0.95; NS Day 90: Enoxaparin: 348/4171 (8.4%) Placebo: 355/4136 (8.6%) RR=1.0 (95% CI 0.8 to 1.1) P= 0.71, NS	
			Cardiopulmonary death (=sudden death or death due to acute myocardial infarction, heart failure, pulmonary failure, or PE)	Day 30: Enoxaparin: 141 (3.4%) Placebo: 135 (3.3%) RR=1.0; 95% CI 0.8 to 1.3; P=0.77 NS Day 14 and day 90: NS	
			Sudden death or pulmonary embolism	Day 14: Enoxaparin: 20 (0.5%) Placebo: 27 (0.7%) RR=0.7; 95% CI 0.4 to 1.3; P=0.29 NS Day 30: Enoxaparin:29 (0.7%) Placebo: 29 (0.7%) RR=1.0; 95% CI 0.6 to 1.7; P=0.97	

	Cooperative Oncology Group performance status score ≤ 2 <u>Exclusion</u> Major surgery or major trauma <6 weeks;Need for ventilatory support ; Symptomatic VTE at enrolment; Multi organ failure; an active bleeding disorder; Contraindication to anticoagulation:Cerebrovascular accident at inclusion (amendment n°1) and within 10 days prior study inclusion (amendment n°2); prosthetic heart valves; confirmed cerebral metastases; Known hypersensitivity to heparin or LMWH, or pork-derived products; History of HIT, HAT, or HITTS; Persistent renal failure creatinine clearance <30mL/min ; severe anemia of unexplained cause ; Patient unlikely to be compliant (e.g. alcohol, other drug abuse etc); Woman of childbearing potential not protected by effective contraception			NS Day 90:NS	ITT:Yes The safety analyses were performed on data from all patients who received at least one dose of a study drug.) Power: "With a rate of death in the placebo group of 4.8% rather than the 7% originally anticipated, our study had 77% power to detect a 25% reduction in the rate of death from any cause and 57% power to detect a 20% reduction" SELECTIVE REPORTING: no Sponsor: Sanofi: Funding and study drugs were provided by the sponsor
			Safety		
			Any bleeding (number of patients) up to 90d	**Enoxaparin: 91 (2.2%)** **Placebo: 60 (1.5%)** **RR=1.5 (95% CI: 1.1 to 2.1)** **P=0.01, SS in favour of placebo**	
			Major bleeding (number of patients) (overt bleeding associated with one of the following: death; need for transfusion of ≥ 2 units of packed red cells or whole blood; a fall in Hb level of ≥20 g /liter; the requirement for a major therapeutic intervention to stop or control bleeding; or a bleeding site that was retroperitoneal, intracranial, or intraocular.)	Enoxaparin: 16 (0.4%) Placebo: 11 (0.3%) RR= 1.4 (95% CI 0.7 to 3.1 ; P=0.35) NS	
			Clinically relevant nonmajor bleeding (a nonmajor hemorrhage leading to discontinuation of the study drug or to hospitalization.)	Enoxaparin: 18 (0.4%) Placebo: 14 (0.3%) RR=1.3 (95% CI 0.6 to 2.6; P=0.49) NS	
			Any minor bleeding (overt bleeding that did not meet thecriteria for major hemorrhage but was associated with clinical features defined in the protocol)	Enoxaparin: 73 (1.8%) Placebo: 47 (1.1%) RR=1.5 (95% CI 1.1 to 2.2; P=0.02) **SS in favor of placebo**	
			Serious adverse events	"The two groups did not differ significantly with respect to the rate of either serious adverse events" Enoxaparin: 5.8% [243 of 4171 patients] Placebo: 5.3% [219 of 4136 patients]	

9.1.2 Summary and conclusions. Heparin versus no heparin in general medical patients (no stroke)

Heparin vs no heparine in hospitalized medical patients with no stroke			
Bibliography: Meta-analysis Lederle 2011(178), included these RCTs: Weber 2008(179), Lederle 2006(181), Mahé 2005(182), Leizorovicz 2004(183), Fraisse 2000(185), Samama 1999(186), Gärdlund 1996(188), Dahan 1986(189), Belch 1981(190), Cohen 2006(180) 1 more recent RCT: Kakkar 2011(199)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Mortality	20717 (10 studies) treatment 6-21d or until discharge FU: 10d-6mo 8323 (1 study) 30d	Lederle 2011 6.5% vs 6.6% OR = 0.94 (95%CI 0.84 to 1.04) NS Kakkar 2011 4.9% vs 4.8% RR=1.0 (95%CI: 0.8 to 1.2) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1: no blinding and unclear allocation concealment in largest trial Consistency:OK Directness:OK Imprecision:OK
Symptomatic DVT	5957 (5 studies) 10d-6mo	Lederle 2011 0.79% vs 0.96% OR = 0.75 (95%CI 0.43 to 1.30) NS	⊕⊕⊖⊖ **LOW** Study quality:-1: no blinding and unclear all conc in largest trial Consistency:OK Directness:OK Imprecision:-1: wide CI
PE	20717 (10 studies) 10d-6mo	Lederle 2011 0.84% vs 1.2% **OR = 0.69 (95%CI, 0.52 to 0.90)** **SS in favour of heparin** Absolute effect per 1000 patients: -4 (95%CI, -6 to -1)	⊕⊕⊕⊖ **MODERATE** Study quality:-1: no blinding and unclear all conc in largest trial Consistency:OK Directness:OK Imprecision:OK
Major bleeding	20447 (9 studies) 10d-6mo 8323 (1 study) 90d	Lederle 2011 0.40% vs 0.25% OR = 1.49 (95%CI, 0.91 to 2.43) NS Kakkar 2011 0.4% vs 0.3% RR= 1.4 (95% CI 0.7 to 3.1) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 no blinding and unclear all conc in largest trial Consistency:OK Directness:OK Imprecision:OK

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

One meta-analysis (Lederle 2011) and one more recent RCT (Kakkar 2011) compared heparin with no heparin in hospitalized patients (excluding stroke patients). Prophylaxis with heparin ranged from 6-21 days, according to study. In the meta-analysis, LMWH was used in 7 trials, UFH in 2 trials and fondaparinux in 1 trial.

Studies were limited to those that provided separate data for medical patients (excluding surgical, trauma, obstetric, or pediatric patients).
In the trial of Kakkar 2011, patients were also wearing elastic compression stockings. In the meta-analysis, it is not clear whether or not patients had additional compression stockings or other mechanical prophylaxis.

Heparin prophylaxis had no statistically significant effect on mortality.
GRADE: MODERATE quality of evidence

There was no statistically significant difference between heparin prophylaxis and no heparin in the risk of symptomatic DVT.
GRADE: LOW quality of evidence

Heparin prophylaxis significantly reduced the risk of pulmonary embolism.
GRADE: MODERATE quality of evidence

Heparin therapy had no statistically significant effect on major bleeding events.
GRADE: MODERATE quality of evidence

9.1.3 Summary and conclusions. Heparin versus no heparin in stroke patients

Heparin (LMWH or UFH) vs no heparin for thromboprophylaxis in stroke patients			
Bibliography: meta-analysis Lederle 2011(178) included these RCTs: International Stroke Trial Collaboration Group 1997(191), Kay 1995(192), Sandset 1990(193), Prins 1989(194), Dickmann 1988(195), Turpie 1987(196), McCarthy 1986(197), McCarthy 1977(198)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Mortality	n= 15405 (8 studies) treatment 6-21 d or until discharge FU 14d-6m	9.4% vs 9.8% OR = 0.91 (95%CI 0.70 to 1.18) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1, largest trial open-label, comparison "usual care" Consistency: OK Directness: OK Imprecision: OK
Symptomatic DVT	n= 206 (1 study) treatment 6-21 d or until discharge FU 14d-6m	0 vs 0.95% OR = 0.14 (95%CI 0.00 to 7.09) NS	⊕⊕⊖⊖ **LOW** Study quality:-1, only one trial Consistency: NA Directness: OK Imprecision:-1: wide CI
PE	n = 14862 (5 studies) treatment 6-21 d or until discharge FU 14d-6m	0.78% vs 0.96% OR = 0.72 (95%CI 0.50 to 1.04) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1, largest trial open-label Consistency: OK Directness: OK Imprecision: OK
Major bleeding	n = 15405 (8 studies) treatment 6-21 d or until discharge FU 14d-6m	1.5% vs 0.88% OR = 1.66 (95%CI 1.20 to 2.28) **SS in favour of no heparin** Absolute effect per 1000 patients: 6 (95%CI 2 to 12)	⊕⊕⊕⊖ **MODERATE** Study quality:- 1, largest trial open-label, comparison "usual care" Consistency: OK Directness: OK Imprecision: OK
All bleeding	n = 522 (6 studies) treatment 6-21 d or until discharge FU 14d-6m	8.8% vs 10% OR = 0.95 (95%CI 0.55 to 1.63) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1, small studies Consistency: OK Directness: OK Imprecision: OK

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

A systematic review and meta-analysis (Lederle 2011) compared heparin (UFH or LMWH) with no heparin treatment in stroke patients. Duration of heparin thromboprophylaxis ranged from 6 to 14 days or until discharge.

No statistically significant difference in number of deaths was observed between treatment groups.
GRADE: MODERATE quality of evidence

One trial reported no significant reduction in the risk of symptomatic DVT through heparin prophylaxis.
GRADE: LOW quality of evidence

Heparin prophylaxis did not result in a statistically significantly smaller number of cases of pulmonary embolism in stroke patients.
GRADE: MODERATE quality of evidence

Significantly more major bleeding events occurred in the group treated with heparin in comparison with no heparin. According to some smaller studies, the overall rate of 'all bleeding' did not differ significantly between treatment groups.
GRADE: MODERATE quality of evidence

9.2 Pharmacological treatment versus pharmacological treatment for thromboprophylaxis in medical patients

9.2.1 Extended duration apixaban versus short duration enoxaparin in medical patients

Study details	n/Population	Comparison	Outcomes		Methodological
Ref: 393 Goldhaber 2011-ADOPT(200) Design RCT:DB PG Setting: in hospital international, multicenter Duration of follow-up:90 d (but results reported for 30 day-period)	n= 6528 Mean age:66,75jaar hospitalized for congestive heart failure, acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease and had an expected hospital stay of at least 3 days. excluded if they had confirmed venous thromboembolism) <u>Inclusion</u> Except for patients with congestive heart failure or respiratory failure, eligible patients had to have at least one of the following additional risk factors: an age of 75 years or older, previous documented venous thromboembolism or a history of venous thromboembolism for which they received anticoagulation for at least 6 weeks, cancer, a	Apixaban oral 2.5mg 2x/d for 30d. + placebo injection for 6-14d vs enoxaparin subcutaneously 40mg 1x/d for 6-14d + placebo tablet for 30 d	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 3184 + 3217 patients = 98 % in safety analysis 2211 + 2284 patients = 69% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT:no Power: inadequate (The ADOPT trial was underpowered. The 13% reduction in the primary outcome favored apixaban, but the between-group difference was not significant,
			Composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis, or asymptomatic proximal-leg deep-vein thrombosis (PO) as detected with the use of systematic bilateral compression ultrasonography on day 30	<u>Treatment period (30 days)</u> Apixaban: 2.71% Enoxaparin: 3.06% RR= 0.87; 95% CI 0.62 to 1.23; p=0.44 two sided for superiority NS <u>Parenteral-treatment period (6-14d)</u> Apixaban: 1.73% Enoxaparin: 1.61% RR= 1.06 (95%CI 0.69 to 1.63) NS
			Symptomatic deep-vein thrombosis	Apixaban: 0.15% Enoxaparin: 0.49% NT <u>Parenteral-treatment period (6-14d)</u> Apixaban: 0.03% Enoxaparin: 0.12% NT
			Fatal or nonfatal pulmonary	<u>Treatment period (30 days)</u> Apixaban: 0.22%

	body-mass index of 30 or more, estrogenic hormone therapy, or chronic heart failure or respiratory failure. In addition, all patients had to be moderately or severely restricted in their mobility. Moderately restricted mobility allowed for walking within the hospital room or to the bathroom. Severely restricted mobility was defined as being confined to bed or to a chair at the bedside <u>Exclusion</u> confirmed venous thromboembolism; a disease requiring ongoing treatment with a parenteral or oral anticoagulant agent; active liver disease, anemia or thrombocytopenia; severe renal disease (creatinine clearance of <30 ml per minute Cockcroft and Gault); allergy to enoxaparin; or prior heparin-induced thrombocytopenia or taking two or more antiplatelet agents or aspirin >165 mg per day ; a surgical procedure in the previous 30 days that might be associated with a risk of		**embolism**	Enoxaparin: 0.24% NT <u>Parenteral-treatment period (6-14d)</u> Apixaban: 0.09% Enoxaparin: 0.09% NT	and thus no clinically directive conclusion can be drawn.) SELECTIVE REPORTING: no Other important methodological remarks Duration of treatment is different between groups Sponsor: Bristol-Myers Squibb and Pfizer
			Death from any cause occurring during the 30-day treatment period	There was no significant difference in the rate of death between the apixaban group and the enoxaparin group (4.1% in each group [131 and 133 patients, respectively]).	
			Death from any cause occurring during the entire 90-day study period	There was no significant difference in the rate of death between the apixaban group and the enoxaparin group (4.1% in each group [131 and 133 patients, respectively]).	
			Safety		
			Bleeding		
			Major bleeding (if it was fatal or overt and was accompanied by one or more of the following: a decrease in hemoglobin of 2 g or more per deciliter over a 24-hour period; transfusion of 2 or more units of packed red cells; or intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding, bleeding that occurred in an operated joint that required	<u>Treatment period (30 days)</u> **Apixaban: 0.47%** **Enoxaparin: 0.19%** **RR = 2.58; 95% CI 1.02 to 7.24, P=0.04** **SS in favour of enoxaparin** <u>Parenteral-treatment period (6-14d)</u> Apixaban: 0.25% Enoxaparin: 0.12%	

	bleeding, had received anticoagulant prophylaxis for venous thromboembolism in the previous 14 days, were actively bleeding or were at high risk for bleeding; or had invasive procedures planned or scheduled during the treatment period, a hemoglobin level of less than 9 g per deciliter, a platelet count of less than 100,000 per cubic millimeter, an ALT level >2xupper limit, or direct or total bilirubin > 1.5 x upper limit; women who might become pregnant, were pregnant, were breast-feeding, or were unwilling or unable to use an acceptable method of contraception		reoperation or intervention, or intramuscular bleeding with the compartment syndrome.)	RR = 2.06 (95%CI 0.62 to 7.85), P=0.23 NS	
			Major and clinically relevant nonmajor bleeding (defined as acute, clinically overt bleeding that did not meet the criteria for classification as a major bleeding event but did meet at least one of the following criteria: epistaxis that required medical attention or persisted for 5 minutes or more, gastrointestinal bleeding containing frank blood or coffee-ground material that tested positive for blood, endoscopically confirmed bleeding, spontaneous hematuria or hematuria persisting for 24 hours or more after urinary-tract catheterization, unusual bruising, radiographically confirmed hematoma, or hemoptysis.)	<u>Treatment period (30 days)</u> Apixaban: 2.67% Enoxaparin: 2.08% RR= 1.28; 95% CI 0.93 to 1.76, P=0.12 NS <u>Parenteral-treatment period (6-14d)</u> Apixaban: 1.82% Enoxaparin: 1.37% RR= 1.33; 95% CI 0.90 to 1.97, P=0.15 NS	
			All bleeding	<u>Treatment period (30 days)</u> Apixaban: 7.73% Enoxaparin: 6.81% RR = 1.13; 95% CI 0.95 to 1.34, P=0.87 NS <u>Parenteral-treatment period (6-14d)</u> Apixaban: 5.34% Enoxaparin 4.86% RR = 1.09; 95% CI 0.88to 1.35,	

				P=0.41 NS	
			Myocardial infarction; stroke; thrombocytopenia; and death from any cause.	The rates of adverse events, including myocardial infarction, stroke, and thrombocytopenia, did not differ significantly between the two groups during the treatment period or the follow-up period.	

9.2.2 Summary and conclusions. Extended duration apixaban versus short duration enoxaparin in medical patients

Apixaban 2.5mg 2x/d for 30d versus enoxaparin subcutaneously 40mg 1x/d for 6-14d			
Bibliography: Goldhaber 2011-ADOPT(200)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	6528 (1 study) 90d	4.1% in each group 'NS'	⊕⊕⊕⊖ **MODERATE** Study quality:-1 poor reporting of this outcome Consistency:NA Directness:OK Imprecision:OK
Composite (symptomatic DVT or asymptomatic proximal DVT, PE, death related to VTE)	6528 (1 study) 30d	<u>6-14d parenteral treatment</u> 1.73% vs 1.61% RR= 1.06 (95%CI 0.69 to 1.63) NS <u>30 days treatment (PO)</u> 2.1% vs 3.06% RR= 0.87 (95%CI 0.62 to 1.23) NS	⊕⊕⊖⊖ **LOW (6-14d)** ⊕⊖⊖⊖ **VERY LOW (30d)** Study quality:-1 69% in efficacy analysis and no ITT Consistency:NA Directness:OK -1 for asymptomatic DVT in composite or -2 comparing different durations Imprecision:OK
Symptomatic deep-vein thrombosis	6528 (1 study) 30d	<u>6-14d parenteral treatment</u> 0.03% vs 0.12% NT <u>30 days treatment</u> 0.15% vs 0.49% NT	Not applicable
Fatal or nonfatal pulmonary embolism	6528 (1 study) 30d	<u>6-14d parenteral treatment</u> 0.09% vs 0.09% NT <u>30 days treatment</u> 0.22% vs 0.24% NS	Not applicable
Major bleeding	6528 (1 study) 30d	<u>6-14d parenteral treatment</u> 0.25% vs 0.12% RR= 2.06 (95%CI 0.62 to 7.85) NS <u>30 days treatment</u> 0.47% vs 0.19% **RR= 2.58 (95%CI 1.02 to 7.24)** **SS**	⊕⊕⊕⊖ **MODERATE (6-14d)** ⊕⊕⊖⊖ **LOW (30d)** Study quality:OK Consistency:NA Directness:Ok or -1 for comparing different durations Imprecision:-1: wide CI, underpowered

In this trial apixaban 2.5mg 2x/d for 30 days was compared with SC enoxaparin 40mg 1x/d for 6-14 days. Patients were hospitalized for medical illness. All patients had to be moderately or severe restricted in their mobility.

There was no statistically significant difference in mortality between both treatment group at 90 days follow up.

GRADE: MODERATE quality of evidence

The primary outcome in this trial was a composite of symptomatic DVT or asymptomatic proximal DVT, PE and death related to VTE at 30 days. There was no statistically significant difference for this outcome between both treatment groups.
GRADE: VERY LOW quality of evidence

At the end of the parenteral treatment period (6-14days), the difference between both groups for this composite outcome was also not significantly different.
GRADE: LOW quality of evidence

The difference in symptomatic deep-vein thrombosis and in total pulmonary embolism was not statistically tested.
GRADE: not applicable

30 day treatment with apixaban was associated with a higher number of major bleedings compared to 6-14days of enoxaparin.
GRADE: LOW quality of evidence

At the end of the parenteral treatment period(6-14days), there was no significant difference in rates of major bleeding between apixaban and enoxaparin.
GRADE: MODERATE quality of evidence

9.2.3 Extended duration rivaroxaban versus short duration enoxaparin in medical patients

Study details	n/Population	Comparison	Outcomes		Methodological
046_Cohen 2013-MAGELLAN(201) Design: Noninferiority/ superiority DB PG RCT Setting: Hospital-based, multicenter trial in 92 countries Duration of follow-up: 35d	n= 8.101 Median age: 71y Previous VTE(DVT/PE): 4.7% Current malignancy: 7.3% Recent surgery: 0.8% Recent trauma: 0.2% Immobilized: NR <u>Inclusion</u> Age ≥40 years; at risk of venous thromboembolic events; hospitalized for the following acute medical conditions: heart failure, active cancer, acute ischemic stroke, acute infectious and inflammatory diseases, acute respiratory insufficiency; Patients with at least one additional risk factor for VTE (not	Subcutaneous placebo for 10±4 days and oral rivaroxaban, 10 mg once daily, for 35±4 days (n=4.050). Vs. subcutaneous enoxaparin, 40 mg once daily, for 10±4 days and oral placebo for 35±4 days (n=4.051)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: unclear Personnel: unclear Assessors: yes FOLLOW-UP: 98.7 % in safety analysis 81.5 % in efficacy analysis at day 10; 75.6% at day 35 Drop-outs and Exclusions: • Described: yes (lack of an adequate assessment of venous thrombo-embolism as the main reason for exclusion) • Balanced across groups: yes ITT: No: • patients were included in the efficacy analysis if they met the study inclusion criteria, had received at least one dose of study
			Composite of asymptomatic proximal deep-vein thrombosis, symptomatic proximal or distal deep-vein thrombosis, symptomatic nonfatal pulmonary embolism, or death *related to venous thromboembolism* (PO) The protocol called for ultrasonography to be performed in all patients for the detection of *asymptomatic* deep-vein thrombosis after the last dose of study medication or matching placebo was administered on day 10±4 and on day 35±4, as described previously. During the follow-up period, clinically suspected cases of deep vein thrombosis were confirmed with the use of ultrasonography or other vascular imaging techniques, and clinically suspected pulmonary embolism was confirmed with the use of thoracic spiral computed tomography, ventilation–perfusion lung scanning with	<u>Up to day 10 (noninferiority analysis)</u>: Rivaroxaban 10 mg: 78/2938 (2.7%) Enoxaparin 40 mg: 82/2993 (2.7%) **RR= 0.97 (95% CI 0.71 to 1.31), p=0.003** (one sided p for noninferiority, calculated in the PP population) <u>Up to day 35 (superiority analysis)</u>: Rivaroxaban 10 mg: 131/2967 (4.4%) Enoxaparin 40 mg: 175/3057 (5.7%) (modified ITT analysis) **RR = 0.77 (95% CI 0.62 to 0.96), SS, p=0.02 in favour of rivaroxaban** (two sided p for superiority, calculated in the modified ITT population) <u>Up to day 10 in the modified ITT population (SO):</u> Rivaroxaban 10 mg: 98/3232 (3.0%) Enoxaparin 40 mg: 100/3271 (3.1%) RR= 0.99 (95% CI 0.75 to 1.30), NS, p=0.95	

	required for patients with heart failure, cancer or acute ischemic stroke); anticipated complete immobilization for ≥1 day during hospitalization + anticipated decreased level of mobility for ≥4 days after randomization + anticipated ongoing decreased mobility thereafter; hospitalized <72h before randomisation <u>Exclusion</u> Contraindications for the use of the LMWH enoxaparin; bleeding risk-related criteria; concomitant conditions or deseases; required drugs or procedures		chest radiography, or pulmonary angiography.		medication, and had an adequate assessment of venous thromboembolism ('modified ITT') • Patients were included in the safety population if they had received at least one dose of study medication. Power: adequate SELECTIVE OUTCOME REPORTING: low risk Other important methodological remarks: -The modified ITT analysis for the PO at 35 days includes only 75.6% of the randomized population. -noninferiority margin of 1.5 -The authors state that the inclusion of asymptomatic proximal deep-vein thrombosis as part of the primary outcome was a limitation of the trial, which may have influenced the trial in two ways: 1)the performance of
			Composite of asymptomatic proximal deep-vein thrombosis, symptomatic proximal or distal deep-vein thrombosis, symptomatic nonfatal pulmonary embolism, or death *from any cause* **Asymptomatic proximal DVT** **Symptomatic proximal or distal DVT** **Symptomatic nonfatal pulmonary embolism**	<u>Up to day 35 (SO)</u>: Rivaroxaban 10 mg: 266/3169 (8.6%) Enoxaparin 40 mg: 293/3169 (9.2%) RR=0.93 (95% CI 0.80 to 1.09), NS, p=0.38 <u>Up to 10 days</u>: Rivaroxaban 10 mg: 71/2938 (2.4%) Enoxaparin 40 mg: 71/2993 (2.4%) NT <u>Up to 35 days:</u> Rivaroxaban 10 mg: 103/2967 (3.5%) Enoxaparin 40 mg: 133/3057 (4.4%) NT <u>Up to 10 days</u>: Rivaroxaban 10 mg: 7/2938 (0.2%) Enoxaparin 40 mg: 6/2993 (0.2%) NT <u>Up to 35 days:</u> Rivaroxaban 10 mg: 13/2967 (0.4%) Enoxaparin 40 mg: 15/3057 (0.5%) NT <u>Up to 10 days</u>: Rivaroxaban 10 mg: 6/2938 (0.2%) Enoxaparin 40 mg: 2/2993 <0.1%) NT	

				Up to 35 days: Rivaroxaban 10 mg: 10/2967 (0.3%) Enoxaparin 40 mg: 14/3057 (0.5%) NT	ultrasonography at day 10 may have influenced the subsequent natural history of the disease because it may have resulted in the treatment of asymptomatic disease. This could account for the risk reduction at day 35 that was lower than anticipated. 2)a substantial subgroup of patients could not be evaluated for the primary outcome because of lack of data. Additional remarks of the bibliography group: -inclusion of asymptomatic DVT in the PE may have resulted in an overestimation of the efficacy of rivaroxaban, because the incidence of asymptomatic DVT was higher in the enoxaparin group, while the incidence of symptomatic DVT did not differ between both groups. Thus, the authors' conclusion that "extended-duration rivaroxaban reduced the risk of venous thromboembolism" has to be interpreted with caution.
			Symptomatic nonfatal VTE	Up to 10 days: Rivaroxaban 10 mg: 18/3997 (0.5%) Enoxaparin 40 mg: 12/4001 (0.3%) RR=1.50 (95% CI 0.72 to 3.11), NS, p=0.28 Up to 35 days: Rivaroxaban 10 mg: 22/3997 (0.6%) Enoxaparin 40 mg: 27/4001 (0.7%) RR= 0.82 (95% CI 0.47 to 1.43), NS, p=0.48	
			Net clinical benefit or harm (composite of a primary efficacy outcome event or an event of major or clinically relevant nonmajor bleeding that occurred during treatment)	Up to 10 days: Rivaroxaban 10 mg: 216/3266 (6.6%) Enoxaparin 40 mg: 151/3291 (4.6%) **RR= 1.44 (1.18 to 1.77), SS, p<0.001 in favour of exonaparin** Up to 35 days: Rivaroxaban 10 mg: 286/3042 (9.4%) Enoxaparin 40 mg: 240/3082 (7.8%) **RR= 1.21 (1.03 to 1.43), SS, p=0.02 in favour of exonaparin**	
			VTE-related death	Up to 10 days: Rivaroxaban 10 mg: 3/2938 (0.1%) Enoxaparin 40 mg: 6/2993 (0.2%) NT Up to 35 days: Rivaroxaban 10 mg: 19/2967 (0.6%) Enoxaparin 40 mg: 30/3057 (1.0%) NT	

			Composite of cardiovascular death, acute myocardial infarction, or acute ischemic stroke up	Up to 10 days: Rivaroxaban 10 mg: 41/3997 (1.0%) Enoxaparin 40 mg: 40/4001 (1.0%) RR= 1.02 (95%CI 0.66–1.58) p=0.91; NS Up to 35 days: Rivaroxaban 10 mg: 71/3997 (1.8%) Enoxaparin 40 mg: 64/4001 (1.6%) RR= 1.11 (0.79–1.55) p=0.55; NS	-the authors could have done an additional analysis with exclusion of asymptomatic DVT in the composite endpoint. This would have increased the sample size and give a better estimate of DVT risk. -the authors state that "The prespecified analysis of net clinical benefit or harm *did not show a benefit* with rivaroxaban at either day 10 or day 35", they should have mentioned that enoxaparin was SS better for this outcome -The active treatment period for the enoxaparin arm is from day 1 to day 10 ± 4 and for the rivaroxaban arm is from day 1 to day 35 ± 4. Because of the difference in the duration of anticoagulation treatment between both groups, the outcome measurement up to day 35 is biased. Sponsor: Bayer HealthCare Pharmaceuticals and Janssen Research and Development; the data were collected and analyzed by the sponsors.
			Safety		
			Clinically relevant bleeding (Composite of major[1] or clinically relevant non-major[2] bleeding) (PO) [1] Bleeding leading to a ≥2 g/dl fall in hemoglobin or a transfusion of ≥2 units of packed red blood cells or whole blood; bleeding into a critical site, or bleeding leading to death [2] Overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, temporary cessation of study treatment or discomfort for the subject such as pain, or impairment of activities of daily life	Up to day 10: Rivaroxaban 10 mg: 111/3997 (2.8%) Enoxaparin 40 mg: 49/4001 (1.2%) **RR = 2.3 (95% CI 1.63 to 3.17), SS, p<0.001 in favour of enoxaparin** (two sided p, calculated in all patients who received at least one dose of study medication) Up to day 35: Rivaroxaban 10 mg: 164/3997 (4.1%) Enoxaparin 40 mg: 67/4001 (1.7%) **RR = 2.5 (95% CI 1.85 to 3.25), SS, p<0.001 in favour of enoxaparin** (two sided p, calculated in all patients who received at least one dose of study medication)	
			Any adverse event during	Rivaroxaban 10 mg: 2616/3997 (65.4%)	

			treatment, excluding bleeding	Enoxaparin 40 mg: 2607/4001 (65.2%) NT	
			Any *serious* adverse event during treatment, excluding bleeding	Rivaroxaban 10 mg: 616/3997 (15.4%) Enoxaparin 40 mg: 569/4001 (14.2%) NT	
			Fatal major bleeding	<u>Up to 10 days</u>: Rivaroxaban 10 mg: 5/3997 (0.1%) Enoxaparin 40 mg: 1/4001 (<0.1%) NT <u>Up to 35 days</u>: Rivaroxaban 10 mg: 7/3997 (0.2%) Enoxaparin 40 mg: 1/4001 (<0.1%) NT *"The seven fatal bleeding events involved pulmonary bleeding (in 3 patients), intracranial bleeding (in 2 patients), and retroperitoneal and gastrointestinal bleeding (each in 1 patient). In the enoxaparin group there was one death due to tracheal bleeding."*	
			Death from any cause	<u>Up to 10 days</u>: Rivaroxaban 10 mg: 72/3281 (2.2%) Enoxaparin 40 mg: 65/3310 (2.0%) NT <u>Up to 35 days</u>: Rivaroxaban 10 mg: 159/3096 (5.1%) Enoxaparin 40 mg: 153/3169 (4.8%) NT *"The incidence of death from any cause over the entire study period was similar in the two groups".*	

9.2.4 Summary and conclusions. Extended duration rivaroxaban versus short duration enoxaparin in medical patients

Extended (35d) rivaroxaban 10mg vs. standard duration enoxaparin 40mg (10d) for thromboprophylaxis in acutely ill medical patients			
Bibliography: Cohen 2013-MAGELLAN(201)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	8101 1 study 35d	5.1% vs 4.8% NT	**NA**
Composite: (asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death related to VTE) (PO)	8101 1 study 35d	At 10 days 2.7% vs 2.7% RR= 0.97 (95%CI 0.71 to 1.31) **p=0.003 for noninferiority** At 35 days 4.4% vs 5.7% **RR = 0.77 (95%CI 0.62 to 0.96)** **SS, in favour of rivaroxaban**	⊕⊕⊖⊖ **LOW (10 days)** ⊕⊖⊖⊖ **VERY LOW (35 days)** Study quality:-1 or -2: no itt, incomplete outcome data, high risk of bias at 35 days. Consistency: NA Directness:-1: composite endpoint incl asympt DVT Imprecision:OK
Symptomatic proximal or distal DVT	8101 1 study 35d	At 10 days 0.2% vs 0.2% NT At 35 days 0.4% vs 0.5% NT	**NA**
Symptomatic nonfatal pulmonary embolism	8101 1 study 35d	At 10 days 0.2% vs <0.1% NT At 35 days 0.3% vs 0.5% NT	**NA**
Major or clinically relevant non-major bleeding (PO)	8101 1 study 35d	At 10 days 2.8% vs 1.2% **RR = 2.3 (95% CI 1.63 to 3.17)** **SS in favour of enoxaparin** At 35 days 4.1% vs 1.7% **RR = 2.5 (95% CI 1.85 to 3.25)** **SS in favour of enoxaparin**	⊕⊕⊕⊕ **HIGH (10 days)** ⊕⊕⊕⊖ **MODERATE (35 days)** Study quality: OK or -1: high risk of bias at 35 days Consistency: NA Directness: OK Imprecision:OK

In this randomized controlled trial acutely ill medical patients received thromboprophylaxis with rivaroxaban 10mg/d for 35 days or with SC enoxaparin 40mg/d for 10 days. Patients had at least one risk factor for VTE. The study was designed to test non-inferiority of rivaroxaban at day 10 and superiority up to day 35.

There was no statistical test for mortality.
GRADE: NA

On the primary outcome, a composite endpoint of asymptomatic proximal deep-vein thrombosis, symptomatic proximal or distal deep-vein thrombosis, symptomatic nonfatal pulmonary embolism, or death related to venous thromboembolim,35 days of rivaroxaban was superior to 10 days of enoxaparin.
GRADE: VERY LOW quality of evidence
At 10 days of treatment, rivaroxaban was non-inferior to enoxaparin for this composite outcome.
GRADE: LOW quality of evidence

There was no statistical test for the outcome DVT.
GRADE: NA

There was no statistical test for the outcome symptomatic pulmonary embolism.
GRADE: NA

Rivaroxaban was associated with statistically significantly more clinically relevant bleedings compared to enoxaparin, when analysed both at day 10 and at day 35.
GRADE: HIGH quality of evidence at day 10
GRADE: MODERATE quality of evidence at day 35

9.2.5 Tinzaparin versus aspirin in acute ischaemic stroke

Study details	n/Population	Comparison	Outcomes		Methodological
Bath 2001(202) Design: DB PG RCT Setting: multicenter in ten countries in Europe (Belgium, Denmark, Finland, France, Germany, Ireland, the Netherlands, Norway, Sweden, and the UK) and Canada Duration of	n= 1.486 Mean age: 74y Previous VTE: NR Previous TIA : 16% Previous stroke: 13% Previous MI: 16% Current malignancy, recent surgery, recent trauma, immobilized: NR Infarct on baseline CT: 60% <u>Inclusion</u> Patients admitted to hospital with a clinical syndrome of a stroke, age 18-90y, could be treated within 48 h of stroke onset <u>Exclusion:</u> CT evidence of intracranial haemorrhage, midline	tinzaparin 175 anti-Xa IU/kg daily; (n=487) +placebo tablets vs. tinzaparin 100 anti-Xa IU/kg daily; (n=508) + placebo tablets vs. aspirin 300 mg daily (n=491) + placebo injections treatment started within 48 h of acute ischaemic stroke and was given for	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: Lost-to follow-up: 3 % The authors state that 77·5% met all the protocol criteria for enrolment and received at least 7 days of treatment (“protocol population”). ITT: Yes (based on 1484 treated participants, all of whom received at least one dose of tinzaparin or aspirin Power: adequate SELECTIVE REPORTING: no Other important methodological remarks: -The direct effect of treatment on
			Proportion of patients with independence at 6-month follow-up (PO) (defined as score on the modified Rankin scale 0-2)	TINZA175: 41.5% TINZA100: 42.4% ASP: 42.5% TINZA175 vs ASP: OR=0.96 (0.74 to 1.24), NS TINZA100 vs ASP: OR=0.99 (0.77 tp 1.28), NS	
			Proportion of patients with neurological deterioration at end of treatment plus 5 days	TINZA175: 12.1% TINZA100: 11.9% ASP: 11.9% TINZA175 vs ASP: OR=1.02 (0.69 to 1.51), NS TINZA100 vs ASP: OR= 1.00 (0.68 to 1.47), NS	
			Proportion of patients achieving a Barthel index of more than 60 at 6 months	TINZA175: 67.5% TINZA100: 67.1% ASP: 67.2% TINZA175 vs ASP: OR=1.01 (0.77 to 1.33), NS TINZA100 vs ASP: OR=0.99 (0.76 to 1.30), NS	
			Safety		
			Death by day 10	TINZA175: 3.7% TINZA100: 5.5% ASP: 3.5% TINZA175 vs ASP: OR=1.07 (0.55 to 2.11), NS TINZA100 vs ASP: OR=1.63 (0.88 to 3.02), NS	
			Death at 6 months	TINZA175: 14.6%	

follow-up: 6 months	shift of more than 5 mm, or a non-stroke diagnosis; coma ; pure sensory stroke; mild stroke; stroke complicating trauma or a medical or surgical procedure; stroke or myocardial infarction within the previous 3 months; preceding moderate or severe disability; confounding neurological or psychiatric disease; a condition mimicking stroke; a congenital bleeding disorder; clinically significant blood loss within the previous 3 months or a current active peptic ulcer; significant hypertension within 6 h of enrolment; significant anaemia, thrombocytopenia, liver dysfunction or renal dysfunction; clinical endocarditis; allergic asthma; recent history of long-term	up to 10 days.		TINZA100: 14.2% ASP: 14.9% TINZA175 vs ASP: OR=0.98 (0.69 to 1.40), NS TINZA100 vs ASP: OR=0.95 (0.67 to 1.35), NS	safety and efficacy events (eg, deep-vein thrombosis and symptomatic intracranial haemorrhage) was assessed at the end of treatment plus 5 days to allow the pharmacodynamic effects of aspirin and tinzaparin to dissipate. - No formal adjustment of p values was made to account for the two comparisons between tinzaparin groups and aspirin or for the multiple outcomes in the study. The robustness of the results to multiplicity adjustment was assessed by the conservative Bonferroni method. Sponsor: Leo Pharmaceutical Products
			Proportion of patients with symptomatic intracranial haemorrhage at end of treatment plus 5 days (a second computed tomography scan was done at the end of treatment to allow the frequency of intracranial bleeding to be assessed)	TINZA175: 1.4% TINZA100: 0.6% ASP: 0.2% **TINZA175 vs ASP: 7.15 (1.10 to 163), SS in favour of aspirin** TINZA100 vs ASP: 2.91 (0.31 to 77.0), NS time TIN175 TIN100 ASP <12 h 4·8% 1·1% 0% 12–24 h 1·4% 1·4% 0% 24–36 h 0% 0% 0·8% >36 h 0·8% 0% 0%	
			Proportion of patients with major bleeding at end of treatment plus 5 days (clinically overt bleeding associated with one or more of transfusion of at least two units of red cells, a fall in haemoglobin of 20 g/L [1·24mmol/L] or more, bleeding leading to permanent cessation of treatment)	TINZA175: 0.8% TINZA100: 0.4% ASP:0.4% TINZA175 vs ASP: OR=2.03 (0.36 to 15.9), NS TINZA100 vs ASP:OR=0.97 (0.10 to 9.33), NS	
			Proportion of patients with symptomatic DVT at end of	TINZA175: 0% TINZA100: 0.6% ASP: 1.8%	

	systemic steroid therapy; recent anticoagulant therapy or need for anticoagulation or thrombolysis; severe concomitant medical conditions (eg, AIDS, metastatic cancer); pregnancy or breastfeeding; previous participation in TAIST; or participation in another trial within the previous 2 weeks.		**treatment plus 5 days** (confirmed by venography or ultrasonography),	TINZA175 vs ASP: OR=0 (0 to 9.29), SS TINZA100 vs ASP: OR=0.32 (0.07 to 1.14), NS	
			Proportion of patients with PE (confirmed by high-probability ventilation perfusion scan, pulmonary angiography, or necropsy)	TINZA175: 0.4% TINZA100:0.8% ASP:0.8% TINZA175 vs ASP: OR=0.50 (0.06 to 2.85), NS TINZA100 vs ASP:OR=0.97 (0.22 to 4.31), NS	
			Proportion of patients with VTE	TINZA175: 0.4% TINZA100: 1.2% ASP: 2.6% **TINZA175 vs ASP: OR=0.15 (0.03 to 0.68), SS in favour of tinzaparin high dose** TINZA100 vs ASP: OR=0.44 (0.17 to 1.17), NS	
			Proportion of patients with recurrent stroke	TINZA175: 3.3% TINZA100: 4.7% ASP: 3.1% TINZA175 vs ASP: OR=1.08 (0.53 to 2.21), NS TINZA100 vs ASP: OR=1.58 (0.82 to 3.04), NS	
			Cardiac failure at end of treatment plus 5 days	TINZA175: 2.3% TINZA100:2.2% ASP:2.2% TINZA175 vs ASP: OR=1.01 (0.43 to 2.35), NS TINZA100 vs ASP: OR=0.97 (0.42 to 2.25), NS	

9.2.6 Summary and conclusions. Tinzaparin versus aspirin in acute ischaemic stroke

Tinzaparin (100 or 175 IU/kg) versus aspirin 300mg for 10 days in acute ischaemic stroke			
Bibliography: Bath 2001(202)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1486 (1 study) 6 mo	TINZA175: 14.6% TINZA100: 14.2% ASP: 14.9% <u>TINZA175 vs ASA:</u> OR=0.98 (0.69 to 1.40), NS <u>TINZA100 vs ASA:</u> OR=0.95 (0.67 to 1.35), NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for unclear allocation concealment and unclear blinding of assessment Consistency:NA Directness:OK Imprecision:OK
Symptomatic DVT	1486 (1 study) +/-15d	TINZA175: 0% TINZA100: 0.6% ASP: 1.8% <u>TINZA175 vs ASA:</u> **OR=0 (0 to 9.29), SS** <u>TINZA100 vs ASA:</u> OR=0.32 (0.07 to 1.14), NS	⊕⊕⊖ ⊖**LOW** Study quality:-1 for unclear allocation concealment and unclear blinding of assessment Consistency:NA Directness:OK Imprecision:-1: wide CI
VTE	1486 (1 study) +/-15d	TINZA175: 0.4% TINZA100: 1.2% ASP: 2.6% <u>TINZA175 vs ASP:</u> **OR=0.15 (0.03 to 0.68),** **SS in favour of tinzaparin** <u>TINZA100 vs ASP:</u> OR=0.44 (0.17 to 1.17), NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 for unclear allocation concealment and unclear blinding of assessment Consistency:NA Directness:OK Imprecision:OK
Major bleeding	1486 (1 study) +/-15d	TINZA175: 0.8% TINZA100: 0.4% ASP:0.4% <u>TINZA175 vs ASP:</u> OR=2.03 (0.36 to 15.9), NS <u>TINZA100 vs ASP:</u> OR=0.97 (0.10 to 9.33), NS	⊕⊕⊖⊖ **LOW** Study quality:-1 for unclear allocation concealment and unclear blinding of assessment Consistency:NA Directness:OK Imprecision:-1: wide CI
Symptomatic intracranial haemorrhage	1486 (1 study) +/-15d	TINZA175: 1.4% TINZA100: 0.6% ASP: 0.2% **<u>TINZA175 vs ASP:</u>** **OR=7.15 (1.10 to 163)** **SS in favour of aspirin** <u>TINZA100 vs ASP:</u> 2.91 (0.31 to 77.0), NS	⊕⊕⊖⊖ **LOW** Study quality:-1 for unclear Study quality:-1 for unclear allocation concealment and unclear blinding of assessment Consistency:NA Directness:OK Imprecision:-1: wide CI

In this randomized controlled trial patients with acute stroke were treated with tinzaparin 175 anti-Xa IU/kg , tinzaparin 100 anti-Xa IU/kg or aspirin 300mg. Treatment started within 48h of acute ischaemic stroke and continued 10 days.

There was no statistically significant difference in mortality between tinzaparin 175 anti-Xa IU/kg , tinzaparin 100 anti-Xa IU/kg and aspirin 300mg.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in symptomatic DVT between tinzaparin 100 anti-Xa IU/kg and aspirin 300mg. The frequency of symptomatic DVT was significantly lower with tinzaparin 175 anti-Xa IU/kg compared to aspirin 300mg. The confidence interval however was very wide.
GRADE: LOW quality of evidence

High dose tinzaparin was statistically significant better in reducing VTE compared to aspirin 300mg. There was no difference between low dose tinzaparin and aspirin.
GRADE: MODERATE quality of evidence

There was no statistically significant difference in major bleeding between tinzaparin 175 anti-Xa IU/kg , tinzaparin 100 anti-Xa IU/kg and aspirin 300mg.
GRADE: LOW quality of evidence

There was more symptomatic intracranial haemorrhage with high dose tinzaparin compared to aspirin 300mg. The confidence interval however was very wide.
There was no difference between low dose tinzaparin and aspirin.
GRADE: LOW quality of evidence

9.3 Duration of thromboprophylaxis in medical patients

9.3.1 Extended duration versus short duration thromboprophylaxis in medical patients

Study details	n/Population	Comparison	Outcomes		Methodological
Ref. 644 Hull 2010-EXCLAIM(203) Design: RCT DB PG Setting: International, multicenter: 370 sites in 20 countries across North and South America, Europe, and Asia. Duration of follow-up: 6 months	n= 6085 preamendment n=4335 postamendment n=1628 Mean age:67y Previous VTE(:402/5963 : - Active or previous cancer: 817/5963Obesity (BMI≥30kg/m^2): 2026/5963 - Venous insufficiency: 815/5963 - Hormone therapy: 130/5963 - Chronic heart failure: 1524/5963 - Chronic respiratory	Enoxaparin 40 mg/d subcutaneously vs Placebo for 28+/-4 days both arms: after receiving open-label enoxaparin for an initial 10+/-4days.	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 98% in safety analysis 82% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT:No (Efficacy: patients who received at least 1 dose of the study treatment during the double-blind treatment period and had at least 1 interpretable ultrasonogram during the treatment period or up to 7 days)
			VTE (=composite of symptomatic or asymptomatic proximal DVT, symptomatic pulmonary embolism, or fatal pulmonary embolism, =PO) (<u>confirmed by</u> bilateral compression ultrasonography or venography to evaluate patients with suspected DVT during the DB treatment period / computed tomography or ventilation–perfusion lung scanning to evaluate suspected symptomatic cases of pulmonary embolism At the end of the double-blind treatment period, patients underwent bilateral ultrasonography of the lower extremities to identify asymptomatic proximal DVT.)	<u>Preamendment:</u> **Enoxaparin: 45/1818 (2.5%)** **Placebo: 78/1867 (4.2%)** **ARD: -1.70 (95% CI -2.86 to -0.55)** **SS in favour of enoxaparin** <u>Postamendment</u> Enoxaparin: 16/667 event (2.4%) Placebo: 22/643 event (3.4%) ARD: -1.02 (95% CI -2.85 to 0.80) SS <u>Total population</u> Enoxaparin: 61/2485 (2.5%) Placebo: 100/2510 (4.0%) ARD: -1.53 (**95**% CI -2.54 to -0.52) **SS in favour of extended-duration enoxaparin**	
			Symptomatic VTE at 1 month	**<u>Total population</u> Enoxaparin: 5/2485 (0.2%) Placebo: 24/2510 (1.0%) ARD: -0.75 (95% CI -1.19 to -0.32) SS in favour of extended enoxaparin**	

	failure: 2374/5963 - Chronic inflammatory disease: 29/5963 - Family history of VTE: 5/5963 - Thrombophilia: 7/5963 <u>Inclusion</u> Acute medical illness, ≥40y, life expectancy > 6 months, and had recently reduced mobility for up to 3 days. and likely to have reduced mobility for at least 3 days after enrollment. ("reduced mobility": requiring total bed rest or being sedentary without bathroom privileges (level 1 immobility) or with bathroom privileges (level 2 immobility). <u>Eligibility criteria for patients with level 2 immobility were amended to include</u>				Power: Adequate SELECTIVE REPORTING: No <u>Other important methodological remarks:</u> Estimates of efficacy and safety for the overall trial population are difficult to interpret because of the change in eligibility criteria during the trial. Composite endpoint consists of frequent low-risk events and infrequent high risk events. Population received open label enoxaparin prior to randomization, thus excluding patients with early adverse events to enoxaparin Sponsor: Sanofi-Aventis.
			Mortality at 1 month	**<u>Total population:</u>** Enoxaparin: 60/2975 (2.1%) Placebo: 65/2988 (2.2%) HR: 0.93 (95% CI 0.65 to 1.32) NS	
			Mortality at 6 months	<u>Total population:</u> Enoxaparin: 220/2975 (8.2%) Placebo: 204/2988 (7.7%) HR: 1.08 (95% CI 0.89 to 1.31) NS	
			Safety		
			Total bleeding events (major and minor)	**<u>Total population:</u>** **Enoxaparin: 186/2975 (6.3%)** **Placebo: 116/2988 (3.9%)** **ARD: 2.37 (95% CI 1.26 to 3.48)** **SS in favour of placebo**	
			Major bleeding events (overt and associated with death; a decrease in hemoglobin level of at least 20 g/L or a transfusion of at least 2 units of packed red blood cells or whole blood; surgical intervention; or retroperitoneal, intracranial, or intraocular bleeding.	**<u>Total Population:</u>** **Enoxaparin: 25/2975 (0.8%)** **Placebo: 10/2988 (0.3%)** **ARD: 0.51% (95% CI, 0.12 to 0.89)** **SS in favour of placebo**	
			Minor bleeding events (overt and did not meet the criteria for a major hemorrhage. These included epistaxis lasting more than 5 minutes or requiring intervention, ecchymosis or hematoma larger than 5 cm, hematuria not associated with	<u>Total Population:</u> Enoxaparin: 164/2975 (5.5%) Placebo: 106/2988 (3.5%) ARD: 1.97 (95% CI 0.91 to 3.02) NS	

	only those who had additional VTE risk factors (age 75 years, history of VTE, or active or previous cancer) after interim analyses suggested lower-thanexpected VTE rates. Exclusion NR		urinary catheter trauma, subconjunctival or gastrointestinal hemorrhage, or wound hematoma. They obtained platelet counts at the end of both the open-label and double-blind treatment phases.)		
			Serious adverse events (resulted in death or persistent or substantial disability or incapability, were life-threatening or considered an important medical event, or required inpatient hospitalization or prolongation of existing hospitalization. Bleeding events and VTE were considered serious adverse events if they met the above criteria.)	Total Population: Enoxaparin: 216 events (7.3%) Placebo: 218 events (7.3%) ARD: -0.04 (-1.35 to 1.28) NS	

9.3.2 Summary and conclusions. Extended duration versus short duration thromboprophylaxis in medical patients

Extended duration (4 week) enoxaparin 40mg/d versus placebo for thromboprophylaxis in medically ill patients, after an initial 10 days of open label enoxaparin			
Bibliography: Hull 2010-EXCLAIM(203)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	6085 (1 study) 6 mo	8.2% vs 7.7% HR: 1.08 (95% CI0.89 to 1.31) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1, run in with enoxaparin, change in eligibility criteria Consistency:NA Directness:OK Imprecision:OK
VTE (composite of symptomatic or asymptomatic proximal DVT, symptomatic pulmonary embolism, or fatal pulmonary embolism) (PO)	6085 (1 study) 1 mo	2.5% vs 4.0% **ARD: -1.53 (95%CI -2.54 to-0.52)** **SS in favour of extended-duration enoxaparin**	⊕⊕⊖⊖ **LOW** Study quality: -1, run in with enoxaparin, change in eligibility criteria Consistency: NA Directness: -1 for composite endpoint incl asympt DVT Imprecision: OK
Symptomatic VTE	6085 (1 study) 1 mo	0.2% vs 1.0% **ARD: -0.75 (95%CI -1.19 to -0.32)** **SS in favour of extended enoxaparin**	⊕⊕⊕⊖ **MODERATE** Study quality:-1, run in with enoxaparin, change in eligibility criteria Consistency:NA Directness:OK Imprecision:OK
Major bleeding	6085 (1 study) 1 mo	0.8% vs 0.3% **ARD: 0.51% (95%CI 0.12 to 0.89)** **SS in favour of placebo**	⊕⊕⊕⊖ **MODERATE** Study quality: -1, run in with enoxaparin, change in eligibility criteria Consistency:NA Directness:OK Imprecision:OK

In this randomized controlled trial acutely ill, hospitalized, medical patients with recently reduced mobility were treated with SC enoxaparin 40mg/d or placebo for 4 weeks. Both groups received open label enoxaparin for an initial 10 +/-4 days prior to randomization. Inclusion criteria for the level of mobility were amended during the trial.

At 6 months, the difference in mortality between treatment groups was not statistically significant.
GRADE: MODERATE quality of evidence

The difference in venous thromboembolic events (including symptomatic or asymptomatic proximal DVT) was statistically significant in favour of extended duration enoxaparin.
GRADE: LOW quality of evidence

There was a significantly lower number of symptomatic VTE with extended duration enoxaparin compared to placebo.
GRADE: MODERATE quality of evidence

Treatment with extended duration enoxaparin resulted in significantly more major bleeding events.
GRADE: MODERATE quality of evidence

9.4 Thromboprophylaxis in travel with prolonged immobilization

No studies met our inclusion criteria (pharmacological treatment versus placebo or versus graduated compression stockings).

A Cochrane systematic review (Clarke 2006(204)) compared graduated compression stockings to no prophylaxis in air travel. Compression stockings reduced the rate of asymptomatic DVT (OR 0.10; 95%CI 0.04 to 0.25). No deaths, pulmonary emboli or symptomatic DVTs were reported.

10 Evidence tables and conclusions: Thromboprophylaxis in cancer patients

10.1 Pharmacological treatment versus placebo for thromboprophylaxis in cancer patients

10.1.1 Heparin versus placebo in cancer patients (without other indication for anticoagulation)

Ref	Comparison	N/n	Outcomes	Result**
ref*578 Akl 2011(205) Design: SR+MA Search date: feb 2010	Heparin (UFH or LMWH) vs placebo	N= 7 n= 1381 (Altinbas 2004, Kakkar 2004, Klerk 2005, Lebeau 1994, Perry 2010, Sideras 2006, Weber 2008)	**Mortality over duration of study**	**no absolute numbers reported** **HR= 0.79 (95% CI 0.67 to 0.93)** **SS in favour of heparine**
		N= 8 (Agnelli 2009, Kakkar 2004, Klerk 2005, Lebeau 1994, Pelzer 2009, Perry 2010, Sideras 2006, Weber 2008)	**1-year mortality**	Heparin: 735/1464 (50.2%) Control: 594/1066 (55.7%) RR= 0.93 (95%CI 0.85 to 1.02) NS
		N= 7 n= 2264 (Altinbas 2004, Agnelli 2009, Perry 2010, Pelzer 2009, Weber 2008, Sideras 2006, Kakkar 2004)	**Symptomatic VTE**	**Heparin: 38/1338 (2.8%)** **Control: 57/926 (6.2%)** **RR: 0.55 (95% CI 0.37 to 0.82)** **SS in favour of heparin**
		N= 9 n= 2843 (Agnelli 2009, Altinbas 2004, Kakkar 2004, Klerk 2005, Lebeau 1994, Pelzer 2009, Perry 2010, Sideras 2006, Weber 2008)	**Major bleeding**	Heparin: 30/1624 (1.8%) Control: 23/1219 (1.9%) RR: 1.30 (95% CI 0.59 to 2.88) NS
		N=7 n=2345 (Agnelli 2009, Altinbas 2004, Kakkar 2004, Klerk 2005, Lebeau 1994, Sideras 2006, Weber 2008)	**Minor bleeding**	Heparin: 85/1365 (6.2%) Control: 50/980 (5.1%) RR: 1.05 (95% CI 0.75 to 1.46) NS

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Methodology
Agnelli 2009(206) Design: DB Prospective Multicentre	1150	Mean age: 62.9 years Patients with metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian or head and neck cancer Age > 18 years Not allowed during study period: Antiplatelet agents, oral anticoagulants, fibrinolytic agents, unfractionated heparin or low molecular weight heparin other than nadroparin	Duration of chemo or up to 120 d (± 10 days)	LMWH (Nadroparin 3800 IU antiXa sc /d) vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Double Incomplete outcome data: Inadequate ITT: Modified ITT Excluded from analysis: 1.4% Selective reporting: no
Altinbas 2004(207) Design: RCT Open study	84	Median age: 58 years Patients with histologically confirmed small cell lung carcinoma Age between 18 and 75 years	Duration of chemo (18 weeks) or stopped with disease progression	LMWH (Dalteparin 5000 IU sc /d) vs placebo	ALLOCATION CONC: unclear RANDO: Unclear BLINDING : Open Incomplete outcome data: Adequate ITT: Yes Lost to follow up: 0% Selective reporting: no
Kakkar 2004(208) Design: RCT DB	385	Mean age: 61.5 years Patients with histologically confirmed locally advanced or metastatic malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary or uterus Patients between 18 and 80 years	12 months or until the patient died	LMWH (Dalteparin 5000 IU sc /d) Vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate Incomplete outcome data: Inadequate ITT: Yes Excluded from analysis: 2.8% Selective reporting: no

Perry 2010(209) Design: RCT DB Multicentre	186	Patients with newly diagnosed, pathologically confirmed WHO grade 3 or grade 4 glioma Age > 18 years	12 months	LMWH (Dalteparin 5000 IU sc /d) Vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Double Incomplete outcome data: Adequate ITT: Yes Excluded from analysis: 0% Selective reporting: Yes No reporting on prespecified outcomes of quality of life and cognition
Sideras 2006(210) Design: RCT	138	Patients with advanced breast cancer who did not respond to first-line chemotherapy, advanced prostate cancer resistant to primary hormonal therapy, advanced lung cancer, or advanced colorectal cancer	18 weeks or until disease progression	First part of the study: double blind (n = 52) LMWH (Dalteparin 5000 IU sc /d) Vs Placebo Second part of the study: open label (n = 86): LMWH (Dalteparin 5000 IU sc /d) Vs Standard care without placebo	ALLOCATION CONC: Unclear RANDO: Unclear BLINDING : Inadequate (open label in second part) Incomplete outcome data: Inadequate ITT: No Excluded from analysis: 2.1% Selective reporting: no
Klerk 2005(211) RCT: double-blind, placebo controlled study	302	patients with different types of solid malignant tumors, “that could not be treated curatively” including: colorectal, breast, lung gastric, oesophageal, liver, gallbladder, Katskin, prostate, pancreatic, cervical,	6 weeks (2 weeks therapeutic dose then 4 weeks prophylactic	LMWH(Nadroparin) Vs Placebo concomitant	Funding: Sanofi provided study medication HR adjusted for: life expectancy (< 6 versus >= 6 months), WHO performance status (1 or less, 2, 3 or more) concomitant treatment (chemotherapy, radiotherapy, hormonal therapy, other antineoplastic treatment), type of

		urothelial, renal, ovarian, melanoma, endometrial and other cancers; minimum life expectancy 1 month, stratified according to life expectancy (< or > 6 months); median age 64; 52% males	dose) Follow up: mean of 12 months	antineoplastic therapy	cancer (breast, colorectal, cervical or other) and histology (adeno, squamous, other) Adequate sequence generation Adequate allocation concealment Blinding: Patients: yes Healthcare providers: yes Data collectors: yes Outcome adjudicators: yes Data analysts: no Incomplete outcome data addressed? Yes Quote: "All patients were observed until death or until the end of the study". "No patients were lost to follow-up" Comment: 100% follow up No selective reporting Free of other bias? Yes ITT analysis: yes (Quote: "All primary analyses were performed on an intention-to-treat principle")
Lebeau 1994(212) RCT	277	patients with histologically diagnosed small cell lung cancer both limited and extensive; 78% had Karnofsky > 80; 85% older than 50; 91% males	Follow up: maximum of 84 months	UFH (prophylactic dose) Vs No intervention for 5 weeks; 2 or 3 daily subcutaneous injections; in combination with chemotherapy	Funding: none Adequate sequence generation Adequate allocation concealment Blinding: Patients: no Providers: no Data collectors: no Outcome adjuficators: no Data analysts: no Incomplete outcome data addressed? Yes Quote: "No patient was lost to follow-up"

					Comment: 100% follow up Selective reporting: unclear Free of other bias? Yes ITT: yes (Quote: “Analysis was made on an intention-to-treat basis”)
Pelzer 2009(213) Open, prospective, randomized, multicenter phase III study	312	Chemotherapy-naive patientswith histologically or cytologically confirmed advanced pancreatic cancer	Median follow up of 30.4 weeks	LMWH (enoxaparin intermediate dose - 1 mg/kg daily for the first 3 months followed by 40 mg daily an additional 3 months) Vs No intervention; simultaneous initiation of palliative systemic chemotherapy	Funding: Forschungsförderung der Charité, Deutsche Krebshilfe, Lilly, Amgen, Sanofiaventis Adequate sequence generation. Adequate allocation concealment Blinding: Patients: no Providers: no Data collectors: no Outcome adjudicators: no Data analysts: yes Incomplete outcome data addressed? Yes 94% follow up for thromboembolic events and 87% follow up for survival (personal communication with author) Selective reporting: unclear Free of other bias? Yes ITT: Cochrane : yes, quote: “ITT and PP analysis)
Weber 2008(179) Prospective, open, randomized study	20	Patients aged 55 to 88 years with advanced cancer (19 solid cancer and 1 hematological cancer) with a minimum life expectancy of 6 months; 45% males	Maximum of 15 months	LMWH (Nadroparin, prophylactic dose) Vs No intervention administered	Funding: not reported Adequate sequence generation Adequate allocation concealment Blinding Patients: no Providers: no

				subcutaneously on a daily basis for unclear duration; with concomitant anticancer treatment	Data collectors: no Outcome adjudicators: no Data analysts: no Incomplete outcome data addressed: Yes Quote: “No patient was lost to follow-up” Comment: 100% follow up Selective reporting: no Free of other bias? Yes ITT: Yes (Quote: “Excluded from the analysis (n = 0)” Comment: all patients randomized to treatment or control group were included in the analysis)

10.1.2 Summary and conclusions. Heparin versus placebo in cancer patients (without other indication for anticoagulation)

Heparin (UFH or LMWH) vs placebo in patients with cancer without a therapeutic or prophylactic indication for antiocagulation			
Bibliography: meta-analysis Akl 2011(205) included these RCTs: Agnelli 2009(206), Altinbas 2004(207), Kakkar 2004(208), Perry 2010(209), Sideras 2006(210), Klerk 2005(211), Lebeau 1994(212), Weber 2008(179), Pelzer 2009(213)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Mortality	1884 (7 studies) 12 m 6w-48mo	**<u>1-year mortality</u>** 50.2% vs 55.7% RR= 0.93 (95%CI 0.85 to 1.02) NS **<u>Mortality over study duration</u>** **HR= 0.79 (95%CI 0.67 to 0.93)** **SS in favour of heparin**	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:-1 Conflicting results (moderate heterogeneity) Directness:OK Imprecision:OK
Symptomatic VTE	2767 (8 studies) 12m	2.8% vs 6.2% **RR: 0.55 (95% CI 0.37 to 0.82)** **SS in favour of heparin**	⊕⊕⊕⊕ **HIGH** Study quality:OK Consistency:OK Directness:OK Imprecision:OK
Major bleeding	3346 (10 studies) 6w-48mo	1.8% vs 1.9% RR: 1.30 (95% CI 0.59 to 2.88) NS	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:OK Directness:OK Imprecision:-1 Wide CI

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

One Cochrane review evaluated the efficacy and safety of parenteral anticoagulants (heparin and low molecular weight heparins) in patients with cancer and no therapeutic or (other) prophylactic indication for anticoagulation.

The effect of heparin therapy on mortality was not statistically significant at 12 months (risk ratio (RR) 0.93; 95% CI 0.85 to 1.02), but it was statistically significant for the duration of the trials.
GRADE: MODERATE quality of evidence

Heparin therapy was associated with a statistically significant reduction in symptomatic venous thromboembolic events.
GRADE: HIGH quality of evidence

Heparin therapy was not associated with a statistically significant effect on major bleeding.
GRADE: MODERATE quality of evidence

10.1.3 LMWH versus placebo in ambulatory cancer patients receiving chemotherapy

Ref	Comparison	N/n	Outcomes	Result**
296 Dinisio 2012(214) Design: SR + MA Search date: May 2011	LMWH (dalteparin) Vs Placebo	N= 4 n= 788 Altinbas 2004 Kakkar 2004 Perry 2010 Sideras 2006	**Symptomatic VTE**	LMWH: 19/399 (4.8%) Placebo: 24/383 (6.2%) RR: 0.75 (95%CI, 0.42 to 1.32) NS
		N= 3 n= 698 Kakkar 2004 Perry 2010 Sideras 2006	**Major bleeding**	LMWH: 8/357 (2.2%) Placebo: 6/341 (1.6%) RR: 1.38 (95%CI, 0.26 to 7.29) NS
			One year mortality	LMWH: 195/357 (54.6%) Placebo: 185/341 (54.3%) RR: 1.04 (95%CI, 0.86 to 1.26) NS
	LMWH (nadroparin) Vs Placebo	N = 1 n = 1150 Agnelli 2009	**Symptomatic VTE**	LMWH: 12/769 (1.6%) Placebo: 12/381 (3.2%) RR: 0.50 (95%CI, 0.22 to 1.09) NS
			Major bleeding	LMWH: 5/769 (0.6%) Placebo: 0/381 (0.0%) RR: 5.46 (95%CI, 0.30 to 98.43) NS
			One year mortality	LMWH: 333/769 (43.3%) Placebo: 155/381 (40.7%) RR: 1.06 (95%CI, 0.92 to 1.23) NS
	LMWH (dalteparin/ nadroparin/ certoparin) Vs	N = 6 n = 2462 Agnelli 2009 Altinbas 2004 Haas 2005	**Symptomatic VTE**	**LMWH: 39/1436 (2.7%)** **Placebo: 51/1028 (5.0%)** **RR: 0.62 (95%CI, 0.41 to 0.93)** **NNT : 60** **SS in favour of LMWH**

	Placebo	Kakkar 2004 Perry 2010 Sideras 2006	**Symptomatic PE**	LMWH: 7/1058 (0.7%) Placebo: 7/652 (1.1%) RR: 0.63 (95%CI, 0.21 to 1.91) NS
			Symptomatic DVT	LMWH: 19/1100 (1.7%) Placebo: 24/694 (3.5%) RR: 0.60 (95%CI, 0.33 to 1.07) NS
			Overall VTE	LMWH: 30/1037 (2.9%) Placebo: 38/645 (5.9%) RR: 0.55 (95%CI, 0.34 to 0.88) SS in favour of LMWH
		N = 5 n = 2394 Agnelli 2009 Haas 2005 Kakkar 2004 Perry 2010 Sideras 2006	**Major bleeding**	LMWH: 23/1399 (1.6%) Placebo: 12/995 (1.2%) RR: 1.57 (95%CI, 0.69 to 3.60) NS
		N=4 n= 1842 Kakkar 2004 Perry 2010 Sideras 2006 Agnelli 2009	**One year mortality**	LMWH: 528/1126 (46.9%) Placebo: 340/722 (47.1%) RR: 1.04 (95%CI, 0.92 to 1.16) NS

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Methodology
Agnelli 2009(206) Design: DB Prospective Multicentre	1150	Mean age: 62.9 years Patients with metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian or head and neck cancer Age > 18 years Not allowed during study period: Antiplatelet agents, oral anticoagulants, fibrinolytic agents, unfractionated heparin or lowmolecular weight heparin other than nadroparin	Duration of chemo or up to 120 d (± 10 days)	LMWH (Nadroparin 3800 IU antiXa sc /d) vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Double Incomplete outcome data: Inadequate ITT: Modified ITT Excluded from analysis: 1.4% Selective reporting: no
Altinbas 2004(207) Design: RCT Open study	84	Median age: 58 years Patients with histologically confirmed small cell lung carcinoma Age between 18 and 75 years	Duration of chemo (18 weeks) or stopped with disease progression	LMWH (Dalteparin 5000 IU sc /d) vs placebo	ALLOCATION CONC: unclear RANDO: Unclear BLINDING : Open Incomplete outcome data: Adequate ITT: Yes Lost to follow up: 0% Selective reporting: no
Haas 2005(215) Design: RCT DB	900	Patients with metastatic or locally advanced lung cancer who received chemotherapy	6 months	LMWH (Certoparin 3000 IU /d) vs placebo	ALLOCATION CONC: unclear RANDO: Unclear BLINDING : Adequate Incomplete outcome data: Unclear ITT: No Selective reporting: Unclear Poor reporting in general
Kakkar 2004(208) Design: RCT DB	385	Mean age: 61.5 years Patients with histologically confirmed locally advanced or metastatic malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary or uterus	12 months or until the patient died	LMWH (Dalteparin 5000 IU sc /d) Vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate Incomplete outcome data: Inadequate

		Patients between 18 and 80 years			ITT: Yes Excluded from analysis: 2.8% Selective reporting: no
Perry 2010(209) Design: RCT DB Multicentre	186	 Patients with newly diagnosed, pathologically confirmed WHO grade 3 or grade 4 glioma Age > 18 years	12 months	LMWH (Dalteparin 5000 IU sc /d) Vs placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Double Incomplete outcome data: Adequate ITT: Yes Excluded from analysis: 0% Selective reporting: Yes No reporting on prespecified outcomes of quality of life and cognition
Sideras 2006(210) Design: RCT	138	Patients with advanced breast cancer who did not respond to first-line chemotherapy, advanced prostate cancer resistant to primary hormonal therapy, advanced lung cancer, or advanced colorectal cancer	18 weeks or until disease progression	First part of the study: double blind (n = 52) LMWH (Dalteparin 5000 IU sc /d) Vs Placebo Second part of the study: open label (n = 86): LMWH (Dalteparin 5000 IU sc /d) Vs Standard care without placebo	ALLOCATION CONC: Unclear RANDO: Unclear BLINDING : Inadequate (open label in second part) Incomplete outcome data: Inadequate ITT: No Excluded from analysis: 2.1% Selective reporting: no

The main effectiveness outcome was symptomatic VTE objectively verified by means of Doppler (compression) ultrasonography or venography for DVT and spiral computed tomography, ventilation/perfusion lung scan, or pulmonary angiography for PE. The main safety outcome was major bleeding, typically defined as including: overt bleeding associated with a fall in haemoglobin of 2 g/dL or more or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleedingthat occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. Minor bleeding was defined as a bleeding event not matching the criteria for major bleeding.

Author's conclusions:
Primary thromboprophylaxis with LMWH significantly reduced the incidence of symptomatic VTE in ambulatory cancer patients treated with chemotherapy. However, the lack of power hampers definite conclusions on the effects on major safety outcomes, which mandates additional studies to determine the risk to benefit ratio of LMWH in this setting.

10.1.4 Summary and conclusions LMWH versus placebo in ambulatory cancer patients receiving chemotherapy

LMWH vs placebo in ambulatory cancer patients receiving chemotherapy			
Bibliography: systematic review and meta-analysis Dinisio 2012 (Dinisio 2012, #39) included these RCTs: Agnelli 2009(206), Altinbas 2004(207), Haas 2005(215), Kakkar 2004(208), Perry 2010(209), Sideras 2006(210)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
One year mortality	1842 (4 studies) 120d-12m	**Dalteparin or nadroparin vs placebo** RR: 1.04 (95%CI, 0.92 to 1.16) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Incomplete outcome data Consistency:OK Directness:OK Imprecision:OK
Symptomatic VTE	788 (4 studies) 18w-12m	**Dalteparin vs placebo** 4.8%vs 6.2% RR: 0.75 (95%CI, 0.42 to 1.32) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Incomplete outcome data Consistency:OK Directness:OK Imprecision:OK
	1150 (1 study) 120d	**Nadroparin vs placebo** 1.6% vs 3.2% RR: 0.50 (95%CI, 0.22 to 1.09) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Incomplete outcome data Consistency:NA Directness:OK Imprecision:OK
	2462 (6 studies) 120d-12m	**Dalteparin/nadroparin/certoparin vs placebo** 2.7% vs 5.0% **RR: 0.62 (95%CI, 0.41 to 0.93)** **SS in favour of LMWH** NNT : 60	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Incomplete outcome data Consistency:OK Directness:OK Imprecision:OK
Major bleeding	698 (3 studies) 18w-12m	**Dalteparin vs placebo** 2.2% vs 1.6% RR: 1.38 (95%CI, 0.26 to 7.29) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Incomplete outcome data Consistency:OK Directness:OK Imprecision:-1 wide CI
	1150 (1 study) 120d	**Nadroparin vs placebo** 0.6% vs 0.0% RR: 5.46 (95%CI 0.30 to 98.43) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Incomplete outcome data Consistency:NA Directness:OK Imprecision:-1 wide CI
	2394 (5 studies) 120d-12m	**Dalteparin/nadroparin/certoparin vs placebo** 1.6% vs 1.2% RR: 1.57 (95%CI, 0.69 to 3.60) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Incomplete outcome data Consistency:OK Directness:OK Imprecision:-1 wide CI

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

A Cochrane systematic review assessed the efficacy and safety of primary thromboprophylaxis in ambulatory cancer patients receiving chemotherapy. Low molecular weight heparins were compared to placebo. 6 RCTs were found. Duration ranged from 120 days till 1 year.

No difference in 1-year mortality rates was found when comparing low molecular weight heparins to placebo.
GRADE: MODERATE quality of evidence

Low molecular weight heparins significantly reduced the incidence of symptomatic VTE. This corresponds with an NNT of 60.
GRADE: MODERATE quality of evidence

The risk of major bleeding was not significantly higher with low molecular weight heparins. Data suggested a (nonsignificant) 60% increase but studies were probably underpowered to detect a statistically significant difference.
GRADE: LOW quality of evidence

10.1.5 Vitamin K antagonists versus placebo in cancer patients (without other indication for anticoagulation)

Ref	Comparison	N/n	Outcomes	Result**
ref*484 Akl 2011(216) Design: SR+MA Search date: feb 2010	Oral anticoagulation (Warfarin) vs no oral anticoagulation	N= 1 n= 315 (Levine 1994)	**Venous thromboembolism**	Warfarin: 1/154 (0.6%) No warfarin: 7/161 (4.3%) RR: 0.15 [95% CI 0.02 to 1.20] NS
		N= 4 n= 1282 (Chahinian 1989, Levine 1994, Maurer 1997, Zacharski 1984)	**Major bleeding**	**Warfarin: 72/650 (11.1%)** **No warfarin: 14/632 (22.2%)** **RR: 4.24 [95% CI 1.85 to 9.68]** **SS in favour of placebo**
		N= 3 n= 851 (Chahinian 1989, Levine 1994, Maurer 1997)	**Minor bleeding**	**Warfarin: 109/435 (25.1%)** **No warfarin: 33/416 (7.9%)** **RR: 3.34 [95% CI 1.66 to 6.74]** **SS in favour of placebo**
		N= 2 n=686 (Daly 1991, Maurer 1997)	**Death at 5 years**	Warfarin: 188/336 (56.0%) No warfarin: 210/350 (60.0%) RR: 0.91 [95% CI 0.83 to 1.01] NS
		N=5 (Chahinian 1989, Daly 1991, Levine 1994, Maurer 1997, Zacharski 1984)	**Death at 1 year**	Warfarin: 360/801 (44.9%) No warfarin: 367/803 (46.0%) RR: 0.94 (95% CI 0.87-1.03) NS

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Methodology
Chahinian 1989(217) RCT	189	Patients with small cell lung cancer undergoing chemotherapy; (CALBG 0-3)	median 5-9 months	Intervention: VKA (PT 1.5-2) Vs Control: no intervention	ALLOCATION CONC:unclear RANDO: unclear BLINDING : Participants: probably not/personnel: probably not/data collectors: probably not/outcome adjudicators: probably not/data analysts: probably not ITT: NR Funding: TJ Martell Foundation Incomplete outcome data addressed? Low risk Follow-up rate: 97% Comment: definitely yes Selective reporting: Study not registered. No published protocol. All outcomes listed in in themethods section were reported on. Probably free of selective reporting Free of other bias? Low risk – Study not stopped early
Daly 1991(218) RCT; 2x2 factorial design	352	Patients with colorectal cancer, mean age 66	2y (FU up to 6y)	Intervention: VKA (doubling of PT) for 2 years Vs Control: no intervention	ALLOCATION CONC: Adequate RANDO: probably adequate BLINDING : Participants: no/personnel: no/data collectors: no/outcome adjudicators: no/data analysts: no Incomplete outcome data addressed? Low risk Follow-up rate: 96%(352 randomized and 339 followed-up) Comment: definitely yes ITT: NR Selective reporting: probably yes (Study not registered. No published protocol. No listing of outcomes in the methods section) Free of other bias? Low risk – Study not stopped early for benefit. Funding: Abbott Europe, Boehringer-Ingelheim & Serono Pharmaceuticals

Levine 1994(219) RCT	315	Patients with breast cancer undergoing chemotherapy; minimum life expectancy 3 months; good performance status (ECOG < 3)	Duration of chemotherapy The mean duration of warfarin therapy was 181 (SD 123) days The mean time at risk of thrombosis (duration of chemotherapy plus 7 days) was 199 (126) days for warfarin treated patients and 188 (137) days for placebo recipients (p=0-45)	Intervention: VKA (INR 1.3 to 1.9) started within 4 weeks of chemotherapy until 1 week after termination of chemotherapy Vs Control: placebo	ALLOCATION CONC: unclear (NR) RANDO: Adequate BLINDING : Participants: yes/personnel:yes/data collectors: yes/outcome adjudicators: yes/ data analysts: yes ITT: probably yes (All patients randomized and received first dose of chemotherapy were included in the analysis. No reports of cross-over) Incomplete outcome data addressed? Low risk Follow-up rate: 98% (315 randomized and 311 followed- up) Comment: definitely yes Selective reporting: probably no Free of other bias? Low risk Study not stopped early for benefit. Funding: National Cancer Institute, Canada
Maurer 1997(220) RCT	347	Patients older than 18 years with small cell lung cancer undergoing chemotherapy and radiotherapy; minimum life expectancy 2 months; (CALBG < 3)	Duration of chemotherapy (+/- 8 weeks, FU up to 8m)	Intervention: VKA (PT 1.4 to 1.6) started with chemotherapy and continued for 3 weeks after last cycle of chemotherapy vs Control: no intervention	ALLOCATION CONC: Adequate RANDO: probably adequate BLINDING : Participants: no/personnel: no/data collectors: no/outcome adjudicators: no/data analysts: no FOLLOW-UP: NR Incomplete outcome data addressed? Unclear risk Follow-up rate: not reported ITT: no Selective reporting: probably no Free of other bias? Low risk Study not stopped early for benefit Funding: National Cancer Institute, USA
Zacharski 1984(221) RCT	431	Patients with different types of cancer undergoing chemotherapy;	?	Intervention: VKA (therapeutic range) vs	ALLOCATION CONC: unclear (NR) RANDO: Adequate BLINDING : Participants: no/personnel: no /data collectors: no/outcome

		minimum life expectancy of 2 months		Control: no intervention	adjudicators: no/data analysts: no ITT: probably no Incomplete outcome data addressed? Low risk Follow-up rate: 98%(431 randomized and 418 followed-up) Comment: definitely yes Selective reporting: probably no Free of other bias? Low risk Study not stopped early for benefit. Funding: Department of Veterans Affairs Medical Research Service

10.1.6 Summary and conclusions. Vitamin K antagonists versus placebo in cancer patients (without other indication for anticoagulation)

Warfarin versus placebo in patients with cancer who have no (other) therapeutic of prophylactic indication of anticoagulation.			
Bibliography: systematic review and meta-analysis Akl 2011(216) included these RCTs: Chahinian 1989(217), Daly 1991(218), Levine 1994(219), Maurer 1997(220), Zacharski 1984(221)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Mortality at 1 year	1604 (5 studies) median 1y	44.9% vs 46.0% RR: 0.94 (95% CI 0.87-1.03) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 no blinding in 4/5, unclear allocation concealment in 2, no ITT in 4/5 Consistency:OK Directness:OK Imprecision:OK
Venous thromboembolism	315 (1 study) 1y	0.6% vs 4.3% RR: 0.15 (95% CI 0.02 to 1.20) NS	⊕⊕⊕⊖ **MODERATE** Study quality:OK Consistency:NA Directness:OK Imprecision:-1 estimate does not exclude important benefit
Major bleeding	1282 (4 studies) Median 1y	11.1% vs 22.2% **RR: 4.24 (95% CI 1.85 to 9.68)** **SS in favour of placebo**	⊕⊕⊕⊖ **MODERATE** Study quality:-1, no blinding in 3/4 Consistency:OK Directness:OK Imprecision:OK

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

This Cochrane review evaluated the efficacy and safety of oral anticoagulants in patients with cancer with no therapeutic or prophylactic indication for anticoagulation. INR target was lower than the usual target of 2-3 in most of the trials.

There was no statistically significant difference in mortality rates at one year.
GRADE: MODERATE quality of evidence

There was no statistically significant difference between warfarin and placebo in reducing the risk of venous thromboembolism. However, this was based on only one trial and the precision of the estimate does not exclude a patient important benefit (the lower limit of RR still suggests a benefit).
GRADE: MODERATE quality of evidence

The risk of major bleeding was significantly higher with warfarin compared to placebo.
GRADE: MODERATE quality of evidence

10.1.7 Vitamin K antagonists versus placebo in ambulatory cancer patients receiving chemotherapy

Ref	Comparison	N/n	Outcomes	Result**
296 Dinisio 2012(214) Design: SR + MA Search date: May 2011	VKA Vs Placebo	N= 1 n= 311 Levine 1994	**Symptomatic VTE**	1/152 (0.7%) vs 7/159 (4.4%) RR: 0.15 (95%CI, 0.02 to 1.20) NS
			Major bleeding	1/152(0.7%) vs 2/159 (1.3%) RR: 0.52 (95%CI, 0.05 to 5.71) NS
			Symptomatic PE	1/152 (0.7%) vs 1/159 (0.6%) RR: 1.05 (95%CI, 0.07 to 16.58) NS
			Symptomatic DVT	0/152 (0%) vs 6/159 (3.8%) RR: 0.08 (95%CI, 0.00 to 1.42) NS
			Minor bleeding	7/152 (4.6%) vs 3/159 (1.9%) RR: 2.44 (95%CI, 0.64 to 9.27) NS

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Methodology
Levine 1994(219) Design: RCT DB Prospective Multicentre	311	Mean age: 56.5 years Patients with metastatic stage IV breast carcinoma who had been receiving first-line or secondline chemotherapy for four weeks or less	Until one week after termination chemo	Warfarine (1 mg daily and then adjusted to INR between 1.3 to 1.9) Vs Placebo	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate Incomplete outcome data: Inadequate ITT: Yes Excluded from analysis: 1.3% Selective reporting: no

The main effectiveness outcome was symptomatic VTE objectively verified by means of Doppler (compression) ultrasonography or venography for DVT and spiral computed tomography, ventilation/perfusion lung scan, or pulmonary angiography for PE. The main safety outcome was major bleeding, typically defined as including: overt bleeding associated with a fall in haemoglobin of 2 g/dL or more or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleedingthat occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. Minor bleeding was defined as a bleeding event not matching the criteria for major bleeding.

10.1.8 Summary and conclusions Vitamin K antagonists versus placebo in ambulatory cancer patients receiving chemotherapy

VKA (INR 1.3-1.9) vs placebo in ambulatory cancer patients receiving chemotherapy			
Bibliography:systematic review Dinisio 2012(214) included 1 RCT: Levine 1994(219)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Symptomatic VTE	311 (1 study) Until 1 week after chemo	0.7% vs 4.4% RR: 0.15 (95%CI, 0.02 to 1.20) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Incomplete outcome data Consistency:NA Directness:OK Imprecision:OK
Symptomatic PE	311 (1 study) Until 1 week after chemo	0.7% vs 0.6% RR: 1.05 (95%CI, 0.07 to 16.58) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Incomplete outcome data Consistency:NA Directness:OK Imprecision:-1 Wide CI
Symptomatic DVT	311 (1 study) Until 1 week after chemo	0% vs 3.8% RR: 0.08 (95%CI, 0.00 to 1.42) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Incomplete outcome data Consistency:NA Directness:OK Imprecision:OK
Major Bleeding	311 (1 study) Until 1 week after chemo	0.7% vs 1.3% RR: 0.52 (95%CI, 0.05 to 5.71) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Incomplete outcome data Consistency:NA Directness:OK Imprecision:-1 Wide CI

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

In this trial patients with metastatic stage IV breast carcinoma who had been receiving first-line or second-line chemotherapy for four weeks or less were treated with warfarin (INR 1.3-1.9) or matching placebo.
No data on mortality were reported.

There was no statistically significant effect on symptomatic VTE.
GRADE: MODERATE quality of evidence

There was no statistically significant effect on symptomatic PE.
GRADE: LOW quality of evidence

There was no statistically significant effect on symptomatic DVT.
GRADE: MODERATE quality of evidence

There was no statistically significant effect on major bleeding.
GRADE: LOW quality of evidence

10.2 Pharmacological treatment versus pharmacological treatment for thromboprophylaxis in cancer patients

10.2.1 LMWH versus vitamin K antagonist in cancer patients receiving chemotherapy

Ref	Comparison	N/n	Outcomes	Result**
296 Dinisio 2012(214) Design: SR + MA Search date: May 2011	LMWH vs Warfarin	N= 1 n= 667 Palumbo 2011	**Symptomatic VTE**	6/219 (2.7%) vs 18/220 (8.2%) RR: 0.33 (95%CI, 0.14 to 0.83) **SS in favour of LMWH**
			Major bleeding	0% vs 0% NS
			Symptomatic PE	0/219 (0%) vs 4/220 (1.8%) RR: 0.11 (95% CI: 0.01 to 2.06) NS
			Symptomatic DVT	6/219 (2.7%) vs 14/220 (6.4%) RR: 0.43 (95% CI: 0.17 to 1.10) NS
			Minor bleeding	3/219 (1.4%) vs 6/220 (2.7%) RR: 0.50 (95% CI: 0.13 to 1.98) NS

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Methodology
Palumbo 2011(222) Design: RCT Open label Multicenter	667	Mean age: 61 years Patients with previously untreated myeloma who received thalidomide-containing regimens	during the 3 cycles of induction therapy in patients ≤ 65 years and during the first 6 cycles of induction therapy in patients > 65 years	Aspirin (100 mg/d) vs Warfarin (1.25 mg/d) vs LMWH (enoxaparin 40 mg/d)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Open Incomplete outcome data: inadequate ITT: Yes Excluded from analysis: 1.36% Selective reporting: Unclear No reporting on adverse events

The main effectiveness outcome was symptomatic VTE objectively verified by means of Doppler (compression) ultrasonography or venography for DVT and spiral computed tomography, ventilation/perfusion lung scan, or pulmonary angiography for PE. The main safety outcome was major bleeding, typically defined as including: overt bleeding associated with a fall in haemoglobin of 2 g/dL or more or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleedingthat occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. Minor bleeding was defined as a bleeding event not matching the criteria for major bleeding.

10.2.2 Summary and conclusions. LMWH versus vitamin K antagonist in cancer patients receiving chemotherapy

Enoxaparin 40mg vs warfarin (1.25mg/d) in patients with cancer receiving chemotherapy			
Bibliography: systematic review Dinisio 2012(214) included 1 RCT: Palumbo 2011(222)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
Symptomatic VTE	667 (1 study) During chemo	2.7% vs 8.2% **RR: 0.33 (95%CI, 0.14 to 0.83)** **SS in favour of LMWH**	⊕⊕⊖⊖ **LOW** Study quality:-2 Open label, incomplete outcome data Consistency:NA Directness:OK Imprecision:OK
Symptomatic PE	667 (1 study) During chemo	0% vs 1.8% RR: 0.11 (95% CI: 0.01 to 2.06) NS	⊕⊕⊖⊖ **LOW** Study quality:-2 Open label, incomplete outcome data Consistency:NA Directness:OK Imprecision:OK
Symptomatic DVT	667 (1 study) During chemo	2.7% vs 6.4% RR: 0.43 (95% CI: 0.17 to 1.10) NS	⊕⊕⊖⊖ **LOW** Study quality:-2 Open label, incomplete outcome data Consistency:NA Directness:OK Imprecision:OK
Major bleeding	667 (1 study) During chemo	0% vs 0% RR 0 NS	⊕⊕⊖⊖ **LOW** Study quality:-2 Open label, incomplete outcome data Consistency:NA Directness:OK Imprecision:OK

* For information on how to interpret the outcome measures of the meta-analysis, see 1.6

A Cochrane systematic review (Dinisio 2012) found one RCT (Palumbo 2011) that compared low molecular weight heparin to a vitamin K antagonist in patients with cancer, receiving chemotherapy. In this study patients with multiple myeloma and receiving thalidomide-containing regimens were treated with enoxaparin 40mg or low dose warfarin (1.25mg/d).

Compared to low dose warfarin, enoxaparin was significantly superior at preventing symptomatic VTE.
GRADE: LOW quality of evidence

Compared to low dose warfarin, enoxaparin was not significantly different in the prevention of symptomatic PE or symptomatic DVT.
GRADE: LOW quality of evidence

The risk of major bleeding with enoxaparin was not significantly different compared to low dose warfarin.
GRADE: LOW quality of evidence

10.2.3 LMWH versus low-dose aspirin in cancer patients receiving chemotherapy

Ref	Comparison	N/n	Outcomes	Result*
296 Dinisio 2012 (214) Design: SR + MA Search date: May 2011	LMWH Vs ASA	N= 1 n= 667 Palumbo 2011	**Symptomatic VTE**	6/219 (2.7%) vs 12/220 (5.5%) RR: 0.50 (95%CI, 0.19 to 1.31) NS
			Major bleeding	0 vs 3/220 (1.4%) RR: 0.14 (95% CI: 0.01 to 2.76) NS
			Symptomatic PE	0 vs 4/220 (1.8%) RR: 0.11 (95% CI: 0.01 to 2.06) NS
			Symptomatic DVT	6/219 (2.7%) vs 8/220 (3.6%) RR: 0.75 (95% CI: 0.26 to 2.13) NS
			Minor bleeding	3/219 (1.4%) vs 1/220 (0.5%) RR: 3.01 (95% CI: 0.32 to 28.75) NS

* Characteristics of included studies: see below

** For information on how to interpret the outcome measures of the meta-analysis, see 1.6

Ref + design	n	Population	Duration	Comparison	Methodology
Palumbo 2011(222) Design: RCT Open label Multicenter	667	Mean age: 61 years Patients with previously untreated myeloma who received thalidomide-containing regimens	during the 3 cycles of induction therapy in patients ≤ 65 years and during the first 6 cycles of induction therapy in patients > 65 years	Aspirin (100 mg/d) Vs Warfarin (1.25 mg/d) vs LMWH (enoxaparin 40 mg/d)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Open Incomplete outcome data: inadequate ITT: Yes Excluded from analysis: 1.36% Selective reporting: Unclear No reporting on adverse events

The main effectiveness outcome was symptomatic VTE objectively verified by means of Doppler (compression) ultrasonography or venography for DVT and spiral computed tomography, ventilation/perfusion lung scan, or pulmonary angiography for PE. The main safety outcome was major bleeding, typically defined as including: overt bleeding associated with a fall in haemoglobin of 2 g/dL or more or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleedingthat occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. Minor bleeding was defined as a bleeding event not matching the criteria for major bleeding.

Study details	n/Population	Comparison	Outcomes		Methodological
Ref.: 443 Larocca 2012(223) Design: prospective, randomised substudy of a phase 3 RCT. RCT OL PG Setting: multicenter (62 centers in Italy and Israel) Duration of follow-up: 6 months	n= 342 Mean age:57,5y Recent surgery: 0% orthopedic surgery Immobilized: NR <u>Inclusion</u> Untreated patients with newly diagnosed MM. Age 18 - 65 y, treated with lenalidomide-based chemotherapy <u>Exclusion</u> History of DVT or arterial thromboembolic events < 12 months. Clear indication or contraindication for antiplatelet or anticoagulant therapy.	Aspirin 100mg/d vs Enoxaparin 40mg/d Prophylaxis was administered during the 10 cycles (280 days) of chemotherapy	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: no Personnel: no Assessors: no FOLLOW-UP: Lost-to follow-up: NR Drop-out and Exclusions: no post-randomisation exclusions apparent ITT:No (all randomly assigned patients who received 1 dose of the study drug) Power: adequate (ranging from 47% to 80% to detect an absolute difference of 7%-11%, respectively, between the groups, with α of 0.05 (2-tailed), assuming a value of 10% for the composite primary end point in the LMWH group)
			Composite primary end point =the first episode of any objectively confirmed symptomatic deep vein thrombosis, pulmonary embolism, arterial thrombosis, acute cardiovascular event (acute myocardial infarction or stroke), or sudden otherwise unexplained death (presumed to be related to pulmonary embolism, acute myocardial infarction, or stroke) in the first 6 months. (PO) (diagnostic tools not reported)	Aspirin:4/176 patients; 2.27% Enoxaparin: 2/166 patients; 1.20% Absolute difference: 1.07% (95% CI -1.69 to 3.83); p=.452 NS	
			Any grade 3/4 thromboembolic event (deep vein thrombosis, pulmonary embolism, arterial thrombosis, acute cardiovascular event)	Aspirin: 4/176 patients; 2.27% Enoxaparin: 2/166 patients; 1,20% Absolute difference: 1.07% (95% CI -1.69 to 3.83); p=.452 NS	
			DVT	Aspirin: 2/176 patients; 1.14% Enoxaparin: 2/166 patients; 1.20% Absolute difference: -0.07 (95% CI -2..35 to 2.21); p= .953 NS	

	Active bleeding or at high risk of bleeding.		**PE**	Aspirin: 3/176patients; 1.70% Enoxaparin: 0/166 patients; 0% Absolute difference: 1.70 (95% CI -0.21 to 3.62); p=0.91 NS	SELECTIVE REPORTING: no Sponsor: Medscape, LLC and the American Society of Hematology
			Safety		
			Major bleeding (fatal bleeding, symptomatic bleeding in a crucial area or organ, or bleeding that caused a reduction in hemoglobin concentration of _ 2 g/dL or that necessitated transfusion of 2 units of whole blood or red blood cells)	Aspirin: 0 patients Enoxaparin: 0 patients	
			Minor bleeding (gastrointestinal bleeding)	Aspirin: 0 patients Enoxaparin: 1 patient Absolute difference: -0.60 (95% CI -1.78 to 0.57); p=.302 NS	

10.2.4 Summary and conclusions. LMWH versus low-dose aspirin in cancer patients receiving chemotherapy

Enoxaparin 40mg vs aspirin 100mg for thromboprophylaxis in patients with cancer receiving chemotherapy			
Bibliography: systematic review Dinisio 2012(214) included 1 RCT: Palumbo 2011(222);1 more recent RCT: Larocca 2012(223)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Symptomatic VTE	667 (1 study) 8 cycles of chemo	**Dinisio 2012 Enoxaparin vs ASA** RR: 0.50 (95%CI, 0.19-1.31) NS	⊕⊕⊖⊖ **LOW** Study quality:-2 Open label, incomplete outcome data. Consistency:NA Directness:OK Imprecision:OK
Symptomatic DVT	342 (1 study) 6 mo	**Larocca 2012: ASA vs enoxaparin** ASA: 1.14% Enoxaparin: 1.20% ARD: -0.07 (95% CI -2..35 to 2.21) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Open label Consistency:NA Directness:OK Imprecision:OK
Symptomatic PE	342 (1 study) 6 mo	**Larocca 2012: ASA vs enoxaparin** ASA: 1.70% Enoxaparin: 0% Absolute difference: 1.70 (95% CI -0.21 to 3.62) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Open label Consistency:NA Directness:OK Imprecision:OK
Major Bleeding	342 (1 study) 6 mo	**Larocca 2012: ASA vs enoxaparin** ASA: 0 Enoxaparin: 0 NT	Not applicable
Composite of symptomatic deep vein thrombosis, pulmonary embolism, arterial thrombosis, acute cardiovascular event (acute myocardial infarction or stroke), or sudden otherwise unexplained death (PO)	342 (1 study) 6 mo	**Larocca 2012 ASA vs enoxaparin** ASA: 2.27% Enoxaparin: 1.20% Absolute difference: 1.07% (95% CI -1.69 to 3.83); NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 Open label Consistency:NA Directness:OK Imprecision:OK

2 trials compared the low molecular weight heparin enoxaparin with acetylsalicylic acid in patient with cancer receiving chemotherapy. In both studies patients were diagnosed with multiple myeloma and treated with thalidomide-containing regimens.

No statistically significant difference was found between LMWH and ASA on the endpoint symptomatic VTE.
GRADE: LOW quality of evidence

No statistically significant difference was found between LMWH and ASA on the endpoints symptomatic PE and symptomatic DVT.
GRADE: MODERATE quality of evidence

No statistically significant difference was found between LMWH and ASA on a composite endpoint containing symptomatic deep vein thrombosis, pulmonary embolism, arterial thrombosis, acute cardiovascular event (acute myocardial infarction or stroke), or sudden otherwise unexplained death.
GRADE: MODERATE quality of evidence

In both treatment groups no patient experienced major bleedings.
GRADE: Not applicable

10.2.5 Vitamin K antagonist versus low dose aspirin in cancer patients receiving chemotherapy

Ref	Comparison	N/n	Outcomes	Result
296 Dinisio 2012(214) Design: SR + MA Search date: May 2011	VKA Vs ASA	N= 1 n= 667 Palumbo 2011	**Symptomatic VTE**	18/220 (8.2%) vs 12/220 (5.5%) RR: 1.50 (95%CI, 0.74 to 3.04) NS
			Symptomatic DVT	14/220 (6.4%) vs 8/220 (3.6%) RR: 1.75 (95% CI: 0.75 to 4.09) NS
			Symptomatic PE	4/219 (1.8%) vs 4/220 (1.8%) RR: 1.00 (95% CI: 0.25 to 3.95) NS
			Major bleeding	0 vs 3/220 (1.4%) RR: 0.14 (95% CI: 0.01 to 2.75) NS
			Minor bleeding	1/220 (0.5%) vs 6/220 (2.7%) RR: 0.17 (95% CI: 0.02 to 1.37) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Palumbo 2011(222) Design: RCT Open label Multicenter	667	Mean age: 61 years Patients with previously untreated myeloma who received thalidomide-containing regimens	during the 3 cycles of induction therapy in patients ≤ 65 years and during the first 6 cycles of induction therapy in patients > 65 years	Aspirin (100 mg/d) Vs Warfarin (1.25 mg/d) vs LMWH (enoxaparin 40 mg/d)	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Open Incomplete outcome data: inadequate ITT: Yes Excluded from analysis: 1.36% Selective reporting: Unclear No reporting on adverse events

The main effectiveness outcome was symptomatic VTE objectively verified by means of Doppler (compression) ultrasonography or venography for DVT and spiral computed tomography, ventilation/perfusion lung scan, or pulmonary angiography for PE. The main safety outcome was major bleeding, typically defined as including: overt bleeding associated with a fall in haemoglobin of 2 g/dL or more or leading to a transfusion of two or more units of packed red blood cells or whole blood; bleedingthat occurred at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal); or bleeding contributing to death. Minor bleeding was defined as a bleeding event not matching the criteria for major bleeding

10.2.6 Summary and conclusions. Vitamin K antagonist versus low dose aspirin in cancer patients receiving chemotherapy

Warfarin 1.25mg/d vs aspirin 100mg in patients with cancer receiving chemotherapy			
Bibliography: systematic review Dinisio 2012(214) included 1 RCT: Palumbo 2011(222); Larocca 2012(223)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Symptomatic VTE	667 (1 study) 8cycles of chemo	8.2% vs 5.5% RR: 1.50 (95%CI: 0.74 to 3.04) NS	⊕⊕⊖⊖ **LOW** Study quality:-2 Open label, incomplete outcome data Consistency:NA Directness:OK Imprecision:OK
Symptomatic DVT	n=667 (1 study) 8 cycles of chemo	6.4% vs 3.6% RR: 1.75 (95% CI: 0.75 to 4.09) NS	⊕⊕⊖⊖ **LOW** Study quality:-2 Open label, incomplete outcome data Consistency:NA Directness:OK Imprecision:OK
Symptomatic PE	n= 667 (1 study) 8 cycles of chemo	1.8% vs 1.8% RR: 1.00 (95% CI: 0.25 to 3.95) NS	⊕⊕⊖⊖ **LOW** Study quality:-2 Open label, incomplete outcome data Consistency:NA Directness:OK Imprecision:OK
Major bleeding	n= 667 (1 study) 8 cycles of chemo	0 % vs 1.4% RR: 0.14 (95% CI: 0.01 to 2.75) NS	⊕⊕⊖⊖ **LOW** Study quality:-2 Open label, incomplete outcome data Consistency:NA Directness:OK Imprecision:OK

A Cochrane systematic review (Dinisio 2012) found one RCT (Palumbo 2011) that compared vitamin K antagonists to low dose aspirin in cancer patients receiving chemotherapy. In this study patients with multiple myeloma receiving thalidomide-containing regimens were treated with low dose warfarin (1.25mg/d) or aspirin 100mg daily.

There was no statistically significant difference between aspirin and warfarin in preventing symptomatic VTE, nor in symptomatic DVT or PE.
GRADE: LOW quality of evidence

There were no cases of major bleeding in the warfarin group as opposed to 3 cases in the aspirin group. However this difference was not statistically significant.
GRADE: LOW quality of evidence

11 Adverse events

11.1 Heparins

11.1.1 Unfractionated heparins

- Bleeding
  (Protamine, in a dose of 1,000 IU intravenously per 1,000 IU of heparin – to be repeated as necessary – neutralises the effect of heparin.)
  There is a risk of bleeding complications with all antithrombotic agents. Combining antithrombotic agents with each other or with other agents which can cause bleeding, such as NSAIDs and SSRIs, increases this risk even further.
- Thrombocytopenia, even in the weeks after stopping administration.
- Hyperkalaemia (due to the anti-aldosterone effect)
- Allergic reactions.
- Osteoporosis with long-term use.
- Heparins are safe during pregnancy and during the breast-feeding period. If possible, the treatment with heparin is discontinued shortly before delivery.

Belgisch Centrum voor Farmacotherapeutische Informatie [Belgian Centre for Pharmacotherapeutic Information]

11.1.2 Low-molecular-weight heparins

- Bleeding
- Thrombocytopenia, but lower risk than with non-fractionated heparins.
- Hyperkalaemia (due to the anti-aldosterone effect)
- Allergic reactions.
- Osteoporosis with long-term use.
- Low-molecular-weight heparins are considered to be safe during pregnancy and the breast-feeding period. If possible the treatment is discontinued shortly before delivery.

Belgisch Centrum voor Farmacotherapeutische Informatie

11.1.3 Low-molecular-weight heparinoids

- Bleeding.
- Thrombocytopenia (rare).
- Raised liver enzyme levels.
- Skin rashes.
- Dose reduction in the case of renal insufficiency.

Belgisch Centrum voor Farmacotherapeutische Informatie

11.2 Vitamin K antagonists

- Bleeding is the main adverse event of vitamin K antagonists. The connection between the intensity of the anticoagulant treatment and the risk of bleeding is very great. Randomised studies show that the cost-benefit relationship is best at an INR of between 2 and 3.
- Allergic reactions are very rare. There is a reduced reaction to skin tests when under treatment with vitamin K antagonists.
- Uricosuria has been reported with dicoumarol.
- Exceptionally, skin necrosis can occur when using vitamin K antagonists; this is the case in 0.01 to 0.1% of patients. The morbidity of this complication is very high, however: in spite of adequate treatment, half of these patents must undergo an operation in which skin grafts may or may not be necessary. Prevention of coumarin-induced skin necrosis can occur by building the dose up carefully, in particular in the case of the elderly.
- Vitamin K antagonists have a vasodilatory effect on coronary arteries, peripheral veins and capillary vessels, resulting in the Raynaud's phenomenon-. Peripheral vasodilation can also be responsible for the cold feeling that some patients experience.
- Only a few cases of liver damage have been reported. Usually it presents as a cholestatic clinical picture, approximately ten days after the beginning of the treatment with vitamin K antagonists.
- Anti-thrombotic treatment during pregnancy is accompanied by a known high risk, both for the mother and for the child. Pregnant women are at an increased risk of miscarriage and perinatal bleeding. Vitamin K antagonists are also teratogenic. They are secreted in the mother's milk, but this should not have an effect on the baby. Nevertheless some experts recommend regularly testing the prothrombin time of babies of mothers who breast-feed while under treatment with vitamin K antagonists and, if necessary, administering 1 mg of vitamin K orally to the babies.

Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), *2006*, *Pages 983-1000*

11.3 Thrombin inhibitors

11.3.1 Dabigatran

- The most common adverse event of dabigatran is bleeding. Bleeding occurred in a total of approximately 14% of patients. The frequency of severe bleeding (including wound bleeding) was less than 2%. Epistaxis and gastrointestinal bleeding frequently occurred in 1 to 10 of the 100 patients treated. This bleeding can lead to anaemia and a reduction in the quantity of haemoglobin.
- Abdominal pain, diarrhoea and nausea are also frequently reported.
- The European Medicines Agency (EMA) recommends that renal function should be measured before starting treatment with dabigatran, and monitored on an annual basis in the case of long-term treatment if renal function has decreased slightly to moderately or if the patient is older than 75 years of age. In the case of severe renal insufficiency (creatinine clearance <30 ml/min), dabigatran is contraindicated.
- Dabigatran may not be used in patients who are currently suffering from bleeding or who are suffering from a condition which is accompanied by a risk of severe bleeding. The agent may not be used at the same time as other anticoagulants (except when switching over).
- Neither should dabigatran be used in patients with severe liver problems or patients who use the antifungals ketoconazole and itraconazole, the immunosuppressants cyclosporine and tacrolimus or dronedarone by mouth or as an injection.
- In a meta-analysis by Uchino and Hernandez (Arch Int Med 2012; doi:10.1001)(224) the use of dabigatran was associated with an increased risk of myocardial infarction and acute coronary syndrome compared with other antithrombotics. These results were confirmed in a more recent meta-analysis by Mak(225).
- The use of dabigatran in children less than 18 years of age is not recommended on account of the absence of safety and efficacy data.
- There are insufficient data on the use of dabigatran in pregnant women and there are no clinical data on the effect of dabigatran in infants who are being breast-fed.
- There is no antidote, which is a disadvantage in the case of severe bleeding. Furthermore, to date there are no laboratory tests available for testing the anticoagulant effect of dabigatran.

- *Belgisch Centrum voor Farmacotherapeutische Informatie*
- *Minerva: Online themadossier. Orale anticoagulatie: nieuwe geneesmiddelen. [Online dossier. Oral anticoagulation: new drugs.] Update 03.02.2013. www.minerva-ebm.be*
- *European Medicines Agency. Accessed April 18, 2013* http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Summary_for_the_public/human/000829/WC500041060.pdf
- *US Food and Drug Administration. Accessed February 6, 2012. www.fda.gov/Drugs/DrugSafety/ucm282724.htm#hcp*
- *Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events. Meta-analysis of noninferiority randomized controlled trials. Arch Int Med 2012; published online January 9, 2012. doi:10.1001/archinternmed.2011.1666*

11.4 Factor Xa inhibitors

11.4.1 Fondaparinux

- As with other anticoagulants, bleeding is the most common adverse event.
- Other adverse events are thrombocytopenia (rare) and anaemia.
- Raised liver enzyme levels (mainly with apixaban and rivaroxaban, to a lesser extent with fondaparinux).
- Nothing is known of any adverse effect during pregnancy; extreme care is advised.
- Fondaparinux may not be prescribed to patients who possibly alreadyare bleeding, who have acute bacterial endocarditis or who suffer from a severe renal disease.
- There is no antidote, which is a disadvantage in the case of severe bleeding. In the case of severe bleeding, fresh plasma or clotting factor concentrates may be necessary.

- *Belgisch Centrum voor Farmacotherapeutische Informatie*
- *European Medicines Agency. Accessed April 18, 2013 http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Summary_for_the_public/human/000403/WC500027736.pdf*

11.4.2 Apixaban

- As with all anticoagulants, the risk of bleeding is also raised with apixaban and this drug may only be administered when haemostasis is reached. Bleeds, anaemias and ecchymoses account for 1-10% of all known adverse events. Gastrointestinal bleeds occur less frequently (1-0.1%)
- Care is needed with the combined use of apixaban with aspirin because of the increased risk of bleeding.
- Apixaban is not recommended in patients with severe renal insufficiency whose creatinine clearance is <15ml/min or in dialysis patients.
- Apixaban is a substrate of CYP3A4 and of P-glycoprotein, with the possibility of interactions with other drugs.
- There is only limited clinical experience with apixaban in the elderly, but, according to the manufacturer, this drug may be administered to patients over 65 years of age. Neither is there any restriction in the case of abnormally low or high body weight (<50kg or >120kg).
- Apixaban is contraindicated in patients with liver conditions accompanied by clotting disorders and a clinically relevant risk of bleeding. The dose does not need to be adjusted in patients with mild to moderately severe liver function disorders.
- There is no data available on the paediatric use of apixaban, therefore administering apixaban to children less than 18 years of age is not recommended.
- Apixaban is not recommended during pregnancy or breast-feeding on account of the fact that the effect is unknown in these circumstances.

- *European Medicines Agency. Accessed April 18, 2013. http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Summary_for_the_public/human/002148/WC500107773.pdf*

- *Belgisch Centrum voor Farmacotherapeutische Informatie. Accessed April 22, 2013*

11.4.3 Rivaroxaban

- The most common adverse event of rivaroxaban is bleeding, possibly post-operatively, sometimes resulting in anaemia and thrombocytopenia. This bleeding manifests itself in the form of epistaxis, gastrointestinal and urological bleeding and haematomas.
- The liver tests on patients under treatment with rivaroxaban must be monitored regularly, since there may an increase in cGT and transaminase values, as well as in LDH and alkaline phosphatase values. Sometimes there is an increase in the bilirubin content of the blood; an increase in conjugated bilirubin levels has been reported on rare occasions.
- Nausea, fever and peripheral oedema occur in 1-10% of patients taking rivaroxaban.
- Less common adverse events occurring with the use of rivaroxaban are dizziness, headache, tachycardia, hypotension, constipation, diarrhoea, abdominal pain, dyspepsia, vomiting, dry mouth, a general reduction in strength and energy, pain in the limbs, increased amylase/lipase levels and greater secretion of wound exudate.
- In exceptional cases fainting can occur due to rivaroxaban. Dermatitis or urticaria also occur in rare cases.
- Rivaroxaban must not be administered to pregnant women or women who are breast-feeding.
- Other contraindications according to the European Medicines Agency (EMA) are active bleeds or liver conditions accompanied by a high risk of bleeding. Rivaroxaban is best avoided in the case of severe renal insufficiency (creatinine clearance <30ml/min); if creatinine clearance is <50ml/min, an adjusted dose is recommended.
- Rivaroxaban is a substrate of CYP3A4 and of P-glycoprotein, with the possibility of interactions with other drugs.
- There is no antidote, which is a disadvantage in the case of severe bleeding.

- *Belgisch Centrum voor Farmacotherapeutische Informatie.*
- *European Medicines Agency. Accessed April 18, 2013*
  http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Summary_for_the_public/human/000944/WC500057109.pdf

12 Appendix 1. Critical reflections – historical background (Fr)

(By Alain Van Meerhaeghe, for the reading committee)

12.1 Traitement de thromboembolies veineuses - Etudes versus placébo

En 1960, Barrit et Jordan(226) publie dans le Lancet le seul essai randomisé à ce jour comparant l'héparine non fractionnée relayée par un anti vitamine K à l'abstention thérapeutique. Cet essai qui est considéré comme l'essai fondateur justifiant le traitement anticoagulant n'a pas été retenu par la Cochrane collaboration dans sa revue systématique(227).

En effet un des problèmes est que le diagnostic d'embolie pulmonaire a été posé cliniquement (pas de scintigraphie à l'époque) et nous savons que le diagnostic clinique n'est pas adéquat. Dans certaines séries publiées 75% des patients avec un diagnostic clinique d'embolie pulmonaire n'en souffraient pas, d'où les efforts considérables des scores cliniques (Wells-Genève..) pour créer une probabilité à priori avant de faire une recherche diagnostique.

Un audit autopsique réalisé sur les patients décédés dans cette étude est repris dans le tableau ci-dessus.

Case No.	Age, yr/sex	Underlying Diagnosis	Anatomic Site of Pulmonary Emboli	Source of Thromboemboli	Coincidental Infection Noted
1	54/female	Extensive breast carcinoma	Left main branch	Right femoral DVT	Mixed organism empyema, bronchopneumonia and abscess
2	56/male	Post operation for intestinal obstruction (adhesions)	Main trunk	Left femoral DVT, hepatic vein thrombosis	Biliary tree sepsis
3	78/female	Post fractured ankle	Main trunk	Bilateral popliteal DVT	Bronchopneumonia, fungal lung abscess
4	57/male	Myocardial infarction	Left lobar	Bilateral femoral DVT, right ventricular mural thrombus	*Staphylococcus aureus* lung abscess
5	41/male	Nephrotic syndrome secondary to primary amyloidosis	Both main branches	Left calf DVT, renal vein thrombosis	None

On peut en retirer notamment les observations suivantes :

1-les co-morbidités étaient extrêmement lourdes et ont pu dans certains cas être la cause de la mort sauf dans l'observation 5.

2-Des thrombus ont été retrouvés au niveau des artères pulmonaires et du réseau périphérique.

3-Ce tableau est consistant avec l'observation qu'environ 95% des patients décédés des suites d'une embolie pulmonaire souffrent de pathologies sévères (chroniques ou aigues).

Egermayer 1981(228) cite d'autres problèmes avec cet essai clinique réalisé fin des années 50.

1- Des médecins autres que les investigateurs ont référés leurs patients pour l'inclusion dans l'étude. Donc problème de sélection non aléatoire.
2- Pas double-blind
3- Aucune information fournie par les investigateurs sur la comparabilité des deux bras de l'essai
4- Pas de données sur des évènements non mortels qui seraient éventuellement survenus.

Malgré le rejet par Cochrane et d'autres (à cause des biais potentiels), j'ai réalisé un test exact de Fisher en vue d'estimer la taille de l'effet chez ces patients sévèrement malades,

Data analyzed

	Dead	Alive	Total
Hep+	0	16	16
	(0%)	(46%)	(46%)
Hep-	5	14	19
	(14%)	(40%)	(54%)
Total	5	30	35

P= 0.0493. J'obtiens un **NNT de 4** (95%CI 2-47)

La recherche d'autres essais cliniques semble n'apporter que les résultats suivants que je recopie ci-dessous :

Published, randomized trials of DVT patients, including un-anticoagulated controls, include:

- *An abstract-only report by Kakkar and colleagues(229) compared heparin, Malayan pit viper venom (Arvin), streptokinase, and placebo, resulting in 2 of 7 deaths in the heparin group and 0 of 6 in the placebo group.*
- *Ott and colleagues(230) published a placebo-controlled trial in which 2 of 11 patients died receiving heparin and warfarin, and 1 of the 12 placebo-treated patients died.*
- *Nielsen and colleagues(231, 232) randomized 90 ambulatory patients with DVT into standard heparin and phenprocoumon vs phenylbutazone (ie, no anticoagulants). Two of 48 patients in the anticoagulated group died (one of PE), whereas 0 of 42 in the un-anticoagulated group died. About 50% of both groups had PE by lung ventilation-perfusion scanning, mostly asymptomatic.*

12.2 Etudes de non-infériorité

L'essai le plus souvent repris pour déterminer la marge de non infériorité est celui publié en 1992 dans le *NEJM* par Brandjes *et al(233)* et qui compare l'acénocoumarol seul versus héparine +acénocoumarol.

Cet essai a été exclu par les membres de la Cochrane(227) car il n'y avait pas de groupe contrôle par placebo or NSAID.

Les auteurs publiant les essais sur les LMWH ont quasi tous utilisé l'essai de Brandjes *et al(233)* comme base pour définir leur marge de non infériorité (étape critique !).

D'abord, ils ont assimilé le bras acénocoumarol (Sintrom) à un placébo. Probablement en raison du temps de latence de l'action anticoagulante des antivitamines K.

Examinons un instant l'essai de Brandjes *et al(233)* qui sert de support aux essais ayant permis l'introduction des LMWH.

Cet essai a été arrêté précocement et n'a donc recruté que 120 patients (60 dans chaque bras). Le bras acénocoumarol avait au moment de l'arrêt jugé nécessaire par le safety committee, 12 events (20%) (symptomatic extension of venous thrombosis, symptomatic pulmonary embolism or symptomatic recurrence of venous thrombosis). Le bras Héparine +Sintrom avait 4 events (6.7%).

Cependant comme l'écrivent les auteurs la différence n'était pas statistiquement significative (p = 0.058). L'ARR était de 13.3% ou 0.13. Les calculs que j'ai faits pour calculer l'IC 95%(0.009 – 0.26).Donc l'IC couvre une zone allant de moins de 1% à 26%.

Comme le signale Pérard et al.(234), les auteurs ont basé la marge de non infériorité sur la valeur centrale de l'intervalle de confiance, ainsi dans l'essai Columbus(235).

Les auteurs écrivent : *On the basis of the previously observed absolute risk reduction of 12 percentage points (13.3%??) associated with the use of unfractionated heparin as compared with placebo (donc acenocoumarol = placebo) (ref 14 dans leur article= Brandjes), we took an increase of 3 percentage points as the threshold value indicating clinical equivalence.*

Ils font donc l'hypothèse que la vraie valeur inconnue de la taille de l'effet (ARR) de l'héparine + acénocoumarol vs acénocoumarol seul est de 12 %

Imaginons comme le laisse supposer les valeurs reprises dans l'IC à 95% qui ont toutes le même poids dans l'appréciation par la statistique inférentielle de la vraie taille de l'effet que celle-ci soit la valeur de la borne inférieure c'est-à-dire plus ou moins 1% alors retirer3 % c'est prendre le risque d'être moins efficace que l'acénocoumarol seul considéré comme placébo !

C'est ce qu'explique Pérard et al(234). La FDA n'avait pas encore écrit ses recommandations à l'usage de l'industrie pour essayer de minimiser les faiblesses inhérentes des conclusions que l'on peut tirer à partir des essais de non infériorité.

Continuons dans la construction du savoir dans le traitement de la maladie veineuse thrombo-embolique.

Les Nouveaux anticoagulants oraux en plus de faiblesses de certains essais (LMWH au début du traitement avant randomisation, open label, patients soigneusement sélectionner pour éviter les

effets secondaires..) sont comparés avec l'aide d'essais de non infériorité aux LMWH avec des marges de non –infériorité parfois importantes.

Voici un tableau récapitulatif des études de non-infériorité dans le domaine cardiovasculaire provenant de Head et al.(236). Seule la partie de droite concerne les anticoagulants oraux.

Pour la maladie veineuse Thromboembolique c'est du même niveau.

Table 2 Examples of recent non-inferiority trials

	Device vs. surgery trials				Pharmacologic trials				
Trial, year	**SYNTAX, 2009**	**PRECOMBAT, 2011**	**PARTNER 1A, 2011**	**EVEREST II, 2011**	**PROTECT AF, 2009**	**RE-LY, 2009**	**RE-LY, 2009**	**ROCKET AF, 2011**	**ARISTOTLE, 2011**
New Rx	TAXUS DES	DES	TAVR	Mitraclip	Watchman LAA closure	Dabigatran 150 mg	Dabigatran 110 mg	Rivaroxaban	Apixaban
Standard Rx	CABG	CABG	SAVR	MV surgery	Warfarin	Warfarin		Warfarin	Warfarin
Primary endpoint	MACCE	MACCE	All-cause mortality	Freedom from death, MV surgery or MR >2+	Stroke, cardiovascular death, and systemic embolism	Stroke or systemic embolism		Stroke or systemic embolism	Stroke or systemic embolism
Standard Rx event rate (expected)	13.2%	13%	32%	90%	6.15% per 100 patient-years	Not specified		2.3% per 100 patient-years	Not specified
Standard Rx event rate (observed)	12.4%	6.7%	26.8%	88%	4.9% per 100 patient-years	1.7% per 100 patient-years		2.2% per 100 patient-years	1.6% per 100 patient-years
Trial power	96%	80%	85%	80%	80%	84%		95%	90%
Alpha	One-sided, 0.05	One-sided, 0.05	One-sided, 0.05	One-sided, 0.05	One-sided, 0.025	One-sided, 0.025		One-sided, 0.025	One-sided, 0.025
Sample size	1800	600	699	279	707	15000		14000	18000
Follow-up duration	1 year	1 year	1 year	1 year	Mean of 1.5 years	Median 2.0 years		Median 1.9 years	Median of 1.8 years
Standard Rx effect	Not quantified	Not quantified	Not quantified	90% (84–96%)	0.36 (0.25–0.53) for stroke and embolism. Not quantified for the endpoint with death included	0.36 (0.25–0.53)		0.36 (0.25–0.53)	0.36 (0.25–0.53)
Non-inferiority margin	ARD = 6.6%	ARD = 7%	ARD = 7.5%	ARD = 31% (PP)	Rate ratio = 2.0	Relative risk = 1.46		Relative risk = 1.46	Relative risk = 1.44
	RR = 1.51	RR = 1.54	RR = 1.23						
% preservation of standard Rx effect	…	…	…	65% of point estimate	…	50% of lower bound of 95% CI of placebo vs. standard		50% of lower bound of 95% CI of placebo vs. standard	50% of lower bound of 95% CI of placebo vs. standard
New Rx vs. standard Rx	ARD = 5.5% (2.8–8.3%)	ARD = 2.0% (−1.6–5.6%)	ARD = −2.6% (−9.3–4.1%)	ARD = 15.4% (4.8–26.1%)	Rate ratio = 0.62 (0.35–1.25)	Relative risk = 0.65 (0.52–0.81)	Relative risk = 0.90 (0.74–1.10)	Hazard ratio = 0.79 (0.66–0.96)	Hazard ratio = 0.79 (0.66–0.95)
	RR = 1.44 (1.15–1.81)	RR = 1.30 (0.81–2.08)	HR = 0.93 (0.71–1.22)	RR = 2.3 (1.2–4.4)					
Non-inferiority met	No	Yes (ARD margin) No (RR margin)	Yes (ARD margin) Yes (RR margin)	Yes (ARD margin)	Yes (RR margin)	Yes (RR margin)	Yes (RR margin)	Yes (RR margin)	Yes (RR margin)
Ancillary advantage	Less invasive, lower stroke	Less invasive, lower stroke	Less invasive	Less invasive, lower bleeding	No lifelong anticoagulation	Lower bleeding, no monitoring		Lower bleeding, no monitoring	Lower bleeding, no monitoring

DES, drug-eluting stent; CABG, coronary artery bypass grafting; TAVR, transcatheter aortic valve replacement; MV, mitral valve; LAA, left atrial appendage; MACCE, major adverse cardiac or cerebrovascular events; ARD, absolute risk difference; RR, relative risk; PP, per-protocol; ITT, intention-to-treat; MR, mitral regurgitation; Rx, treatment.
[a]Estimations based on the rates provided in the papers.

Bien entendu, il peut paraître incongru d'aller contre les forces issues de beaucoup d'essais randomisés. Je ne prétends nullement dire que les traitements ne sont pas efficaces, je prétends que nous n'avons pas à cause de toute cette construction du savoir commençant avec Baritt et Jordan(226) une idée précise de la taille de l'effet des traitements. Comme clinicien nous sommes incapables de déterminer avec certitude le nombre de patients à traiter pour éviter à l'un d'eux un adverse event.

12.3 Le diagnostic moderne des embolies pulmonaires

Reprenons l'essai fondateur de Baritt et Jordan(226), les patients ont été diagnostiqués sur base clinique, étaient hypotendus, présentaient une décompensation cardiaque droite aigue et des hémoptysies, avec en plus selon les autopsies des 5 patients décédés sur les 35 enrôlés, des pathologies d'accompagnement ou préexistantes gravissimes.

Qu'en est-il aujourd'hui en termes de types de patients?

L'étude observationnelle la plus complète a été publiée en 2008 par Kline et al(237). Armé de tout l'arsenal diagnostique moderne, parmi les 8138 patients testés pour suspicion d'embolie pulmonaire dans les services d'urgence des hôpitaux participants, 500 diagnostics ont été retenus et la mortalité par embolie pulmonaire a été de 2.6% (13/500) pour les embolies pulmonaires confirmées. Si l'on s'en tient à la suspicion clinique qui était le moyen diagnostique dans l'essai de Baritt et Jordan(226) , la mortalité est de 0.2% (13/8138). Cette diminution par un facteur 100 de la mortalité par rapport à l'essai de Baritt et Jordan(226) n'est vraisemblablement pas due au traitement.

La modification du pronostic est aussi due à un autre facteur : le patient actuel.

Avec les méthodes diagnostiques modernes comme l'angioscanner, nous élargissons le diagnostic de l'embolie pulmonaire et cette partie du spectre de la maladie n'a probablement plus rien à voir avec les embolies pulmonaires fatales des patients souffrant de pathologies graves et terminales. Tout médecin dans sa formation a été impressionné par la présence de maladies veineuses thromboemboliques dans les autopsies réalisées sur des patients décédés dans le cadre de pathologies graves. Nous avons un ancrage heuristique sur cette situation clinique et nous en projetons la gravité sur tout cas d'embolie pulmonaire. Avons-nous raison ou tort de penser comme cela ?

Dans l'étude PIOPED(238) publiée en 1990, 30% des 931 avec scintigraphie V/Q venaient des services d'urgence ou d'une salle d'hospitalisation. 20 patients avec un diagnostic d'embolie pulmonaire confirmé par angiographie ont échappé au traitement. 3 mois après le diagnostic, ces patients ont été revus pour déterminer l'histoire naturelle.

Bien entendu, le petit nombre de patients ne permet pas de conclusion formelle, mais 1 patient est décédé durant cette période de suivi (5%) et 1 patient a eu une récidive d'embolie pulmonaire non fatale. Pas d'autres évènements ont été rapportés durant le suivi de 4 à 12 mois. Tous les patients non traités avaient < 3 « mismatched segments ». L'angiographie montrait des thrombus au niveau segmentaire ou sous segmentaire dans 16 (84%) des patients, comparés à 36% chez les patients traités.

Il y a ici une indication empirique (de valeur faible bien entendu = petite série de cas) que : « Mild untreated PE carries a lower immediate mortality and lower mortality from recurrent PE than overt PE described in prior decades " comme concluent les auteurs.

Le fait probant le plus marquant est l'étude de Nielsen et al(231) comprenant 90 patients relativement en bonne santé diagnostiqués au niveau d'institutions de soins de première ligne avec une phlébographie et embolie pulmonaire asymptomatique diagnostiquée par scintigraphie de V/Q. Ces embolies pulmonaires asymptomatiques étaient présente chez 50% des patients enrôlés. 48 ont reçu un traitement classique et 42 pas d'anticoagulation. Les deux groupes étaient identiques en termes d'âge (57 ans), sexe, facteurs de risques thrombotiques (72% versus 63% dans le groupe non anti coagulé). Ici pas de différence de mortalité ou de taux de progression ou régression du thrombus entre les deux groupes. **L'étude concernait des patients qui étaient ambulatoires au moment du diagnostic, hémodynamiquement stables, avec peu de comorbidités et porteurs pour la moitié d'entre eux d'une embolie pulmonaire asymptomatique**.

Des études autopsiques (239), suivi de cohortes(240) et éditoriaux(241) suggèrent que chez les patients sans comorbidités importantes et hémodynamiquement stables, le bénéfice du traitement est indéfini et probablement faible, peut être nul.

Nous sommes par les qualités des démarches diagnostiques de l'embolie pulmonaire devant un élargissement du phénotype, nous diagnostiquons des embolies à valeurs pathologiques plus faibles et nous n'avons pas modifié notre approche thérapeutique. Cette position qui est de traiter des patients susceptibles de résoudre physiologiquement leur embolie pulmonaire, les met alors sous le risque des effets secondaires hémorragiques sans bénéfice en contrepartie.

De plus, la recherche diagnostique d'embolies pulmonaires asymptomatique ou peu symptomatiques chez des individus par ailleurs en bonne santé est peut-être plus dangereuse qu'utile car la spécificité de l'angioscanner n'est pas de 100% mais est comprise entre 90-94%(242) et donc génératrice de faux positifs qui eux aussi seront exposés aux traitements.

Il faut ajouter à cela les risques de cancérisation induits par les irradiations par angioscanner.

Seul un essai randomisé pourrait apporter la réponse, il me semble cependant que cela ne se fera jamais (ethique).

Note :

For more information on calculating non-inferiority margins and applying these to trials on treatment of VTE, see the following reference : (243)

Prins MH, Lensing AW. Derivation of the non-inferiority margin for the evaluation of direct oral anticoagulants in the treatment of venous thromboembolism. Thrombosis journal. 2013;11(1):13.

For information on non-inferiority margins in trials on prevention of VTE, see this reference :(3)

Wangge G, Roes KC, de Boer A, Hoes AW, Knol MJ. The challenges of determining noninferiority margins: a case study of noninferiority randomized controlled trials of novel oral anticoagulants. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(3):222-7.

13 Appendix 1 bis. Critical reflections – historical background (Nl)

(By Alain Van Meerhaeghe, for the reading committee)

13.1 Behandeling van veneuze trombo-embolie - Placebogecontroleerde studies

In 1960 hebben Barrit en Jordan (226) in The Lancet de tot nog toe enige gerandomiseerde studie gepubliceerd waarin niet-gefractioneerde heparine gevolgd door een vitamine K-antagonist werd vergeleken met geen behandeling. Die studie, die de aanzet heeft gegeven tot een antistollingstherapie, werd niet opgenomen in de systematische review van de Cochrane collaboration(227).

Eén van de problemen is inderdaad dat de diagnose van longembolie klinisch werd gesteld (scintigrafie bestond nog niet) en we weten dat de klinische diagnose ontoereikend is. In sommige publicaties vertoonde 75% van de patiënten bij wie een klinische diagnose van longembolie was gesteld, geen longembolie. Daarom werden klinische scores (Wells-Genève..) opgesteld om de a priori waarschijnlijkheid van longembolie te ramen voor er verder diagnostisch onderzoek wordt uitgevoerd.

De onderstaande tabel vat de bevindingen samen van de autopsie die werd uitgevoerd bij de patiënten die in deze studie overleden zijn.

Case No.	Age, yr/sex	Underlying Diagnosis	Anatomic Site of Pulmonary Emboli	Source of Thromboemboli	Coincidental Infection Noted
1	54/female	Extensive breast carcinoma	Left main branch	Right femoral DVT	Mixed organism empyema, bronchopneumonia and abscess
2	56/male	Post operation for intestinal obstruction (adhesions)	Main trunk	Left femoral DVT, hepatic vein thrombosis	Biliary tree sepsis
3	78/female	Post fractured ankle	Main trunk	Bilateral popliteal DVT	Bronchopneumonia, fungal lung abscess
4	57/male	Myocardial infarction	Left lobar	Bilateral femoral DVT, right ventricular mural thrombus	*Staphylococcus aureus* lung abscess
5	41/male	Nephrotic syndrome secondary to primary amyloidosis	Both main branches	Left calf DVT, renal vein thrombosis	None

We onthouden daarbij het volgende:

1- De patiënten vertoonden een uiterst zware comorbiditeit en mogelijk is die in sommige gevallen de doodsoorzaak geweest, behalve bij patiënt nr. 5.
2- Er werden trombi teruggevonden in de longslagaders en in perifere aders.
3- De tabel strookt met de observatie dat ongeveer 95% van de patiënten die sterven na een longembolie, ernstige (acute of chronische) aandoeningen vertoont.

Egermayer 1981(228) haalt nog andere problemen aan in deze klinische studie die einde van de jaren vijftig werd uitgevoerd.

5- De patiënten werden door andere artsen dan de vorsers verwezen voor inclusie in de studie. Dus mogelijk geen aselecte steekproef.
6- Niet dubbelblind
7- De vorsers hebben geen informatie gegeven over de vergelijkbaarheid van de twee behandelingsgroepen
8- Geen gegevens over niet-fatale accidenten die eventueel zijn opgetreden.

Hoewel de studie van Barritt door Cochrane en anderen wordt verworpen (wegens mogelijke bias), heb ik een Fisher-exacttest uitgevoerd om de grootte van het effect bij die zwaar zieke patiënten te ramen.

Data analyzed

	Dead	Alive	Total
Hep+	0	16	16
	(0%)	(46%)	(46%)
Hep-	5	14	19
	(14%)	(40%)	(54%)
Total	5	30	35

P= 0,0493. Met een berekende NNT van 4 (95% BI 2-47)

Andere klinische studies hebben de volgende resultaten opgeleverd (ik vat ze hieronder samen):

Published, randomized trials of DVT patients, including un-anticoagulated controls, include:

- *An abstract-only report by Kakkar and colleagues(229) compared heparin, Malayan pit viper venom (Arvin), streptokinase, and placebo, resulting in 2 of 7 deaths in the heparin group and 0 of 6 in the placebo group.*
- *Ott and colleagues(230) published a placebo-controlled trial in which 2 of 11 patients died receiving heparin and warfarin, and 1 of the 12 placebo-treated patients died.*
- *Nielsen and colleagues(232) randomized 90 ambulatory patients with DVT into standard heparin and phenprocoumon vs phenylbutazone (ie, no anticoagulants). Two of 48 patients in the anticoagulated group died (one of PE), whereas 0 of 42 in the un-anticoagulated group died. About 50% of both groups had PE by lung ventilation-perfusion scanning, mostly asymptomatic.*

13.2 Non-inferioriteitsstudies

De studie die meestal wordt aangehaald om de non-inferioriteitsmarge te berekenen, is de studie die in 1992 door Brandjes et al. werd gepubliceerd in the *NEJM(233)*. In die studie werd acenocoumarol alleen vergeleken met heparine + acenocoumarol.

Deze studie werd door de leden van de Cochrane collaboration verworpen (227) omdat er geen controlegroep was (placebo of NSAID).

Nagenoeg alle auteurs die studies met LMWH hebben gepubliceerd, hebben de studie van Brandjes *et al (233)* gebruikt als basis om hun marge van non-inferioriteit te bepalen (dit is een kritiek punt).

Vooreerst hebben ze de acenocoumarolgroep (Sintrom) gelijkgesteld met een placebogroep. Waarschijnlijk gezien de latentietijd in de werkzaamheid van vitamine K-antagonisten.

Laten we even de studie van Brandjes *et al (233)* onder de loep nemen, de studie die de basis is geweest van de studies die hebben geleid tot de registratie van LMWH.

Deze studie werd voortijdig stopgezet en er werden dus maar 120 patiënten gerekruteerd (60 in elke groep). Op het ogenblik dat de studie door het veiligheidscomité werd stopgezet, hadden er zich 12 accidenten (20%) voorgedaan in de acenocoumarolgroep *(symptomatic extension of venous thrombosis, symptomatic pulmonary embolism or symptomatic recurrence of venous thrombosis).* In de groep heparine + Sintrom waren dat er 4 (6,7%).

Nochtans was het verschil, zoals de auteurs schrijven, niet statistisch significant (p = 0,058). De ARR bedroeg 13,3% of 0,13. Ik berekende hierbij het 95% betrouwbaarheidsinterval (BI) :(0,009-0,26). Het BI dekt dus een zone van minder dan 1% tot 26%.

Zoals Pérard et al. (234) hebben gesignaleerd, hebben de auteurs de non-inferioriteitsmarge gebaseerd op de centrale waarde van het betrouwbaarheidsinterval, zoals bijvoorbeeld in de Columbusstudie(235).

De auteurs schrijven: *On the basis of the previously observed absolute risk reduction of 12 percentage points (13.3%??) associated with the use of unfractionated heparin as compared with placebo (dus acenocoumarol = placebo) (ref. 14 in hun artikel= Brandjes), we took an increase of 3 percentage points as the threshold value indicating clinical equivalence.*

Ze gaan dus uit van de hypothese dat de echte onbekende waarde van de grootte van het effect (ARR) van heparine + acenocoumarol vs. acenocoumarol alleen 12% bedraagt.

Laten we er even van uitgaan, ons baserend op het 95% BI, waarbij de waarden alle hetzelfde gewicht hebben bij het ramen van de echte grootte van het effect door middel van inferentiële statistiek, dat de grootte van het effect gelijk is aan de ondergrens, dus ongeveer 1%. Als je dan 3% aftrekt, loop je het risico minder efficiënt te zijn dan acenocoumarol alleen beschouwd als placebo.

Dat leggen Pérard et al (234) uit. De FDA had haar aanbevelingen betreffende non-inferioriteitsstudies ten behoeve van de industrie toen nog niet gepubliceerd. Die aanbevelingen proberen de inherente zwaktes te verminderen van conclusies die kunnen worden getrokken uit non-inferioriteitsstudies.

Laten we nu even verder kijken naar de behandeling van veneuze trombo-embolie.

Wat de nieuwe orale anticoagulantia betreft, zijn er de inherente zwaktes van sommige studies (toediening van LMWH voor randomisatie, open studies, patiënten zorgvuldig geselecteerd om bijwerkingen te voorkomen ….). Bovendien worden de nieuwe orale anticoagulantia in non-inferioriteitsstudies vergeleken met LMWH met een soms grote non-inferioriteitsmarge.

Head et al. (236) hebben de non-inferioriteitsstudies op cardiovasculair vlak in een tabel samengevat. Alleen het rechterdeel gaat over orale anticoagulantia.

Voor veneuze trombo-embolie is dit vergelijkbaar.

Table 2 **Examples of recent non-inferiority trials**

	Device vs. surgery trials				Pharmacologic trials				
Trial, year	**SYNTAX, 2009**	**PRECOMBAT, 2011**	**PARTNER 1A, 2011**	**EVEREST II, 2011**	**PROTECT AF, 2009**	**RE-LY, 2009**	**RE-LY, 2009**	**ROCKET AF, 2011**	**ARISTOTLE, 2011**
New Rx	TAXUS DES	DES	TAVR	Mitraclip	Watchman LAA closure	Dabigatran 150 mg	Dabigatran 110 mg	Rivaroxaban	Apixaban
Standard Rx	CABG	CABG	SAVR	MV surgery	Warfarin	Warfarin		Warfarin	Warfarin
Primary endpoint	MACCE	MACCE	All-cause mortality	Freedom from death, MV surgery or MR >2+	Stroke, cardiovascular death, and systemic embolism	Stroke or systemic embolism		Stroke or systemic embolism	Stroke or systemic embolism
Standard Rx event rate (expected)	13.2%	13%	32%	90%	6.15% per 100 patient-years	Not specified		2.3% per 100 patient-years	Not specified
Standard Rx event rate (observed)	12.4%	6.7%	26.8%	88%	4.9% per 100 patient-years	1.7% per 100 patient-years		2.2% per 100 patient-years	1.6% per 100 patient-years
Trial power	96%	80%	85%	80%	80%	84%		95%	90%
Alpha	One-sided, 0.05	One-sided, 0.05	One-sided, 0.05	One-sided, 0.05	One-sided, 0.025	One-sided, 0.025		One-sided, 0.025	One-sided, 0.025
Sample size	1800	600	699	279	707	15000		14000	18000
Follow-up duration	1 year	1 year	1 year	1 year	Mean of 1.5 years	Median 2.0 years		Median 1.9 years	Median of 1.8 years
Standard Rx effect	Not quantified	Not quantified	Not quantified	90% (84–96%)	0.36 (0.25–0.53) for stroke and embolism. Not quantified for the endpoint with death included	0.36 (0.25–0.53)		0.36 (0.25–0.53)	0.36 (0.25–0.53)
Non-inferiority margin	ARD = 6.6%	ARD = 7%	ARD = 7.5%	ARD = 31% (PP)	Rate ratio = 2.0	Relative risk = 1.46		Relative risk = 1.46	Relative risk = 1.44
	RR = 1.51	RR = 1.54	RR = 1.23						
% preservation of standard Rx effect	…	…	…	65% of point estimate	…	50% of lower bound of 95% CI of placebo vs. standard		50% of lower bound of 95% CI of placebo vs. standard	50% of lower bound of 95% CI of placebo vs. standard
New Rx vs. standard Rx	ARD = 5.5% (2.8–8.3%)	ARD = 2.0% (−1.6–5.6%)	ARD = −2.6% (−9.3–4.1%)	ARD = 15.4% (4.8–26.1%)	Rate ratio = 0.62 (0.35–1.25)	Relative risk = 0.65 (0.52–0.81)	Relative risk = 0.90 (0.74–1.10)	Hazard ratio = 0.79 (0.66–0.96)	Hazard ratio = 0.79 (0.66–0.95)
	RR = 1.44 (1.15–1.81)	RR = 1.30 (0.81–2.08)	HR = 0.93 (0.71–1.22)	RR = 2.3 (1.2–4.4)					
Non-inferiority met	No	Yes (ARD margin) No (RR margin)	Yes (ARD margin) Yes (RR margin)	Yes (ARD margin)	Yes (RR margin)	Yes (RR margin)	Yes (RR margin)	Yes (RR margin)	Yes (RR margin)
Ancillary advantage	Less invasive, lower stroke	Less invasive, lower stroke	Less invasive	Less invasive, lower bleeding	No lifelong anticoagulation	Lower bleeding, no monitoring		Lower bleeding, no monitoring	Lower bleeding, no monitoring

DES, drug-eluting stent; CABG, coronary artery bypass grafting; TAVR, transcatheter aortic valve replacement; MV, mitral valve; LAA, left atrial appendage; MACCE, major adverse cardiac or cerebrovascular events; ARD, absolute risk difference; RR, relative risk; PP, per-protocol; ITT, intention-to-treat; MR, mitral regurgitation; Rx, treatment.
[a]Estimations based on the rates provided in the papers.

Het kan uiteraard ongehoord lijken in te gaan tegen de kracht van veel gerandomiseerde studies. Ik beweer helemaal niet dat de behandelingen niet werken. Ik wil alleen zeggen dat we wegens die constructie, die begint met Baritt en Jordan (226), geen precies idee hebben over de grootte van het effect van de behandelingen. Wij als clinici kunnen niet met zekerheid zeggen hoeveel patiënten we moeten behandelen om een ongewenst effect bij één van die patiënten te voorkomen.

13.3 De moderne diagnose van longembolie

Laten we even teruggaan naar de basisstudie van Baritt en Jordan (226). De diagnose werd op klinische gronden gesteld. De patiënten hadden een lage bloeddruk en vertoonden een acute rechterhartdecompensatie en hemoptoë met bovendien, volgens de autopsie van de 5 patiënten die overleden zijn op een totaal van 35 patiënten, zeer ernstige andere, al dan niet vooraf bestaande aandoeningen.

Over welke patiënten gaat het nu?

De meest volledige observationele studie werd in 2008 gepubliceerd door Kline et al (237). Bij de 8.138 patiënten die op de spoedafdeling van de deelnemende ziekenhuizen waren opgenomen wegens vermoeden van longembolie, hebben ze met het hele moderne diagnostische arsenaal 500 gevallen van longembolie gediagnosticeerd. De sterfte aan longembolie was 2,6% (13 op de 500 gevallen van bewezen longembolie). Als we ons baseren op het klinische vermoeden zoals in de studie van Baritt en Jordan(226) , bedroeg de sterfte 0,2% (13/8.138). De sterfte is dus 100 keer lager dan in de studie van Baritt en Jordan (226) en dat is waarschijnlijk niet toe te schrijven aan de behandeling.

De prognose is ook veranderd als gevolg van een andere factor: de huidige patiënt.

Met moderne diagnostische technieken zoals een angio-CT-scan verbreden we de diagnose van longembolie en dat deel van het ziektespectrum heeft waarschijnlijk niets meer te maken met de fatale longembolie die optreedt bij patiënten met een ernstige, terminale aandoening. Elke arts is tijdens zijn opleiding onder de indruk geweest van de trombo-embolische complicaties die werden vastgesteld bij autopsie van patiënten die waren overleden in het kader van ernstige aandoeningen. Dat beeld zit in ons geheugen gegrift en daarom denken we dat een longembolie altijd ernstig is. Is dat terecht of niet?

In de PIOPED-studie(238) die werd gepubliceerd in 1990, kwam 30% van de 931 met een ventilatie-perfusiescintigrafie van de spoedafdeling of een ziekenhuisafdeling. 20 patiënten met een angiografisch bewezen longembolie werden niet behandeld. Drie maanden na de diagnose werden die patiënten teruggezien om het natuurlijke verloop te evalueren.

Gezien het kleine aantal patiënten kan uiteraard geen formele conclusie worden getrokken, maar tijdens die follow-upperiode is 1 patiënt (5%) overleden en heeft 1 patiënt een nieuwe niet-fatale longembolie ontwikkeld. Tijdens de follow-up van 4-12 maanden werden geen andere problemen gerapporteerd. Alle niet-behandelde patiënten hadden < 3 ‘mismatched segments’. De angiografie toonde segmentale of subsegmentale trombi bij 16 patiënten (84%) tegen 36% bij de behandelde patiënten.

Dat geeft toch een empirische aanwijzing (die uiteraard gezien het kleine aantal gevallen beperkt is): *"Mild untreated PE carries a lower immediate mortality and lower mortality from recurrent PE than overt PE described in prior decades",* zoals de auteurs concluderen.

Bijzonder markant is de studie van Nielsen et al(231) die werd uitgevoerd bij 90 vrij gezonde patiënten bij wie in eerstelijnsziekenhuizen een diagnose van diepe veneuze trombose werd gesteld met een flebografie en een diagnose van asymptomatische longembolie met een ventilatie-perfusiescintigrafie. 50% van de patiënten vertoonde een asymptomatische longembolie. 48 hebben een klassieke behandeling gekregen en 42 hebben geen anticoagulantia gekregen. De twee groepen waren vergelijkbaar qua leeftijd (57 jaar), geslacht, risicofactoren voor trombose (72% versus 63% in de groep zonder antistollingstherapie). Er was geen verschil in sterfte of de mate van progressie of regressie van de trombus tussen de twee groepen. **De studie werd uitgevoerd bij patiënten die op het ogenblik van de diagnose ambulant en hemodynamisch stabiel waren en weinig comorbiditeit vertoonden en toch vertoonde de helft van de patiënten een asymptomatische longembolie.**

Autopsiestudies (239), cohortonderzoeken (240) en redactionele artikels (241) wijzen erop dat de gunstige effecten van de behandeling bij hemodynamisch stabiele patiënten zonder belangrijke comorbiditeit niet duidelijk zijn en waarschijnlijk zelfs laag of onbestaande zijn.

We staan we door de betere kwaliteit van het diagnostische beleid voor een verbreding van het fenotype van longembolie. We diagnosticeren gevallen van longembolie met een zwakkere pathologische waarde en we hebben ons therapeutische beleid niet aangepast. Als we patiënten behandelen die anders spontaan van hun longembolie zouden kunnen genezen, lopen ze een risico op bloedingen zonder dat daar enig gunstig effect tegenover staat.

Het opsporen van asymptomatische of weinig symptomatische longembolieën bij overigens gezonde mensen is misschien gevaarlijker dan nuttig. De specificiteit van een angio-CT-scan bedraagt immers geen 100%, maar 90-94% (242). Een angio-CT-scan kan dus fout-positieve uitkomsten geven en ook die zullen dan worden behandeld.

Daar komt nog het risico op kanker bij als gevolg van de stralingsdosis bij een angio-CT-scan.

Alleen een gerandomiseerde studie kan daar een antwoord op geven, maar ik denk dat er nooit een dergelijke studie zal worden uitgevoerd (ethiek).

Note :

For more information on calculating non-inferiority margins and applying these to trials on treatment of VTE, see the following reference : (243)

Prins MH, Lensing AW. Derivation of the non-inferiority margin for the evaluation of direct oral anticoagulants in the treatment of venous thromboembolism. Thrombosis journal. 2013;11(1):13.

For information on non-inferiority margins in trials on prevention of VTE, see this reference :(3)

Wangge G, Roes KC, de Boer A, Hoes AW, Knol MJ. The challenges of determining noninferiority margins: a case study of noninferiority randomized controlled trials of novel oral anticoagulants. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(3):222-7.

14 List of excluded publications

Our systematic search in pubmed yielded +/- 1000 articles. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.
The following references were excluded after reading the full article.

- *Adam SS, McDuffie JR, Lachiewicz PF, Ortel TL, Williams JW. Comparative Effectiveness of Newer Oral Anticoagulants and Standard Anticoagulant Regimens for Thromboprophylaxis in Patients Undergoing Total Hip or Knee Replacement. VA Evidence-based Synthesis Program Reports. Washington (DC)2012.*
- *Adam SS, McDuffie JR, Ortel TL, Williams JW, Jr. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. Annals of internal medicine. 2012;157(11):796-807.*
- *Akl EA, Vasireddi SR, Gunukula S, Barba M, Sperati F, Terrenato I, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane database of systematic reviews. 2011(2):CD006649.*
- *Akl EA, Vasireddi SR, Gunukula S, Yosuico VE, Barba M, Sperati F, et al. Anticoagulation for patients with cancer and central venous catheters. Cochrane database of systematic reviews. 2011(4):CD006468.*
- *Albertsen IE, Larsen TB, Rasmussen LH, Overvad TF, Lip GY. Prevention of venous thromboembolism with new oral anticoagulants versus standard pharmacological treatment in acute medically ill patients: a systematic review and meta-analysis. Drugs. 2012;72(13):1755-64.*
- *Alexander M, Kirsa S, Mellor JD. Thalidomide thromboprophylaxis in multiple myeloma: a review of current evidence. Asia-Pacific journal of clinical oncology. 2012;8(4):319-24.*
- *Alhazzani W, Lim W, Jaeschke RZ, Murad MH, Cade J, Cook DJ. Heparin Thromboprophylaxis in Medical-Surgical Critically Ill Patients: A Systematic Review and Meta-Analysis of Randomized Trials. Critical care medicine. 2013.*
- *Alikhan R, Cohen AT. Heparin for the prevention of venous thromboembolism in general medical patients (excluding stroke and myocardial infarction). Cochrane database of systematic reviews. 2009(3):CD003747.*
- *Alves C, Batel-Marques F, Macedo AF. Apixaban and rivaroxaban safety after hip and knee arthroplasty: a meta-analysis. Journal of cardiovascular pharmacology and therapeutics. 2012;17(3):266-76.*
- *Andersen LV, Lip GY, Lindholt JS, Frost L. Upper limb arterial thromboembolism: a systematic review on incidence, risk factors, and prognosis, including a meta-analysis of risk-modifying drugs. Journal of thrombosis and haemostasis : JTH. 2013;11(5):836-44.*
- *Andras A, Sala Tenna A, Crawford F. Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism. Cochrane database of systematic reviews. 2012;10:CD002001.*
- *Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control amongst atrial fibrillation patients on warfarin:The SAMe-TT2R2 (Sex female, Age less than 60, Medical history, Treatment strategy [rhythm control], Tobacco use [doubled], Race [doubled] score. Chest. 2013.*
- *As-Sultany M, Pagkalos J, Yeganeh S, Craigs CL, Korres N, West RM, et al. Use of Oral Direct Factor Xa Inhibiting Anticoagulants in Elective Hip and Knee Arthroplasty: A Meta-analysis of Efficacy and Safety Profiles Compared with those of Low-Molecular-Weight Heparins. Current vascular pharmacology. 2013;11(3):366-75.*
- *Auer R, Scheer A, Wells PS, Boushey R, Asmis T, Jonker D, et al. The use of extended perioperative low molecular weight heparin (tinzaparin) to improve disease-free survival following surgical resection of colon cancer: a pilot randomized controlled trial. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2011;22(8):760-2.*
- *Baldwin MJ, Moore HM, Rudarakanchana N, Gohel M, Davies AH. Post-thrombotic syndrome: a clinical review. Journal of thrombosis and haemostasis : JTH. 2013;11(5):795-805.*
- *Barra SN, Paiva L, Providencia R, Fernandes A, Marques AL. A Review on State-of-the-Art Data Regarding Safe Early Discharge Following Admission for Pulmonary Embolism: What Do We Know? Clinical cardiology. 2013.*

- *Bauersachs RM. Diagnosis and treatment of superficial vein thrombosis. Hamostaseologie. 2013;33(3).*
- *Bergmann JF, Lloret-Linares C, Rami A, Cohen AT, Garay RP, Kakkar AK, et al. [Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): results obtained in France]. Presse medicale (Paris, France : 1983). 2011;40(12 Pt 1):e528-37.*
- *Bergqvist D. Venous thromboembolism after surgery for benign prostatic hyperplasia. World journal of surgery. 2011;35(8):1824-8.*
- *Bottaro FJ, Elizondo MC, Doti C, Bruetman JE, Perez Moreno PD, Bullorsky EO, et al. Efficacy of extended thrombo-prophylaxis in major abdominal surgery: what does the evidence show? A meta-analysis. Thrombosis and haemostasis. 2008;99(6):1104-11.*
- *Botticelli Investigators WC, Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. Journal of thrombosis and haemostasis : JTH. 2008;6(8):1313-8.*
- *Boutitie F, Pinede L, Schulman S, Agnelli G, Raskob G, Julian J, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. Bmj. 2011;342:d3036.*
- *Brotman DJ, Shihab HM, Prakasa KR, Kebede S, Haut ER, Sharma R, et al. Pharmacologic and Mechanical Strategies for Preventing Venous Thromboembolism After Bariatric Surgery: A Systematic Review and Meta-analysis. JAMA surgery. 2013:1-12.*
- *Bump GM, Dandu M, Kaufman SR, Shojania KG, Flanders SA. How complete is the evidence for thromboembolism prophylaxis in general medicine patients? A meta-analysis of randomized controlled trials. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2009;4(5):289-97.*
- *Canadian Agency for D, Technologies in H. Dabigatran or rivaroxaban versus other anticoagulants for thromboprophylaxis after major orthopedic surgery: systematic review of comparative clinical-effectiveness and safety. CADTH technology overviews. 2010;1(2):e0111.*
- *Cao YB, Zhang JD, Shen H, Jiang YY. Rivaroxaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. European journal of clinical pharmacology. 2010;66(11):1099-108.*
- *Chalayer E, Augeul-Meunier K, Tardy-Poncet B, Cathebras P, Guyotat D, Tardy B. [Newly diagnosed multiple myeloma: Do we need to propose thromboprophylaxis?]. La Revue de medecine interne / fondee par la Societe nationale francaise de medecine interne. 2012;33(12):693-6.*
- *Che DH, Cao JY, Shang LH, Man YC, Yu Y. The efficacy and safety of low-molecular-weight heparin use for cancer treatment: A meta-analysis. European journal of internal medicine. 2013.*
- *Chen HL, Wang XD. Heparin for venous thromboembolism prophylaxis in patients with acute spinal cord injury: a systematic review and meta-analysis. Spinal cord. 2013.*
- *Cho KY, Kim KI, Khurana S, Bae DK, Jin W. Is routine chemoprophylaxis necessary for prevention of venous thromboembolism following knee arthroplasty in a low incidence population? Archives of orthopaedic and trauma surgery. 2013;133(4):551-9.*
- *Choi M, Hector M. Management of venous thromboembolism for older adults in long-term care facilities. Journal of the American Academy of Nurse Practitioners. 2012;24(6):335-44.*
- *Cohen A, Drost P, Marchant N, Mitchell S, Orme M, Rublee D, et al. The efficacy and safety of pharmacological prophylaxis of venous thromboembolism following elective knee or hip replacement: systematic review and network meta-analysis. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2012;18(6):611-27.*
- *Cohen JM, Akl EA, Kahn SR. Pharmacologic and compression therapies for postthrombotic syndrome: a systematic review of randomized controlled trials. Chest. 2012;141(2):308-20.*
- *Cohen T, Boyd RA, Mandema J, Dicarlo L, Pak R. An Adaptive-design Dose-ranging Study of PD 0348292, an Oral Factor Xa Inhibitor, for Thromboprophylaxis After Total Knee Replacement Surgery. Journal of thrombosis and haemostasis : JTH. 2013.*
- *Colwell CW, Hardwick ME. Thromboprophylaxis in elderly patients undergoing major orthopaedic surgery. Drugs & aging. 2008;25(7):551-8.*
- *Comerota AJ. The ATTRACT trial: rationale for early intervention for iliofemoral DVT. Perspectives in vascular surgery and endovascular therapy. 2009;21(4):221-4; quiz 4-5.*
- *Cundiff DK, Manyemba J, Pezzullo JC. Anticoagulants versus non-steroidal anti-inflammatories or placebo for treatment of venous thromboembolism. Cochrane database of systematic reviews. 2006(1):CD003746.*

- *Dager WE. Warfarin for venous thromboembolism prophylaxis after elective hip or knee arthroplasty: exploring the evidence, guidelines, and challenges remaining. The Annals of pharmacotherapy. 2012;46(1):79-88.*
- *Dahl OE, Kurth AA, Rosencher N, Noack H, Clemens A, Eriksson BI. Thromboprophylaxis in patients older than 75 years or with moderate renal impairment undergoing knee or hip replacement surgery [corrected]. International orthopaedics. 2012;36(4):741-8.*
- *De Martino RR, Wallaert JB, Rossi AP, Zbehlik AJ, Suckow B, Walsh DB. A meta-analysis of anticoagulation for calf deep venous thrombosis. Journal of vascular surgery. 2012;56(1):228-37 e1; discussion 36-7.*
- *Douketis J. ACP journal club. Rivaroxaban was noninferior to enoxaparin for preventing short-term recurrent VTE and superior to placebo in continued treatment. Annals of internal medicine. 2011;154(10):JC5-06, JC5-7.*
- *Eriksson BI, Rosencher N, Friedman RJ, Homering M, Dahl OE. Concomitant use of medication with antiplatelet effects in patients receiving either rivaroxaban or enoxaparin after total hip or knee arthroplasty. Thrombosis research. 2012;130(2):147-51.*
- *Ettema HB, Kollen BJ, Verheyen CC, Buller HR. Prevention of venous thromboembolism in patients with immobilization of the lower extremities: a meta-analysis of randomized controlled trials. Journal of thrombosis and haemostasis : JTH. 2008;6(7):1093-8.*
- *Flierl U, Fraccarollo D, Micka J, Bauersachs J, Schafer A. The direct factor Xa inhibitor Rivaroxaban reduces platelet activation in congestive heart failure. Pharmacological research : the official journal of the Italian Pharmacological Society. 2013;74c:49-55.*
- *Friedman RJ, Dahl OE, Rosencher N, Caprini JA, Kurth AA, Francis CW, et al. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. Thrombosis research. 2010;126(3):175-82.*
- *Garcia D, Akl EA, Carr R, Kearon C. Antiphospholipid antibodies and the risk of recurrence after a first episode of venous thromboembolism: a systematic review. Blood. 2013.*
- *Geeganage CM, Sprigg N, Bath MW, Bath PM. Balance of Symptomatic Pulmonary Embolism and Symptomatic Intracerebral Hemorrhage with Low-dose Anticoagulation in Recent Ischemic Stroke: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2012.*
- *Ginsberg JS, Hirsh J, Julian J, Vander LaandeVries M, Magier D, MacKinnon B, et al. Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Archives of internal medicine. 2001;161(17):2105-9.*
- *Gonzalez-Fajardo JA, Martin-Pedrosa M, Castrodeza J, Tamames S, Vaquero-Puerta C. Effect of the anticoagulant therapy in the incidence of post-thrombotic syndrome and recurrent thromboembolism: Comparative study of enoxaparin versus coumarin. Journal of vascular surgery. 2008;48(4):953-9.*
- *Grimm SA, Pfiffner TJ. Anaplastic astrocytoma. Current treatment options in neurology. 2013;15(3):302-15.*
- *Haines DE, Mead-Salley M, Salazar M, Marchlinski FE, Zado E, Calkins H, et al. Dabigatran versus warfarin anticoagulation before and after catheter ablation for the treatment of atrial fibrillation. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing. 2013.*
- *Handoll HH, Farrar MJ, McBirnie J, Tytherleigh-Strong G, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. Cochrane database of systematic reviews. 2002(4):CD000305.*
- *Holmes M, Carroll C, Papaioannou D. Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip or knee surgery: a NICE single technology appraisal. PharmacoEconomics. 2012;30(2):137-46.*
- *Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET. New Oral Anticoagulants Increase Risk for Gastrointestinal Bleeding: A Systematic Review and Meta-analysis. Gastroenterology. 2013.*
- *Huang J, Cao Y, Liao C, Wu L, Gao F. Apixaban versus enoxaparin in patients with total knee arthroplasty. A meta-analysis of randomised trials. Thrombosis and haemostasis. 2011;105(2):245-53.*
- *Hull RD, Liang J, Townshend G. Long-term low-molecular-weight heparin and the post-thrombotic syndrome: a systematic review. The American journal of medicine. 2011;124(8):756-65.*
- *Hull RD, Pineo GF, Brant R, Liang J, Cook R, Solymoss S, et al. Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome. The American journal of medicine. 2009;122(8):762-9.e3.*
- *Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. The American journal of medicine. 2007;120(1):72-82.*

- *Huo MH, Muntz J. Extended thromboprophylaxis with low-molecular-weight heparins after hospital discharge in high-risk surgical and medical patients: a review. Clinical therapeutics. 2009;31(6):1129-41.*
- *Hutten BA, Prins MH. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. Cochrane database of systematic reviews. 2006(1):CD001367.*
- *Januel JM, Chen G, Ruffieux C, Quan H, Douketis JD, Crowther MA, et al. Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: a systematic review. JAMA : the journal of the American Medical Association. 2012;307(3):294-303.*
- *Jorgensen M, Nielsen JD. The low-molecular-weight-heparin, tinzaparin, is effective and safe in the treatment and prophylaxis of venous thromboembolic disease during pregnancy. Blood. 2004;104(11):492a-a.*
- *Jubelirer SJ, Reyes B, Broce M, Elhabyan AK, Mimnagh K, Rosencrance JG, et al. Pharmacological thromboembolic prophylaxis for medical patients in a tertiary care, teaching community hospital: room for improvement. The West Virginia medical journal. 2008;104(1):10-4.*
- *Kachroo S, Boyd D, Bookhart BK, LaMori J, Schein JR, Rosenberg DJ, et al. Quality of life and economic costs associated with postthrombotic syndrome. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2012;69(7):567-72.*
- *Kahn SR, Shbaklo H, Shapiro S, Wells PS, Kovacs MJ, Rodger MA, et al. Effectiveness of compression stockings to prevent the post-thrombotic syndrome (the SOX Trial and Bio-SOX biomarker substudy): a randomized controlled trial. BMC cardiovascular disorders. 2007;7:21.*
- *Kakkos SK, Warwick D, Nicolaides AN, Stansby GP, Tsolakis IA. Combined (mechanical and pharmacological) modalities for the prevention of venous thromboembolism in joint replacement surgery. The Journal of bone and joint surgery British volume. 2012;94(6):729-34.*
- *Kalyani BS, Roberts CS. Low molecular weight heparin: current evidence for its application in orthopaedic surgery. Current vascular pharmacology. 2011;9(1):19-23.*
- *Kanaan AO, Lepage JE, Djazayeri S, Donovan JL. Evaluating the Role of Compression Stockings in Preventing Post thrombotic Syndrome: A Review of the Literature. Thrombosis. 2012;2012:694851.*
- *Kolbach DN, Sandbrink MW, Hamulyak K, Neumann HA, Prins MH. Non-pharmaceutical measures for prevention of post-thrombotic syndrome. Cochrane database of systematic reviews. 2004(1):CD004174.*
- *Kolbach DN, Sandbrink MW, Neumann HA, Prins MH. Compression therapy for treating stage I and II (Widmer) post-thrombotic syndrome. Cochrane database of systematic reviews. 2003(4):CD004177.*
- *Konstantinides S, Lankeit M. Pulmonary embolism hotline 2012. Recent and expected trials. Hamostaseologie. 2013;33(1):43-50.*
- *Koracevic GP. Optimal initial anticoagulant therapy in pulmonary thromboembolism: randomized trial suggested. The American journal of emergency medicine. 2013;31(2):407-9.*
- *Kulshrestha V, Kumar S. DVT Prophylaxis After TKA: Routine Anticoagulation Vs Risk Screening Approach - A Randomized Study. The Journal of arthroplasty. 2013.*
- *Kwok CS, Pradhan S, Yeong JK, Loke YK. Relative effects of two different enoxaparin regimens as comparators against newer oral anticoagulants: meta-analysis and adjusted indirect comparison. Chest. 2013.*
- *Lam S. Apixaban: a new factor xa inhibitor for stroke prevention in patients with nonvalvular atrial fibrillation. Cardiology in review. 2013;21(4):207-12.*
- *Lankeit M, Konstantinides S. Is it time for home treatment of pulmonary embolism? The European respiratory journal. 2012;40(3):742-9.*
- *Laporte S, Bertoletti L, Romera A, Mismetti P, Perez de Llano LA, Meyer G. Long-term treatment of venous thromboembolism with tinzaparin compared to vitamin K antagonists: a meta-analysis of 5 randomized trials in non-cancer and cancer patients. Thrombosis research. 2012;130(6):853-8.*
- *Lassen MR, Gent M, Kakkar AK, Eriksson BI, Homering M, Berkowitz SD, et al. The effects of rivaroxaban on the complications of surgery after total hip or knee replacement: results from the RECORD programme. The Journal of bone and joint surgery British volume. 2012;94(11):1573-8.*
- *Lavau-Denes S, Lacroix P, Maubon A, Preux PM, Genet D, Venat-Bouvet L, et al. Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study. Cancer chemotherapy and pharmacology. 2013;72(1):65-73.*
- *Lee AY, Bauersachs R, Janas MS, Jarner MF, Kamphuisen PW, Meyer G, et al. CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients. BMC cancer. 2013;13(1):284.*

- *Leighl NB, Bennouna J, Yi J, Moore N, Hambleton J, Hurwitz H. Bleeding events in bevacizumab-treated cancer patients who received full-dose anticoagulation and remained on study. British journal of cancer. 2011;104(3):413-8.*
- *Levine MN, Gu C, Liebman HA, Escalante CP, Solymoss S, Deitchman D, et al. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. Journal of thrombosis and haemostasis : JTH. 2012;10(5):807-14.*
- *Li XM, Sun SG, Zhang WD. Apixaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. Chinese medical journal. 2012;125(13):2339-45.*
- *Liem TK, Deloughery TG. Randomised controlled trial: extended-duration dabigatran is non-inferior to warfarin and more effective than placebo for symptomatic VTE. Evidence-based medicine. 2013.*
- *Lindhoff-Last E, Ansell J, Spiro T, Samama MM. Laboratory testing of rivaroxaban in routine clinical practice: When, how, and which assays. Annals of medicine. 2013.*
- *Lloyd NS, Douketis JD, Moinuddin I, Lim W, Crowther MA. Anticoagulant prophylaxis to prevent asymptomatic deep vein thrombosis in hospitalized medical patients: a systematic review and meta-analysis. Journal of thrombosis and haemostasis : JTH. 2008;6(3):405-14.*
- *Loomba RS, Arora RR, Chandrasekar S, Shah PH. Thigh-length versus knee-length compression stockings for deep vein thrombosis prophylaxis in the inpatient setting. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2012;23(2):168-71.*
- *Louzada ML, Majeed H, Wells PS. Efficacy of low- molecular- weight- heparin versus vitamin K antagonists for long term treatment of cancer-associated venous thromboembolism in adults: a systematic review of randomized controlled trials. Thrombosis research. 2009;123(6):837-44.*
- *Luba M, Firek A, Kochanowski Z. [Two models of thromboprophylaxis in acutely ill medical inpatients]. Polskie Archiwum Medycyny Wewnetrznej. 2007;117(4):31-7.*
- *Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(17):2189-204.*
- *Maraveyas A, Waters J, Roy R, Fyfe D, Propper D, Lofts F, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. European journal of cancer. 2012;48(9):1283-92.*
- *Masuda EM, Kistner RL, Musikasinthorn C, Liquido F, Geling O, He Q. The controversy of managing calf vein thrombosis. Journal of vascular surgery. 2012;55(2):550-61.*
- *McLean S, Ryan K, O'Donnell JS. Primary thromboprophylaxis in the palliative care setting: a qualitative systematic review. Palliative medicine. 2010;24(4):386-95.*
- *McManus RJ, Fitzmaurice DA, Murray E, Taylor C. Thromboembolism. Clinical evidence. 2011;2011.*
- *Musani MH, Matta F, Yaekoub AY, Liang J, Hull RD, Stein PD. Venous compression for prevention of postthrombotic syndrome: a meta-analysis. The American journal of medicine. 2010;123(8):735-40.*
- *Neumann I, Rada G, Claro JC, Carrasco-Labra A, Thorlund K, Akl EA, et al. Oral direct Factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis. Annals of internal medicine. 2012;156(10):710-9.*
- *Nieto JA, Espada NG, Merino RG, Gonzalez TC. Dabigatran, rivaroxaban and apixaban versus enoxaparin for thromboprophylaxis after total knee or hip arthroplasty: pool-analysis of phase III randomized clinical trials. Thrombosis research. 2012;130(2):183-91.*
- *Nitzki-George D, Wozniak I, Caprini JA. Current state of knowledge on oral anticoagulant reversal using procoagulant factors. The Annals of pharmacotherapy. 2013;47(6):841-55.*
- *Nunn KP, Bridgett MR, Walters MR, Walker I. All I want for coagulation. Scottish medical journal. 2011;56(4):183-7.*
- *Ojike NI, Bhadra AK, Giannoudis PV, Roberts CS. Venous thromboembolism in shoulder surgery: a systematic review. Acta orthopaedica Belgica. 2011;77(3):281-9.*
- *Orken DN, Kenangil G, Ozkurt H, Guner C, Gundogdu L, Basak M, et al. Prevention of deep venous thrombosis and pulmonary embolism in patients with acute intracerebral hemorrhage. The neurologist. 2009;15(6):329-31.*
- *Paciaroni M, Agnelli G, Venti M, Alberti A, Acciarresi M, Caso V. Efficacy and safety of anticoagulants in the prevention of venous thromboembolism in patients with acute cerebral hemorrhage: a meta-analysis of controlled studies. Journal of thrombosis and haemostasis : JTH. 2011;9(5):893-8.*

- *Pebanco GD, Kaiser SA, Haines ST. New pharmacologic methods to prevent venous thromboembolism in older adults: a meta-analysis. The Annals of pharmacotherapy. 2013;47(5):605-16.*
- *Pengas I, Nash W, Reed N, Kumar S. Evidence for treatment of muscular vein thrombosis in orthopaedic patients. Journal of orthopaedics and traumatology : official journal of the Italian Society of Orthopaedics and Traumatology. 2013.*
- *Perez A, Eraso LH, Merli GJ. Implications of new anticoagulants in primary practice. International journal of clinical practice. 2013;67(2):139-56.*
- *Perry JR, Julian JA, Laperriere NJ, Geerts W, Agnelli G, Rogers LR, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. Journal of thrombosis and haemostasis : JTH. 2010;8(9):1959-65.*
- *Pineo GF, Gallus AS, Raskob GE, Chen D, Ramirez LM, Ramacciotti E, et al. Apixaban after hip or knee arthroplasty versus enoxaparin: efficacy and safety in key clinical subgroups. Journal of thrombosis and haemostasis : JTH. 2013;11(3):444-51.*
- *Pinero-Saavedra M, Castano MP, Camarero MO, Milla SL. DRESS syndrome induced by acenocoumarol with tolerance to warfarin and dabigatran: a case report. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2013;24(5):576-8.*
- *Pop TR, Vesa SC, Trifa AP, Crisan S, Buzoianu AD. An acenocoumarol dose algorithm based on a South-Eastern European population. European journal of clinical pharmacology. 2013.*
- *Poultsides LA, Gonzalez Della Valle A, Memtsoudis SG, Ma Y, Roberts T, Sharrock N, et al. Meta-analysis of cause of death following total joint replacement using different thromboprophylaxis regimens. The Journal of bone and joint surgery British volume. 2012;94(1):113-21.*
- *Qayyum F, Holbrook A, Lam J, Kovacs MJ, Schulman S. Should vitamin K antagonist therapy be started simultaneously with parenteral anticoagulation: a meta-analysis? Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2012;23(8):705-13.*
- *Rahn DD, Mamik MM, Sanses TV, Matteson KA, Aschkenazi SO, Washington BB, et al. Venous thromboembolism prophylaxis in gynecologic surgery: a systematic review. Obstetrics and gynecology. 2011;118(5):1111-25.*
- *Rajasekhar A, Beyth R, Crowther MA. Newer anticoagulants in critically ill patients. Critical care clinics. 2012;28(3):427-51, vii.*
- *Raskob GE, Gallus AS, Pineo GF, Chen D, Ramirez LM, Wright RT, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip or knee replacement: pooled analysis of major venous thromboembolism and bleeding in 8464 patients from the ADVANCE-2 and ADVANCE-3 trials. The Journal of bone and joint surgery British volume. 2012;94(2):257-64.*
- *Roberts C. Towards evidence-based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 4: thromboprophylaxis reduces venous thromboembolism rate in ambulatory patients immobilised in above-knee plaster cast. Emergency medicine journal : EMJ. 2012;29(5):425-6.*
- *Roberts C. Towards evidence-based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 3: thromboprophylaxis significantly reduces venous thromboembolism rate in ambulatory patients immobilised in below-knee plaster cast. Emergency medicine journal : EMJ. 2012;29(5):424-5.*
- *Romualdi E, Donadini MP, Ageno W. Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-extension study). Expert review of cardiovascular therapy. 2011;9(7):841-4.*
- *Rondelli F, Manina G, Agnelli G, Becattini C. Venous thromboembolism after laparoscopic cholecystectomy: clinical burden and prevention. Surgical endoscopy. 2013;27(6):1860-4.*
- *Rosencher N, Noack H, Feuring M, Clemens A, Friedman RJ, Eriksson BI. Type of anaesthesia and the safety and efficacy of thromboprophylaxis with enoxaparin or dabigatran etexilate in major orthopaedic surgery: pooled analysis of three randomized controlled trials. Thrombosis journal. 2012;10(1):9.*
- *Salazar CA, Malaga G, Malasquez G. Direct thrombin inhibitors versus vitamin K antagonists or low molecular weight heparins for prevention of venous thromboembolism following total hip or knee replacement. Cochrane database of systematic reviews. 2010(4):CD005981.*
- *Salmaggi A, Simonetti G, Trevisan E, Beecher D, Carapella CM, Dimeco F, et al. Perioperative thromboprophylaxis in patients with craniotomy for brain tumours: a systematic review. Journal of neuro-oncology. 2013;113(2):293-303.*
- *Saunders JH, Arya PH, Abisi S, Yong YP, Macsweeney S, Braithwaite B, et al. Catheter-directed thrombolysis for iliofemoral deep vein thrombosis. The British journal of surgery. 2013;100(8):1025-9.*

- *Schade VL, Roukis TS. Antithrombotic pharmacologic prophylaxis use during conservative and surgical management of foot and ankle disorders: a systematic review. Clinics in podiatric medicine and surgery. 2011;28(3):571-88.*
- *Shariff N, Aleem A, Levin V, Desai RV, Nanda S, Martinez MW, et al. Venous thromboembolism in patients with heart failure: in-hospital and chronic use of anti-coagulants for prevention. Recent patents on cardiovascular drug discovery. 2012;7(1):53-8.*
- *Sheth NP, Lieberman JR, Della Valle CJ. DVT prophylaxis in total joint reconstruction. The Orthopedic clinics of North America. 2010;41(2):273-80.*
- *Sjalander A, Jansson JH, Bergqvist D, Eriksson H, Carlberg B, Svensson P. Efficacy and safety of anticoagulant prophylaxis to prevent venous thromboembolism in acutely ill medical inpatients: a meta-analysis. Journal of internal medicine. 2008;263(1):52-60.*
- *Slobogean GP, Lefaivre KA, Nicolaou S, O'Brien PJ. A systematic review of thromboprophylaxis for pelvic and acetabular fractures. Journal of orthopaedic trauma. 2009;23(5):379-84.*
- *Sobieraj DM, Coleman CI, Tongbram V, Chen W, Colby J, Lee S, et al. Comparative effectiveness of low-molecular-weight heparins versus other anticoagulants in major orthopedic surgery: a systematic review and meta-analysis. Pharmacotherapy. 2012;32(9):799-808.*
- *Sobieraj DM, Coleman CI, Tongbram V, Lee S, Colby J, Chen WT, et al. Venous Thromboembolism Prophylaxis in Orthopedic Surgery. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2012.*
- *Spyropoulos AC, Turpie AG. Venous thromboembolism management: where do novel anticoagulants fit? Current medical research and opinion. 2013;29(7):783-90.*
- *Stark JE, Smith WJ. Standard or extended-duration prophylaxis in medical patients? A review of the evidence. Journal of thrombosis and thrombolysis. 2011;32(3):318-27.*
- *Stevenson M, Scope A, Holmes M, Rees A, Kaltenthaler E. Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal. Health technology assessment. 2009;13 Suppl 3:43-8.*
- *Suri RM, Thourani VH, He X, Brennan JM, O'Brien SM, Rankin JS, et al. Variation in warfarin thromboprophylaxis after mitral valve repair: does equipoise exist and is a randomized trial warranted? The Annals of thoracic surgery. 2013;95(6):1991-9.*
- *Tasker A, Harbord R, Bannister GC. Meta-analysis of low molecular weight heparin versus placebo in patients undergoing total hip replacement and post-operative morbidity and mortality since their introduction. Hip international : the journal of clinical and experimental research on hip pathology and therapy. 2010;20(1):64-74.*
- *Ten Cate-Hoek AJ, Ten Cate H, Tordoir J, Hamulyak K, Prins MH. Individually tailored duration of elastic compression therapy in relation to incidence of the postthrombotic syndrome. Journal of vascular surgery. 2010;52(1):132-8.*
- *Testroote M, Stigter W, de Visser DC, Janzing H. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-leg immobilization. Cochrane database of systematic reviews. 2008(4):CD006681.*
- *Turpie AG, Hull RD, Schellong SM, Tapson VF, Monreal M, Samama MM, et al. Venous thromboembolism risk in ischemic stroke patients receiving extended-duration enoxaparin prophylaxis: results from the EXCLAIM study. Stroke; a journal of cerebral circulation. 2013;44(1):249-51.*
- *van Doormaal FF, Di Nisio M, Otten HM, Richel DJ, Prins M, Buller HR. Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(15):2071-6.*
- *Vardi M, Haran M. Venous thromboembolism prophylaxis of acutely ill hospitalized medical patients. Are we over-treating our patients? European journal of internal medicine. 2012;23(3):231-5.*
- *Warkentin TE, Sheppard JA, Heels-Ansdell D, Marshall JC, McIntyre L, Rocha MG, et al. Heparin-induced thrombocytopenia in medical surgical critical illness. Chest. 2013.*
- *Wasserlauf G, Grandi SM, Filion KB, Eisenberg MJ. Meta-Analysis of Rivaroxaban and Bleeding Risk. The American journal of cardiology. 2013.*
- *Watson HG, Baglin TP. Guidelines on travel-related venous thrombosis. British journal of haematology. 2011;152(1):31-4.*
- *Wells PS, Anderson DR, Rodger MA, Forgie MA, Florack P, Touchie D, et al. A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. Archives of internal medicine. 2005;165(7):733-8.*
- *Whiteley WN, Adams HP, Jr., Bath PM, Berge E, Sandset PM, Dennis M, et al. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an*

individual patient data meta-analysis of randomised controlled trials. Lancet neurology. 2013;12(6):539-45.

- *Williamson DR, Albert M, Heels-Ansdell D, Arnold DM, Lauzier F, Zarychanski R, et al. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. Chest. 2013.*
- *Wu JJ, Yang L. [Analysis of hospitalization costs for 278 venous thromboeboembolism patients with health insurance in China]. Beijing da xue xue bao Yi xue ban = Journal of Peking University Health sciences. 2013;45(3):437-42.*
- *Wu JP, Sun X, Wu Q, Du ZZ, Li L, Wu Q, et al. Effect of low-molecular-weight heparin and urokinase on pulmonary arteries involved in pulmonary embolism. Chinese medical journal. 2013;126(12):2254-9.*
- *Yokote R, Matsubara M, Hirasawa N, Hagio S, Ishii K, Takata C. Is routine chemical thromboprophylaxis after total hip replacement really necessary in a Japanese population? The Journal of bone and joint surgery British volume. 2011;93(2):251-6.*
- *Yoshida Rde A, Yoshida WB, Maffei FH, El Dib R, Nunes R, Rollo HA. Systematic review of randomized controlled trials of new anticoagulants for venous thromboembolism prophylaxis in major orthopedic surgeries, compared with enoxaparin. Annals of vascular surgery. 2013;27(3):355-69.*
- *Zhang J, Zhang YL, Ma KX, Qu JM. Efficacy and safety of adjunctive anticoagulation in patients with lung cancer without indication for anticoagulants: a systematic review and meta-analysis. Thorax. 2013;68(5):442-50.*

15 References

1. Chevalier P. Non-inferioriteitsstudies: het nut, de beperkingen en de valkuilen. Minerva. 2009;8(6):88.
2. Chevalier P. Non-inferioriteitsstudies: de keuze van de non-inferioriteitsmarges. Minerva. 2013;12(5):64.
3. Wangge G, Roes KC, de Boer A, Hoes AW, Knol MJ. The challenges of determining noninferiority margins: a case study of noninferiority randomized controlled trials of novel oral anticoagulants. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(3):222-7.
4. Einstein Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, et al. Oral rivaroxaban for symptomatic venous thromboembolism. The New England journal of medicine. 2010;363(26):2499-510.
5. Einstein-Pe Investigators, Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. The New England journal of medicine. 2012;366(14):1287-97.
6. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. New England Journal of Medicine. 2013;369(9):799-808.
7. Schwarz T, Buschmann L. Therapy of isolated calf muscle vein thrombosis. A prospective study. Journal of vascular surgery. 2010;52:1246-50.
8. National Clinical Guideline Centre. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. Clinical Guideline. Methods, evidence and recommendations.
2012;http://www.nice.org.uk/nicemedia/live/13767/59711/59711.pdf
9. Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. Thrombosis and haemostasis. 2003;89(6):953-8.
10. Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, Sfiridis P, Nikolaou A, Dimitroulis D, et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2005;29(6):638-50.
11. Gonzalez-Fajardo JA, Arreba E, Castrodeza J, Perez JL, Fernandez L, Agundez I, et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. Journal of vascular surgery. 1999;30(2):283-92.
12. Gonzalez-Fajardo JA, Martin-Pedrosa M, Castrodeza J, Tamames S, Vaquero-Puerta C. Effect of the anticoagulant therapy in the incidence of post-thrombotic syndrome and recurrent thromboembolism: Comparative study of enoxaparin versus coumarin. Journal of vascular surgery. 2008;48(4):953-9.
13. Hamann H. Prevention of recurrence after deep vein thrombosis - Oral anticoagulation or subcutaneous low molecular weight heparin? . Vasomed. 1998;10(3):133-6.
14. Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. World journal of surgery. 1996;20(5):521-6; discussion 6-7.
15. Lopaciuk S, Bielska-Falda H, Noszczyk W, Bielawiec M, Witkiewicz W, Filipecki S, et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. Thrombosis and haemostasis. 1999;81(1):26-31.

16. Lopez-Beret P, Orgaz A, Fontcuberta J, Doblas M, Martinez A, Lozano G, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. Journal of vascular surgery. 2001;33(1):77-90.
17. Pini M, Aiello S, Manotti C, Pattacini C, Quintavalla R, Poli T, et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. Thrombosis and haemostasis. 1994;72(2):191-7.
18. Veiga F, Escriba A, Maluenda MP, Lopez Rubio M, Margalet I, Lezana A, et al. Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. Thrombosis and haemostasis. 2000;84(4):559-64.
19. Cesarone M. Three-month, outpatient, oral anticoagulant treatment in comparison with low-molecular-weight heparin in cancer patients. Circulation. 2003;108(17 suppl):2875.
20. Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J, et al. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2006;12(4):389-96.
21. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. The American journal of medicine. 2006;119(12):1062-72.
22. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. The New England journal of medicine. 2003;349(2):146-53.
23. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Archives of internal medicine. 2002;162(15):1729-35.
24. Perez-de-Llano LA, Leiro-Fernandez V, Golpe R, Nunez-Delgado JM, Palacios-Bartolome A, Mendez-Marote L, et al. Comparison of tinzaparin and acenocoumarol for the secondary prevention of venous thromboembolism: a multicentre, randomized study. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2010;21(8):744-9.
25. Romera A, Cairols MA, Vila-Coll R, Marti X, Colome E, Bonell A, et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2009;37(3):349-56.
26. Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials. Bmj. 2012;345:e7498.
27. Schulman S, Kakkar AK, Schellong SM, Goldhaber SZ, Henry E, Mismetti P, et al. A Randomized Trial of Dabigatran Versus Warfarin in the Treatment of Acute Venous Thromboembolism (RE-COVER II). Blood. 2011;118(21):95-6.
28. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. The New England journal of medicine. 2009;361(24):2342-52.
29. Akl EA, Labedi N, Barba M, Terrenato I, Sperati F, Muti P, et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. Cochrane database of systematic reviews. 2011(6):CD006650. DOI: 10.1002/14651858.CD006650.pub3.
30. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. The New England journal of medicine. 2013;368(8):709-18.

31. Campbell IA, Bentley DP, Prescott RJ, Routledge PA, Shetty HG, Williamson IJ. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. Bmj. 2007;334(7595):674.
32. Schulman S, Lockner D, Juhlin-Dannfelt A. The duration of oral anticoagulation after deep vein thrombosis. A randomized study. Acta medica Scandinavica. 1985;217(5):547-52.
33. Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Annals of internal medicine. 2003;139(1):19-25.
34. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. The New England journal of medicine. 2001;345(3):165-9.
35. Eischer L, Gartner V, Schulman S, Kyrle PA, Eichinger S, investigators A-F. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Annals of hematology. 2009;88(5):485-90.
36. Farraj RS. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? Saudi medical journal. 2004;25(7):848-51.
37. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. The New England journal of medicine. 1999;340(12):901-7.
38. Schulman S, Granqvist S, Holmstrom M, Carlsson A, Lindmarker P, Nicol P, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. The New England journal of medicine. 1997;336(6):393-8.
39. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for extended treatment of venous thromboembolism. The New England journal of medicine. 2013;368(8):699-708.
40. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. The New England journal of medicine. 2012;367(21):1979-87.
41. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, et al. Aspirin for preventing the recurrence of venous thromboembolism. The New England journal of medicine. 2012;366(21):1959-67.
42. Othieno R, Abu Affan M, Okpo E. Home versus in-patient treatment for deep vein thrombosis. Cochrane database of systematic reviews. 2007(3):Cd003076. DOI: 10.1002/14651858.CD003076.pub2.
43. Boccalon H, Elias A, Chale JJ, Cadene A, Gabriel S. Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin: the Vascular Midi-Pyrenees study. Archives of internal medicine. 2000;160(12):1769-73.
44. Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH, Group ADS. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. Journal of thrombosis and thrombolysis. 2005;19(3):173-81.
45. Koopman MM, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, van der Meer J, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. The New England journal of medicine. 1996;334(11):682-7.
46. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. The New England journal of medicine. 1996;334(11):677-81.
47. Ramacciotti E, Araujo GR, Lastoria S, Maffei FH, Karaoglan de Moura L, Michaelis W, et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. Thrombosis research. 2004;114(3):149-53.

48. Otero R, Uresandi F, Jimenez D, Cabezudo MA, Oribe M, Nauffal D, et al. Home treatment in pulmonary embolism. Thrombosis research. 2010;126(1):e1-5.
49. Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet. 2011;378(9785):41-8.
50. Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet. 1997;349(9054):759-62.
51. Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Annals of internal medicine. 2004;141(4):249-56.
52. Aschwanden M, Jeanneret C, Koller MT, Thalhammer C, Bucher HC, Jaeger KA. Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. Journal of vascular surgery. 2008;47(5):1015-21.
53. Prandoni P, Noventa F, Quintavalla R, Bova C, Cosmi B, Siragusa S, et al. Thigh-length versus below-knee compression elastic stockings for prevention of the postthrombotic syndrome in patients with proximal-venous thrombosis: a randomized trial. Blood. 2012;119(6):1561-5.
54. National Clinical Guideline Centre Acute and Chronic Conditions Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. Methods, evidence and guidance. 2010;http://www.nice.org.uk/nicemedia/live/12695/47920/47920.pdf
55. Dechavanne M, Ville D, Viala JJ, Kher A, Faivre J, Pousset MB, et al. Controlled trial of platelet anti-aggregating agents and subcutaneous heparin in prevention of postoperative deep vein thrombosis in high risk patients. Haemostasis. 1975;4(2):94-100.
56. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. The New England journal of medicine. 1988;318(18):1162-73.
57. Bergqvist D, Efsing HO, Hallbook T, Hedlund T. Thromboembolism after elective and post-traumatic hip surgery--a controlled prophylactic trial with dextran 70 and low-dose heparin. Acta chirurgica Scandinavica. 1979;145(4):213-8.
58. Dechavanne M, Saudin F, Viala JJ, Kher A, Bertrix L, de Mourgues G. [Prevention of venous thrombosis. Success of high doses of heparin during total hip replacement for osteoarthritis]. La Nouvelle presse medicale. 1974;3(20):1317-9.
59. Gallus AS, Hirsh J, Tutle RJ, Trebilcock R, O'Brien SE, Carroll JJ, et al. Small subcutaneous doses of heparin in prevention of venous thrombosis. The New England journal of medicine. 1973;288(11):545-51.
60. Hampson WG, Harris FC, Lucas HK, Roberts PH, McCall IW, Jackson PC, et al. Failure of low-dose heparin to prevent deep-vein thrombosis after hip-replacement arthroplasty. Lancet. 1974;2(7884):795-7.
61. Lowe LW. Venous thrombosis and embolism. The Journal of bone and joint surgery British volume. 1981;63-B(2):155-67.
62. Venous thrombosis clinical study group. Small doses of subcutaneous sodium heparin in the prevention of deep vein thrombosis after elective hip operations. The British journal of surgery. 1975;62(5):348-50.
63. Welin-Berger T, Bygdeman S, Mebius C. Deep vein thrombosis following hip surgery. Relation to activated factor X inhibitor activity: effect of heparin and dextran. Acta orthopaedica Scandinavica. 1982;53(6):937-45.
64. Mannucci PM, Citterio LE, Panajotopoulos N. Low-dose heparin and deep-vein thrombosis after total hip replacement. Thrombosis and haemostasis. 1976;36(1):157-64.

65. Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. The New England journal of medicine. 1986;315(15):925-9.
66. Lassen MR, Borris LC, Christiansen HM, Moller-Larsen F, Knudsen VE, Boris P, et al. Heparin/dihydroergotamine for venous thrombosis prophylaxis: comparison of low-dose heparin and low molecular weight heparin in hip surgery. The British journal of surgery. 1988;75(7):686-9.
67. Torholm C, Broeng L, Jorgensen PS, Bjerregaard P, Josephsen L, Jorgensen PK, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo controlled study. The Journal of bone and joint surgery British volume. 1991;73(3):434-8.
68. Yoo MC, Kang CS, Kim YH, Kim SK. A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement. International orthopaedics. 1997;21(6):399-402.
69. Zufferey P, Laporte S, Quenet S, Molliex S, Auboyer C, Decousus H, et al. Optimal low-molecular-weight heparin regimen in major orthopaedic surgery. A meta-analysis of randomised trials. Thrombosis and haemostasis. 2003;90(4):654-61.
70. Lahnborg G. Effect of low-dose heparin and dihydroergotamine on frequency of postoperative deep-vein thrombosis in patients undergoing post-traumatic hip surgery. Acta chirurgica Scandinavica. 1980;146(5):319-22.
71. Svend-Hansen H, Bremerskov V, Gotrik J, Ostri P. Low-dose heparin in proximal femoral fractures. Failure to prevent deep-vein thrombosis. Acta orthopaedica Scandinavica. 1981;52(1):77-80.
72. Xabregas A, Gray L, Ham JM. Heparin prophylaxis of deep vein thrombosis in patients with a fractured neck of the femur. The Medical journal of Australia. 1978;1(11):620-2.
73. Galasko CS, Edwards DH, Fearn CB, Barber HM. The value of low dosage heparin for the prophylaxis of thromboembolism in patients with transcervical and intertrochanteric femoral fractures. Acta orthopaedica Scandinavica. 1976;47(3):276-82.
74. Jorgensen PS, Knudsen JB, Broeng L, Josephsen L, Bjerregaard P, Hagen K, et al. The thromboprophylactic effect of a low-molecular-weight heparin (Fragmin) in hip fracture surgery. A placebo-controlled study. Clinical orthopaedics and related research. 1992(278):95-100.
75. Sourmelis S, Patoulis G, Tzortzis G. Prevention of deep vein thrombosis with low molecular weight heparin in fractures of the hip. Journal of bone and joint surgery British Volume. 1995;77(suppl 2):173.
76. Borgstrom S, Greitz T, Van der Linden W. Anticoagulation prophylaxis of venous thrombosis in patients with fractured neck of the femur. Acta chirurgica Scandinavica. 1965;129:500-8.
77. Eskeland G, Solheim K, Skjorten F. Anticoagulant prophylaxis, thromboembolism and mortality in elderly patients with hip fractures. A controlled clinical trial. Acta chirurgica Scandinavica. 1966;131(1):16-29.
78. Hamilton HW, Crawford JS, Gardiner JH, Wiley AM. Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulation. The Journal of bone and joint surgery British volume. 1970;52(2):268-89.
79. Morris GK, Mitchell JR. Warfarin sodium in prevention of deep venous thrombosis and pulmonary embolism in patients with fractured neck of femur. Lancet. 1976;2(7991):869-72.
80. Myhre HO, Holen A. [Thrombosis prophylaxis. Dextran or warfarin-sodium? A controlled clinical study]. Nordisk medicin. 1969;82(49):1534-8.
81. Powers PJ, Gent M, Jay RM, Julian DH, Turpie AG, Levine M, et al. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. Archives of internal medicine. 1989;149(4):771-4.
82. Colwell CW, Jr., Collis DK, Paulson R, McCutchen JW, Bigler GT, Lutz S, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. The Journal of bone and joint surgery American volume. 1999;81(7):932-40.

83. Francis CW, Pellegrini VD, Jr., Totterman S, Boyd AD, Jr., Marder VJ, Liebert KM, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. The Journal of bone and joint surgery American volume. 1997;79(9):1365-72.
84. Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial Investigators. Archives of internal medicine. 2000;160(14):2199-207.
85. Eriksson BI, Dahl OE, Huo MH, Kurth AA, Hantel S, Hermansson K, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. Thrombosis and haemostasis. 2011;105(4):721-9.
86. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet. 2007;370(9591):949-56.
87. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. The New England journal of medicine. 2010;363(26):2487-98.
88. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. The New England journal of medicine. 2008;358(26):2765-75.
89. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008;372(9632):31-9.
90. Anderson DR, Dunbar MJ, Bohm ER, Belzile E, Kahn SR, Zukor D, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. Annals of internal medicine. 2013;158(11):800-6.
91. Fuji T, Ochi T, Niwa S, Fujita S. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association. 2008;13(5):442-51.
92. Lassen MR, Borris LC, Christiansen HM, Boll KL, Eiskjaer SP, Nielsen BW, et al. Prevention of thromboembolism in 190 hip arthroplasties. Comparison of LMW heparin and placebo. Acta orthopaedica Scandinavica. 1991;62(1):33-8.
93. Samama CM, Clergue F, Barre J, Montefiore A, Ill P, Samii K. Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. Arar Study Group. British journal of anaesthesia. 1997;78(6):660-5.
94. Warwick D, Bannister GC, Glew D, Mitchelmore A, Thornton M, Peters TJ, et al. Perioperative low-molecular-weight heparin. Is it effective and safe. The Journal of bone and joint surgery British volume. 1995;77(5):715-9.
95. Bergqvist D, Benoni G, Bjorgell O, Fredin H, Hedlundh U, Nicolas S, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. The New England journal of medicine. 1996;335(10):696-700.
96. Hull RD, Pineo GF, Stein PD, Mah AF, MacIsaac SM, Dahl OE, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Annals of internal medicine. 2001;135(10):858-69.
97. Sobieraj DM, Lee S, Coleman CI, Tongbram V, Chen W, Colby J, et al. Prolonged versus standard-duration venous thromboprophylaxis in major orthopedic surgery: a systematic review. Annals of internal medicine. 2012;156(10):720-7.
98. Comp PC, Spiro TE, Friedman RJ, Whitsett TL, Johnson GJ, Gardiner GA, Jr., et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group. The Journal of bone and joint surgery American volume. 2001;83-A(3):336-45.

99. Dahl OE, Andreassen G, Aspelin T, Muller C, Mathiesen P, Nyhus S, et al. Prolonged thromboprophylaxis following hip replacement surgery--results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). Thrombosis and haemostasis. 1997;77(1):26-31.
100. Lassen MR, Borris LC, Anderson BS, Jensen HP, Skejo Bro HP, Andersen G, et al. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty--the Danish Prolonged Prophylaxis (DaPP) Study. Thrombosis research. 1998;89(6):281-7.
101. Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Compan D, et al. Efficacy and safety of postdischarge administration of enoxaparin in the prevention of deep venous thrombosis after total hip replacement. A prospective randomised double-blind placebo-controlled trial. Drugs. 1996;52 Suppl 7:47-54.
102. Heit JA, Elliott CG, Trowbridge AA, Morrey BF, Gent M, Hirsh J. Ardeparin sodium for extended out-of-hospital prophylaxis against venous thromboembolism after total hip or knee replacement. A randomized, double-blind, placebo-controlled trial. Annals of internal medicine. 2000;132(11):853-61.
103. Prandoni P, Bruchi O, Sabbion P, Tanduo C, Scudeller A, Sardella C, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. Archives of internal medicine. 2002;162(17):1966-71.
104. Leclerc JR, Geerts WH, Desjardins L, Jobin F, Laroche F, Delorme F, et al. Prevention of deep vein thrombosis after major knee surgery--a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. Thrombosis and haemostasis. 1992;67(4):417-23.
105. Chin PL, Amin MS, Yang KY, Yeo SJ, Lo NN. Thromboembolic prophylaxis for total knee arthroplasty in Asian patients: a randomised controlled trial. Journal of orthopaedic surgery. 2009;17(1):1-5.
106. Fitzgerald RH, Jr., Spiro TE, Trowbridge AA, Gardiner GA, Jr., Whitsett TL, O'Connell MB, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. The Journal of bone and joint surgery American volume. 2001;83-A(6):900-6.
107. Heit JA, Berkowitz SD, Bona R, Cabanas V, Corson JD, Elliott CG, et al. Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: a double-blind, dose-ranging study. Ardeparin Arthroplasty Study Group. Thrombosis and haemostasis. 1997;77(1):32-8.
108. Leclerc JR, Geerts WH, Desjardins L, Laflamme GH, L'Esperance B, Demers C, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. Annals of internal medicine. 1996;124(7):619-26.
109. Friedman HZ, Cragg DR, Glazier SM, Gangadharan V, Marsalese DL, Schreiber TL, et al. Randomized prospective evaluation of prolonged versus abbreviated intravenous heparin therapy after coronary angioplasty. Journal of the American College of Cardiology. 1994;24(5):1214-9.
110. Hamulyak K, Lensing AW, van der Meer J, Smid WM, van Ooy A, Hoek JA. Subcutaneous low-molecular weight heparin or oral anticoagulants for the prevention of deep-vein thrombosis in elective hip and knee replacement? Fraxiparine Oral Anticoagulant Study Group. Thrombosis and haemostasis. 1995;74(6):1428-31.
111. Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. The New England journal of medicine. 1993;329(19):1370-6.
112. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. Journal of thrombosis and haemostasis : JTH. 2007;5(11):2178-85.

113. Re-Mobilize Writing Committee, Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, et al. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. The Journal of arthroplasty. 2009;24(1):1-9.
114. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet. 2010;375(9717):807-15.
115. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. The New England journal of medicine. 2009;361(6):594-604.
116. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. The New England journal of medicine. 2008;358(26):2776-86.
117. Turpie AGG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009;373(9676):1673-80.
118. Barrellier MT, Lebel B, Parienti JJ, Mismetti P, Dutheil JJ, Vielpeau C, et al. Short versus extended thromboprophylaxis after total knee arthroplasty: a randomized comparison. Thrombosis research. 2010;126(4):e298-304.
119. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. Bmj. 2012;344:e3675.
120. Hamidi V, Ringerike T, Hagen G, Reikvam A, Klemp M. NEW ANTICOAGULANTS AS THROMBOPROPHYLAXIS AFTER TOTAL HIP OR KNEE REPLACEMENT. International journal of technology assessment in health care. 2013;29(3):234-43.
121. Loke YK, Kwok CS. Dabigatran and rivaroxaban for prevention of venous thromboembolism--systematic review and adjusted indirect comparison. Journal of clinical pharmacy and therapeutics. 2011;36(1):111-24.
122. Turun S, Banghua L, Yuan Y, Zhenhui L, Ying N, Jin C. A systematic review of rivaroxaban versus enoxaparin in the prevention of venous thromboembolism after hip or knee replacement. Thrombosis research. 2011;127(6):525-34.
123. Russell RD, Huo MH. Apixaban and Rivaroxaban Decrease Deep Venous Thrombosis But Not Other Complications After Total Hip and Total Knee Arthroplasty. The Journal of arthroplasty. 2013:doi: 10.1016/j.arth.2013.02.016. [Epub ahead of print].
124. Ramos J, Perrotta C, Badariotti G, Berenstein G. Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. Cochrane database of systematic reviews. 2008(4):CD005259. DOI: 10.1002/14651858.CD005259.pub3.
125. Canata G, Chiey A. Prevention of venous thromboembolism after ACL reconstruction: a prospective,randomized study. . ISAKOS (International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine). 2003;Vol. Poster 71–2003.
126. Michot M, Conen D, Holtz D, Erni D, Zumstein MD, Ruflin GB, et al. Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low--molecular weight heparin. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2002;18(3):257-63.
127. Roth P. Prophylaxis of deep vein thrombosis in outpatients undergoing arthroscopic meniscus operation [Thromboembolieprophylaxe bei ambulant durchgefürten arthroskopischen Meniskusoperationen]. . Orthopädische Praxis 1995;5:345-8.
128. Wirth T, Schneider B, Misselwitz F, Lomb M, Tuylu H, Egbring R, et al. Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): Results of a randomized controlled trial. Arthroscopy : the journal of arthroscopic & related surgery : official

publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2001;17(4):393-9.
129. Camporese G, Bernardi E, Prandoni P, Noventa F, Verlato F, Simioni P, et al. Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial. Annals of internal medicine. 2008;149(2):73-82.
130. Marlovits S, Striessnig G, Schuster R, Stocker R, Luxl M, Trattnig S, et al. Extended-duration thromboprophylaxis with enoxaparin after arthroscopic surgery of the anterior cruciate ligament: a prospective, randomized, placebo-controlled study. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2007;23(7):696-702.
131. Jorgensen PS, Warming T, Hansen K, Paltved C, Vibeke Berg H, Jensen R, et al. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. Thrombosis research. 2002;105(6):477-80.
132. Kock HJ, Schmit-Neuerburg KP, Hanke J, Rudofsky G, Hirche H. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. Lancet. 1995;346(8973):459-61.
133. Kujath P, Spannagel U, Habscheid W. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. Haemostasis. 1993;23 Suppl 1:20-6.
134. Lapidus LJ, Rosfors S, Ponzer S, Levander C, Elvin A, Larfars G, et al. Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. Journal of orthopaedic trauma. 2007;21(1):52-7.
135. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. The New England journal of medicine. 2002;347(10):726-30.
136. Goel DP, Buckley R, deVries G, Abelseth G, Ni A, Gray R. Prophylaxis of deep-vein thrombosis in fractures below the knee: a prospective randomised controlled trial. The Journal of bone and joint surgery British volume. 2009;91(3):388-94.
137. Lapidus LJ, Ponzer S, Elvin A, Levander C, Larfars G, Rosfors S, et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. Acta orthopaedica. 2007;78(4):528-35.
138. Osman Y, Kamal M, Soliman S, Sheashaa H, Shokeir A, Shehab el-Dein AB. Necessity of routine postoperative heparinization in non-risky live-donor renal transplantation: results of a prospective randomized trial. Urology. 2007;69(4):647-51.
139. Ballard RM, Bradley-Watson PJ, Johnstone FD, Kenney A, McCarthy TG. Low doses of subcutaneous heparin in the prevention of deep vein thrombosis after gynaecological surgery. The Journal of obstetrics and gynaecology of the British Commonwealth. 1973;80(5):469-72.
140. Clark-Pearson DL, DeLong E, Synan IS, Soper JT, Creasman WT, Coleman RE. A controlled trial of two low-dose heparin regimens for the prevention of postoperative deep vein thrombosis. Obstetrics and gynecology. 1990;75(4):684-9.
141. Abernethy EA, Hartsuck JM. Postoperative pulmonary embolism. A prospective study utilizing low dose heparin. American journal of surgery. 1974;128(6):739-42.
142. Allen NH, Jenkins JD, Smart CJ. Surgical haemorrhage in patients given subcutaneous heparin as prophylaxis against thromboembolism. British medical journal. 1978;1(6123):1326.
143. Bejjani BB, Chen DC, Nolan NG, Edson M. Minidose heparin in transurethral prostatectomy. Urology. 1983;22(3):251-4.
144. Bergqvist D, Hallbook T. Prophylaxis of postoperative venous thrombosis in a controlled trial comparing dextran 70 and low-dose heparin. World journal of surgery. 1980;4(2):239-43.
145. Clarke-Pearson DL, Coleman RE, Synan IS, Hinshaw W, Creasman WT. Venous thromboembolism prophylaxis in gynecologic oncology: a prospective, controlled trial of low-dose heparin. American journal of obstetrics and gynecology. 1983;145(5):606-13.

146. Coe NP, Collins RE, Klein LA, Bettmann MA, Skillman JJ, Shapiro RM, et al. Prevention of deep vein thrombosis in urological patients: a controlled, randomized trial of low-dose heparin and external pneumatic compression boots. Surgery. 1978;83(2):230-4.
147. Gordon-Smith IC, Le Quesne LP, Grundy DJ, Newcombe JF, Bramble FJ. Controlled trial of two regimens of subcutaneous heparin in prevention of postoperative deep-vein thrombosis. Lancet. 1972;1(7761):1133-5.
148. Groote Schuur Hospital Thromboembolus Study Group. Failure of low-dose heparin to prevent significant thromboembolic complications in high-risk surgical patients: interim report of prospective trial. Groote Schuur Hospital Thromboembolus Study Group. British medical journal. 1979;1(6176):1447-50.
149. Hedlund PO, Blomback M. The effect of prophylaxis with low dose heparin on blood coagulation parameters. A double blind study in connection with transvesical prostatectomy. Thrombosis and haemostasis. 1979;41(2):337-45.
150. Jourdan M, McColl I. The use of prophylactic subcutaneous heparin in patients undergoing hernia repairs. The British journal of clinical practice. 1984;38(9):298-300.
151. Kruse-Blinkenberg HO, Gormsen J. The influence of low dose heparin in elective surgery on blood coagulation, fibrinolysis, platelet function, antithrombin III and antiplasmin. Acta chirurgica Scandinavica. 1980;146(6):375-82.
152. Lahnborg G, Bergstrom K. Clinical and haemostatic parameters related to thromboembolism and low-dose heparin prophylaxis in major surgery. Acta chirurgica Scandinavica. 1975;141(7):590-5.
153. Lahnborg G, Lagergren H, Hedenstierna G. Effect of low-dose heparin prophylaxis on arterial oxygen tension after high laparotomy. Lancet. 1976;1(7950):54-6.
154. Lawrence JC, Xabregas A, Gray L, Ham JM. Seasonal variation in the incidence of deep vein thrombosis. The British journal of surgery. 1977;64(11):777-80.
155. MacIntyre I, Vasilescu C, Jones D. Heparin versus dextran in the prevention of deep-vein thrombosis. A multi-unit controlled trial. The Lancet. 1974;2(7873):118-20.
156. Marchetti V, Beati C, Pogliani EM, Vincre G. [Low-dose calcium-heparin prophylaxis in thoracic surgery. Bleeding, changes in coagulation and fibrinolysis]. Minerva medica. 1983;74(28-29):1745-8.
157. Plante J, Boneu B, Vaysse C, Barret A, Gouzi M, Bierme R. Dipyridamole-aspirin versus low doses of heparin in the prophylaxis of deep venous thrombosis in abdominal surgery. Thrombosis research. 1979;14(2-3):399-403.
158. Ribaudo JM, Hoellrich RG, McKinnon WM, Shuler SE. Evaluation of mini-dose heparin administration as a prophylaxis against postoperative pulmonary embolism: a prospective double-blind study. The American surgeon. 1975;41(5):289-95.
159. Sagar S, Massey J, Sanderson JM. Low-dose heparin prophylaxis against fatal pulmonary embolism. British medical journal. 1975;4(5991):257-9.
160. Sasahara A, DiSerio F, Singer J. Dihydroergotamine-heparin prophylaxis of postoperative deep vein thrombosis. A multicenter trial. JAMA: the journal of the American Medical Association. 1984;251(22):2960-6.
161. Strand L, Bank-Mikkelsen OK, Lindewald H. Small heparin doses as prophylaxis against deep-vein thrombosis in major surgery. Acta chirurgica Scandinavica. 1975;141(7):624-7.
162. Taberner DA, Poller L, Burslem RW, Jones JB. Oral anticoagulants controlled by the British comparative thromboplastin versus low-dose heparin in prophylaxis of deep vein thrombosis. British medical journal. 1978;1(6108):272-4.
163. Torngren S. Prophylaxis of postoperative deep venous thrombosis. Studies on low-dose heparin, blood coagulation, infection as a risk factor and the half-life of fibrinogen in patients after gastrointestinal surgery. Acta chirurgica Scandinavica Supplementum. 1979(495):1-69.
164. Wu TK, Tsapogas MJ, Jordan FR. Prophylaxis of deep venous thrombosis by hydroxychloroquine sulfate and heparin. Surgery, gynecology & obstetrics. 1977;145(5):714-8.

165. Balas P. Efficiacy and safety of nadroparin (Fraxiparine) versus placebo in the prophylactic treatment of deep vein thrombosis in patients with high thrombo-embolic risk undergoing general surgery. . Thrombosis research. 1992;65(Suppl 1):S113.
166. Marassi A, Balzano G, Mari G, D'Angelo SV, Della Valle P, Di Carlo V, et al. Prevention of postoperative deep vein thrombosis in cancer patients. A randomized trial with low molecular weight heparin (CY 216). International surgery. 1993;78(2):166-70.
167. Le Gagneux F, Steg A, Le Guillou M. Subcutaneous enoxaparine (Lovenox) versus placebo for preventing deep vein thrombosis (DVT) after transurethral prostatectomy(TUP). Thrombosis and haemostasis. 1987;58:166.
168. Ockelford PA, Patterson J, Johns AS. A double-blind randomized placebo controlled trial of thromboprophylaxis in major elective general surgery using once daily injections of a low molecular weight heparin fragment (Fragmin). Thrombosis and haemostasis. 1989;62(4):1046-9.
169. Ho YH, Seow-Choen F, Leong A, Eu KW, Nyam D, Teoh MK. Randomized, controlled trial of low molecular weight heparin vs. no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian patients. Diseases of the colon and rectum. 1999;42(2):196-202; discussion -3.
170. Pezzuoli G, Neri Serneri GG, Settembrini P, Coggi G, Olivari N, Buzzetti G, et al. Prophylaxis of fatal pulmonary embolism in general surgery using low-molecular weight heparin Cy 216: a multicentre, double-blind, randomized, controlled, clinical trial versus placebo (STEP). STEP-Study Group. International surgery. 1989;74(4):205-10.
171. Valle I, Sola G, Origone A. Controlled clinical study of the efficacy of a new low molecular weight heparin administered subcutaneously to prevent post-operative deep venous thrombosis. Current medical research and opinion. 1988;11(2):80-6.
172. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane database of systematic reviews. 2009(1):CD004318. DOI: 10.1002/14651858.CD004318.pub2.
173. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. The New England journal of medicine. 2002;346(13):975-80.
174. Lausen I, Jensen R, Jorgensen LN, Rasmussen MS, Lyng KM, Andersen M, et al. Incidence and prevention of deep venous thrombosis occurring late after general surgery: randomised controlled study of prolonged thromboprophylaxis. The European journal of surgery = Acta chirurgica. 1998;164(9):657-63.
175. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P, Nielsen JD, Horn A, Mohn AC, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. Journal of thrombosis and haemostasis : JTH. 2006;4(11):2384-90.
176. Jorgensen LN LI, Rasmussen MS, Wille-Jørgensen P, Bergqvist D. Prolonged thromboprophylaxis with low molecular weight heparin following major general surgery: an individual patient data meta-analysis. Blood. 2002;100(abstract 1952 (poster)).
177. Akl EA, Terrenato I, Barba M, Sperati F, Muti P, Schunemann HJ. Extended perioperative thromboprophylaxis in patients with cancer. A systematic review. Thrombosis and haemostasis. 2008;100(6):1176-80.
178. Lederle FA, Zylla D, MacDonald R, Wilt TJ. Venous thromboembolism prophylaxis in hospitalized medical patients and those with stroke: a background review for an American College of Physicians Clinical Practice Guideline. Annals of internal medicine. 2011;155(9):602-15.
179. Weber C, Merminod T, Herrmann FR, Zulian GB. Prophylactic anti-coagulation in cancer palliative care: a prospective randomised study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2008;16(7):847-52.
180. Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Bmj. 2006;332(7537):325-9.

181. Lederle FA, Sacks JM, Fiore L, Landefeld CS, Steinberg N, Peters RW, et al. The prophylaxis of medical patients for thromboembolism pilot study. The American journal of medicine. 2006;119(1):54-9.
182. Mahe I, Bergmann JF, d'Azemar P, Vaissie JJ, Caulin C. Lack of effect of a low-molecular-weight heparin (nadroparin) on mortality in bedridden medical in-patients: a prospective randomised double-blind study. European journal of clinical pharmacology. 2005;61(5-6):347-51.
183. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation. 2004;110(7):874-9.
184. Kucher N, Leizorovicz A, Vaitkus PT, Cohen AT, Turpie AG, Olsson CG, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Archives of internal medicine. 2005;165(3):341-5.
185. Fraisse F, Holzapfel L, Couland JM, Simonneau G, Bedock B, Feissel M, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. American journal of respiratory and critical care medicine. 2000;161(4 Pt 1):1109-14.
186. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. The New England journal of medicine. 1999;341(11):793-800.
187. Alikhan R, Cohen AT. Heparin for the prevention of venous thromboembolism in general medical patients (excluding stroke and myocardial infarction). Cochrane database of systematic reviews. 2009(3):CD003747. DOI: 10.1002/14651858.CD003747.pub2.
188. Gardlund B. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. The Heparin Prophylaxis Study Group. Lancet. 1996;347(9012):1357-61.
189. Dahan R, Houlbert D, Caulin C, Cuzin E, Viltart C, Woler M, et al. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. Haemostasis. 1986;16(2):159-64.
190. Belch JJ, Lowe GD, Ward AG, Forbes CD, Prentice CR. Prevention of deep vein thrombosis in medical patients by low-dose heparin. Scottish medical journal. 1981;26(2):115-7.
191. Group ISTc. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997;349(9065):1569-81.
192. Kay R, Wong KS, Yu YL, Chan YW, Tsoi TH, Ahuja AT, et al. Low-molecular-weight heparin for the treatment of acute ischemic stroke. The New England journal of medicine. 1995;333(24):1588-93.
193. Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B, Abildgaard U. A double-blind and randomized placebo-controlled trial of low molecular weight heparin once daily to prevent deep-vein thrombosis in acute ischemic stroke. Seminars in thrombosis and hemostasis. 1990;16 Suppl:25-33.
194. Prins MH, Gelsema R, Sing AK, van Heerde LR, den Ottolander GJ. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin) in stroke patients. Haemostasis. 1989;19(5):245-50.
195. Dickmann U, Voth E, Schicha H, Henze T, Prange H, Emrich D. Heparin therapy, deep-vein thrombosis and pulmonary embolism after intracerebral hemorrhage. Klinische Wochenschrift. 1988;66(23):1182-3.
196. Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, et al. Double-blind randomised trial of Org 10172 low-molecular-weight heparinoid in prevention of deep-vein thrombosis in thrombotic stroke. Lancet. 1987;1(8532):523-6.
197. McCarthy ST, Turner J. Low-dose subcutaneous heparin in the prevention of deep-vein thrombosis and pulmonary emboli following acute stroke. Age and ageing. 1986;15(2):84-8.

198. McCarthy ST, Turner JJ, Robertson D, Hawkey CJ, Macey DJ. Low-dose heparin as a prophylaxis against deep-vein thrombosis after acute stroke. Lancet. 1977;2(8042):800-1.
199. Kakkar AK, Cimminiello C, Goldhaber SZ, Parakh R, Wang C, Bergmann JF, et al. Low-molecular-weight heparin and mortality in acutely ill medical patients. The New England journal of medicine. 2011;365(26):2463-72.
200. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. The New England journal of medicine. 2011;365(23):2167-77.
201. Cohen AT, Spiro TE, Spyropoulos AC, Committee MS. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. The New England journal of medicine. 2013;368(20):1945-6.
202. Bath PM, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, et al. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. Lancet. 2001;358(9283):702-10.
203. Hull RD, Schellong SM, Tapson VF, Monreal M, Samama MM, Nicol P, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Annals of internal medicine. 2010;153(1):8-18.
204. Clarke M, Hopewell S, Juszczak E, Eisinga A, Kjeldstrom M. Compression stockings for preventing deep vein thrombosis in airline passengers. Cochrane database of systematic reviews. 2006(2):CD004002. 10.1002/14651858.CD004002.pub2
205. Akl EA, Gunukula S, Barba M, Yosuico VE, van Doormaal FF, Kuipers S, et al. Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Cochrane database of systematic reviews. 2011(1):CD006652. DOI: 10.1002/14651858.CD006652.pub2.
206. Agnelli G, Gussoni G, Bianchini C, Verso M, Mandala M, Cavanna L, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. The lancet oncology. 2009;10(10):943-9.
207. Altinbas M, Coskun HS, Er O, Ozkan M, Eser B, Unal A, et al. A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. Journal of thrombosis and haemostasis : JTH. 2004;2(8):1266-71.
208. Kakkar AK, Levine MN, Kadziola Z, Lemoine NR, Low V, Patel HK, et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004;22(10):1944-8.
209. Perry JR, Julian JA, Laperriere NJ, Geerts W, Agnelli G, Rogers LR, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. Journal of thrombosis and haemostasis : JTH. 2010;8(9):1959-65.
210. Sideras K, Schaefer PL, Okuno SH, Sloan JA, Kutteh L, Fitch TR, et al. Low-molecular-weight heparin in patients with advanced cancer: a phase 3 clinical trial. Mayo Clinic proceedings Mayo Clinic. 2006;81(6):758-67.
211. Klerk CP, Smorenburg SM, Otten HM, Lensing AW, Prins MH, Piovella F, et al. The effect of low molecular weight heparin on survival in patients with advanced malignancy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(10):2130-5.
212. Lebeau B, Chastang C, Brechot JM, Capron F, Dautzenberg B, Delaisements C, et al. Subcutaneous heparin treatment increases survival in small cell lung cancer. "Petites Cellules" Group. Cancer. 1994;74(1):38-45.
213. Pelzer U, Deutschinoff G. A prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy - first results of the CONKO 004 trial. Onkologie - DGHO meeting oct 2009;580:abstract.
214. Di Nisio M, Porreca E, Ferrante N, Otten HM, Cuccurullo F, Rutjes AW. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane database of systematic reviews. 2012;2:CD008500. DOI: 10.1002/14651858.CD008500.pub2.

215. Haas S, Kakkar A, Kemkes-Matthes B, Freund M, Gatzemeier U, Heilmann L. Prevention of venous thromboembolism with low-molecular-weight heparin in patients with metastatic breast or lung cancer - Results of the TOPIC studies. Journal of Thrombosis and Haemostasis 2005;3(1. Abstract number: OR059.).
216. Akl EA, Vasireddi SR, Gunukula S, Yosuico VE, Barba M, Terrenato I, et al. Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Cochrane database of systematic reviews. 2011(6):CD006466. DOI: 10.1002/14651858.CD006466.pub3.
217. Chahinian AP, Propert KJ, Ware JH, Zimmer B, Perry MC, Hirsh V, et al. A randomized trial of anticoagulation with warfarin and of alternating chemotherapy in extensive small-cell lung cancer by the Cancer and Leukemia Group B. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1989;7(8):993-1002.
218. Daly L. The first international urokinase/warfarin trial in colorectal cancer. Clinical & experimental metastasis. 1991;9(1):3-11.
219. Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. Lancet. 1994;343(8902):886-9.
220. Maurer LH, Herndon JE, 2nd, Hollis DR, Aisner J, Carey RW, Skarin AT, et al. Randomized trial of chemotherapy and radiation therapy with or without warfarin for limited-stage small-cell lung cancer: a Cancer and Leukemia Group B study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1997;15(11):3378-87.
221. Zacharski LR, Henderson WG, Rickles FR, Forman WB, Cornell CJ, Jr., Forcier RJ, et al. Effect of warfarin anticoagulation on survival in carcinoma of the lung, colon, head and neck, and prostate. Final report of VA Cooperative Study #75. Cancer. 1984;53(10):2046-52.
222. Palumbo A, Cavo M, Bringhen S, Zamagni E, Romano A, Patriarca F, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(8):986-93.
223. Larocca A, Cavallo F, Bringhen S, Di Raimondo F, Falanga A, Evangelista A, et al. Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. Blood. 2012;119(4):933-9; quiz 1093.
224. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Archives of internal medicine. 2012;172(5):397-402.
225. Mak KH. Coronary and mortality risk of novel oral antithrombotic agents: a meta-analysis of large randomised trials. BMJ open. 2012;2(5):doi. 10.1136/bmjopen-2012-001592.
226. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet. 1960;1(7138):1309-12.
227. Cundiff DK, Manyemba J, Pezzullo JC. Anticoagulants versus non-steroidal anti-inflammatories or placebo for treatment of venous thromboembolism. Cochrane database of systematic reviews. 2006(1):CD003746. DOI: 10.1002/14651858.CD003746.pub2.
228. Egermayer P. Value of anticoagulants in the treatment of pulmonary embolism: a discussion paper. Journal of the Royal Society of Medicine. 1981;74(9):675-81.
229. Kakkar VV, Flanc C, O'Shea M, Flute P, Howe CT, Clarke MB. Treatment of deep-vein thrombosis--a random trial. The British journal of surgery. 1968;55(11):858.
230. Ott P, Eldrup E, Oxholm P. [Value of anticoagulant therapy in deep venous thrombosis in the lower limb in elderly, mobilized patients. A double-blind placebo controlled study with open therapeutic guidance]. Ugeskrift for laeger. 1988;150(4):218-21.
231. Nielsen HK, Husted SE, Krusell LR, Fasting H, Charles P, Hansen HH. Silent pulmonary embolism in patients with deep venous thrombosis. Incidence and fate in a randomized, controlled trial of anticoagulation versus no anticoagulation. Journal of internal medicine. 1994;235(5):457-61.

232. Nielsen HK, Husted SE, Krusell LR, Fasting H, Charles P, Hansen HH, et al. Anticoagulant therapy in deep venous thrombosis. A randomized controlled study. Thrombosis research. 1994;73(3-4):215-26.
233. Brandjes DP, Heijboer H, Buller HR, de Rijk M, Jagt H, ten Cate JW. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. The New England journal of medicine. 1992;327(21):1485-9.
234. Pérard L, Hot A, Cucherat M. Non-inferiority trial used in venous thromboembolic disease. A warily interpretation is necessary! La Revue de Médecine interne. 2007;28:731-6.
235. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators. The New England journal of medicine. 1997;337(10):657-62.
236. Head SJ, Kaul S, Bogers AJ, Kappetein AP. Non-inferiority study design: lessons to be learned from cardiovascular trials. European heart journal. 2012;33(11):1318-24.
237. Kline JA, Courtney DM, Kabrhel C, Moore CL, Smithline HA, Plewa MC, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. Journal of thrombosis and haemostasis : JTH. 2008;6(5):772-80.
238. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. JAMA : the journal of the American Medical Association. 1990;263(20):2753-9.
239. Havig O. Deep vein thrombosis and pulmonary embolism. An autopsy study with multiple regression analysis of possible risk factors. Acta chirurgica Scandinavica Supplementum. 1977;478:1-120.
240. Engelke C, Rummeny EJ, Marten K. Pulmonary embolism at multi-detector row CT of chest: one-year survival of treated and untreated patients. Radiology. 2006;239(2):563-75.
241. Perrier A, Bounameaux H. Accuracy or outcome in suspected pulmonary embolism. The New England journal of medicine. 2006;354(22):2383-5.
242. Hayashino Y, Goto M, Noguchi Y, Fukui T. Ventilation-perfusion scanning and helical CT in suspected pulmonary embolism: meta-analysis of diagnostic performance. Radiology. 2005;234(3):740-8.
243. Prins MH, Lensing AW. Derivation of the non-inferiority margin for the evaluation of direct oral anticoagulants in the treatment of venous thromboembolism. Thrombosis journal. 2013;11(1):13.