INSTITUT NATIONAL D'ASSURANCE MALADIE-INVALIDITE
SERVICE DES SOINS DE SANTE
COMITE D'ÉVALUATION DES PRATIQUES MÉDICALES EN MATIÈRE DE MÉDICAMENTS

THE EFFICIENT PHARMACEUTICAL APPROACH TO PREVENTION AND TREATMENT OF CEREBROVASCULAR PATHOLOGIES IN PRIMARY HEALTH CARE

Systematic literature review: full report

Réunion de consensus

10 mai 2012
AUDITORIUM LIPPENS (BIBLIOTHEQUE ROYALE)
BRUXELLES

Cette analyse de la littérature a été effectuée par vzw Farmaka asbl et a été suivie par un comité de lecture.

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1. Methodology (French)

1.1. Introduction et formulation de la question

Cette recherche de la littérature est exécutée en préparation à la conférence de consensus sur la "Prise en charge médicamenteuse efficiente en prévention et en traitement des pathologies cérébrovasculaires en première ligne de soins".

Les questions de recherche sont formulées ainsi par le comité d'organisation de l'INAMI:

1. Urgence: AVC ou AIT aigu

1.1. Quelles sont les interventions utiles et celles qui sont nuisibles à la phase initiale d'un AIT/AVC ?
1.2. Appel du médecin ou de l'ambulance ?
1.3. Gestes à ne pas faire avant l'hospitalisation?

2. Fibrillation auriculaire et prévention thrombo-embolique (pas le traitement antiarythmique)

2.1. Quel (s) est (sont) le(s) score(s) d'évaluation de risque utile(s) ?
2.2. Quelles sont l'efficacité et la sécurité (comparatives) des antiagrégants plaquettaires ?
2.3. Quelles sont l'efficacité et la sécurité (comparatives) des anti vitamine K ?
2.4. Quelles sont l'efficacité et la sécurité (comparatives) des nouveaux anticoagulants oraux ?
2.5. Quelle stratégie thérapeutique préventive recommander ?
2.6. Les interventions validées sont-elles identiques en post AVC/AIT ischémique ?
2.7. Les interventions validées sont-elles identiques en post AVC hémorragique ?

3. Sténose carotidienne documentée

3.1. Asymptomatique (pas d'AVC, ni d'AIT)

- Quels sont les arguments pour préférer un traitement uniquement médical ou un traitement chirurgical (+ médical)?
- Existe-t-il des particularités pour le traitement médical dans cette indication versus prévention primaire cardiovasculaire classique ?

3.2. Symptomatique (post AVC ou AIT)

- Quels sont les arguments pour préférer un traitement uniquement médical ou un traitement chirurgical (+ médical)?
- Existe-t-il des particularités pour le traitement médical dans cette indication versus prévention secondaire (post-AVC) classique décrite au point 4 ?

4. Post AVC ou AIT

4.1. Antiagrégants plaquettaires (hors FA)

- Quels sont les traitements antiagrégants efficaces post AVC ou AIT et quelle est leur sécurité ?
- Quelles sont les associations d'antiagrégants entre eux ou d'antiagrégants avec d'autres médicaments (particulièrement les anticoagulants) qui sont à recommander ou à éviter ?

- Quelles sont l'efficacité et la sécurité comparatives ?

4.2. Anticoagulants (hors FA)

- Quelles sont l'efficacité et la sécurité des anti vitamine K en traitement d'entretien post AVC/AIT ?
- Quelles sont l'efficacité et la sécurité des nouveaux anticoagulants oraux en traitement d'entretien post AVC/AIT ?

4.3. Autres traitements

- Quels sont les médicaments autres que les antiagrégants plaquettaires et anticoagulants efficaces post AVC/AIT (statines, anti-hypertenseurs) ? Quelle est leur sécurité ?

Population examinée

- Réduction du risque cardiovasculaire après AVC/AIT chez la personne sans fibrillation auriculaire
- Réduction du risque cardiovasculaire après AVC/AIT chez la personne atteinte de fibrillation auriculaire
- Réduction du risque cardiovasculaire chez la personne atteinte de fibrillation auriculaire, sans antécédents d'AVC/AIT

Eindpunten

- AVC, AIT, embolie périférique
- AVC hémorragique
- hémorragies: mineure, majeure, fatale, non-fatale, …
- infarctus du myocarde et autres critères de jugement cardiaques
- critères de jugement cardiovasculaires composites
- mortalité: cardiaque, totale
- Qol (qualité de vie)
- autres effets indésirables hors saignement

Critères d'étude

- Design d'étude:

  - Efficacité: RCT
  - Au moins 'single blind'
  - Sécurité : manuel 'Meyler's Side Effects of Drugs, Fifteenth Edition' (pour la plupart des
  - produits, nous avons consulté le Répertoire Commenté des Médicaments du CBIP, qui à son tour est basé sur le manuel Meyler's)

- Durée d'étude : 6 mois de traitement au moins
- Nombre minimum de participants par bras d'étude : minimum 40 ou un total de 40 pour les études de permutation, sauf si une étude ne répondant pas aux critères d'inclusion était incluse dans une méta-analyse.
- Antiagrégants, antihypertenseurs, hypolipidémiants: seulements les produits avec une indication enregistrée en Belgique
- Anticoagulants: fenprocoumon, warfarine, acenocoumarol, apixaban, dabigatran, rivaroxaban

Guides de Pratique Clinique (GPC)

- Uniquement les GPC évoquant des niveaux de preuves / recommandation
- Sommaire des points communs et des contradictions
- Uniquement les GPC à partir de 2005.
- GPC sélectionnés (en concertation avec le comité d'organisation):

Atrial Fibrillation

European Society of Cardiology	Guidelines for the management of atrial fibrillation. European Heart Journal (2010) 31, 2369-2429. Doi:10.1093/eurheart/ehq278
European Stroke Organization	Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008, update january 2009, eso-stroke.org Guideline covers ischemic stroke and transient ischemic attact (TIA).
Canadian Cardiovascular Society	Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter. Canadian Journal of Cardiology 27 (2011) 74-90.
American College of Cardiology /American Heart Association	ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation Circulation 2006, 114:e257-e354 most recent update: 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline) : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011, 123:104-123
American College of Chest Physicians	Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition) Chest 2012;141;531S-575S

Secondary Prevention of Stroke

SIGN	Management of patients with stroke of TIA: Assesment, investigation, immediate management and secondary prevention. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2008. 103 p. (SIGN publication; no. 108)
CBO	Richtlijn Diagnostiek, behandeling en zorg voor patiënten met een beroerte. 2008 Nederlandse Vereniging voor Neurologie
Catalan Agency for Health Technology Assessment and Research	Development group of the stroke prevention Guideline. Iberoamerican Cochrane Centre, coordinator. Clinical Practice Guideline for Primary and Secondary Prevention of Stroke. Madrid: Quality Plan for the National Health System of the Ministry of Health and Consumer Affairs; Catalan Agency for Health Technology Assessment and Research; 2008. Clinical Practice Guideline: AATRM Number 2006/15. Edition: 1/March/2009
American Heart Association/American Stroke Association Council on Stroke	Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke. Stroke 2006, 37:577-617 doi: 10.1161/01.STR.0000199147.30016.74
National Stroke Foundation Australia	National Stroke Foundation. Clinical Guidelines for Stroke Management. 2010. Melbourne Australia. www.strokefoundation.com.au
European Stroke Organization	Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008, update january 2009, eso-stroke.org Guideline covers ischemic stroke and transient ischemic attact (TIA).

Carotid artery stenosis

European Society of Cardiology	Guidelines on the diagnosis and treatment of peripheral artery diseases. 2011 European Heart Journal (2011) 32, 2851–2906, doi:10.1093/eurheartj/ehr211
CBO	Richtlijn Diagnostiek, behandeling en zorg voor patiënten met een beroerte. 2008 Nederlandse Vereniging voor Neurologie
American Heart Association/American Stroke Association Council on Stroke	Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke. Stroke 2006, 37:577-617 doi: 10.1161/01.STR.0000199147.30016.74
European Stroke Organization	Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008, update january 2009, eso-stroke.org

1.2. Procédure de sélection

Nous avons appliqué les critères d'inclusion suivants lors de la sélection des *méta-analyses et des synthèses méthodiques (systematic reviews):*

- concordance entre la question abordée dans la publication et la problématique de notre recherche dans la littérature
- description de la stratégie de recherche
- inclusion d'études randomisées
- mention d'un résultat clinique pertinent

Les critères d'inclusion pour les *études randomisées contrôlées (RCTs)* sont mentionnés plus haut dans le §1 avec mention des interventions, critères de jugement et d'étude pertinents.

Deux chercheurs ont effectué la sélection des références pertinentes, indépendamment l'un de l'autre. Les différences ont été résolues en consensus après discussion. Nous avons effectué une première sélection des références sur base du titre et de l'abstract. Lorsque le titre ou l'abstract ne donnait pas une réponse suffisamment concluante sur l'inclusion, nous avons recherché et analysé la publication.

Diverses publications ont été exclues pour des raisons pratiques:
- les publications non disponibles en bibliothèque en Belgique
- les publications dans des langues autres que celles d'Europe de l'Ouest.

1.3. Stratégie de recherche

1.3.1. Principes de recherche systématique

En procédant par paliers, nous avons fait une recherche systématique de la littérature pertinente:

- Dans un premier temps, nous avons consulté les sources qui utilisent les données provenant de synthèses méthodiques, de méta-analyses et d'études originales et qui en plus les commentent: Clinical Evidence[1], La Revue Prescrire, Minerva[2]. Nous avons consulté les guides de pratique clinique (guidelines) à la recherche de références pertinentes supplémentaires.
- Dans un deuxième temps, nous avons recherché par voie électronique et manuelle les métaanalyses et les synthèses méthodiques.
- Dans un troisième temps, nous avons recherché les études randomisées et contrôlées en double aveugle (RCTs), parues après la date de recherche des synthèses méthodiques / méta-analyses sélectionnées.

Les *banques de données électroniques* suivantes ont été consultées:
- Medline (PubMed)
- Cochrane Library
- Database of Abstracts of Reviews of Effectiveness (DARE).

Les guides de pratique clinique ou *recommandations de bonne pratique* ont été recherchés au départ des liens vers les "evidence-based guidelines", disponibles sur le site web de vzw Farmaka asbl (www.farmaka.be).

Des recherches manuelles ont été effectuées à partir d'autres sources: les références bibliographiques données dans les publications pertinentes sur le sujet, l'index des publications disponibles à la bibliothèque de vzw Farmaka asbl, particulièrement des revues indépendantes qui sont membres de l'ISDB (International Society of Drug Bulletins) telles que l'Arzneimittelbrief (Allemagne), les Folia Pharmacotherapeutica (Belgique), le Geneesmiddelenbulletin (Pays Bas), la Revue Prescrire (France), Drug & Therapeutics Bulletin (Royaume Uni), Therapeutics Letter (Canada), Formul R/info (Belgique), Arzneimittelbrief (Allemagne),….

1.3.2. Détails concernant la stratégie de recherche

Les synthèses méthodiques ou méta-analyses suivantes ont été sélectionnées. Ensuite, nous avons consulté Pubmed pour rechercher les RCTs parues après la date de recherche de ces publications.

Lip GY, Kalra L. Stroke: secondary prevention. BMJ Clinical Evidence [online] 2011 [cited September 15] www.clinicalevidence.bmj.com

Afin de retrouver les RCTs parues après la date de recherche des publications ci-dessus, une recherche systématique a été executée dans Pubmed avec les mots-clés suivants : (http://www.ncbi.nlm.nih.gov/pubmed/). Dans certains cas, lorsque les synthèses méthodiques / métaanalyses ne suffisaient pas, des RCTs supplémentaires (parues avant la date de recherche) ont été recherché.

(
(
(
(cerebrovascular accident OR CVA OR transient ischemic attack OR TIA)
AND
(
(
atrial fibrillation
AND
prevention
AND
(
(antiplatelet treatment OR antiplatelet* OR aspirin* OR acetylsalicylic acid OR dipyridamol* OR clopidogrel OR prasugrel OR ticlopidin* OR thienopyridin*)
OR
(anticoagulation OR vitamin K antagonist OR warfarin* OR acenocoumarol OR fenprocoumon OR dabigatran OR thrombin inhibitor OR rivaroxaban OR apixaban OR factor Xa inhibitor)
)
)
OR
(
secondary prevention
AND
(
(antiplatelet treatment OR antiplatelet* OR aspirin* OR acetylsalicylic acid OR dipyridamol* OR clopidogrel OR ticlopidin* OR thienopyridin*)
OR
(anticoagulation OR vitamin K antagonist OR warfarin* OR acenocoumarol OR fenprocoumon OR dabigatran OR thrombin inhibitor OR rivaroxaban OR apixaban OR factor Xa inhibitor)
OR
(antihypertensive therapy OR antihypertensives OR diuretics OR beta-antagonists OR angiotensin converting enzyme inhibitors OR angiotensin receptor antagonists OR calcium antagonists OR renin inhibitors)
OR
(hypolipidemic agents OR cholesterol reduction OR statins OR fibrates OR ezetimibe OR nicotinic acid)
)
)
)
)
OR
(
carotid stenosis
AND
(
(surgery OR endarterectomy OR stent*)
AND
(medical therapy OR drug therapy)
)
)
)

AND
("2009/01"[PDat] : "2011/10/15"[PDat])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
)

1.4. Evaluation de la qualité des preuves disponibles

Afin d'évaluer la qualité des preuves disponibles, nous avons utilisé le système GRADE. Dans d'autres systèmes qui attribuent des « niveaux de preuves », les méta-analyses sont souvent perçues comme le plus haut niveau de preuve. Par contre, GRADE n'évalue que la qualité des études originales. La sommation ou non des résultats dans la méta-analyse n'a pas d'importance pour la qualité des preuves. Le système GRADE[3,4,5] évalue les points suivants :

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 guide-line panel will judge the quality of the evidence to be lower.

Pour davantage d'informations, veuillez consulter le site http://www.gradeworkinggroup.org

Dans cette recherche de la littérature, l'item « publication bias » et les items spécialement prévus pour les études d'observation du système GRADE (voir tableau ci-dessus) ne sont pas cotés. Cette version adaptée du système GRADE évalue donc les points suivants:

I

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

Lors de l'évaluation des différents items, nous avons suivi la méthode de travail suivante:

Study design
Toutes les études de cette recherche de la littérature sont par définition des RCT (critères d'inclusion). "Study design" n'est donc pas repris séparément comme critère d'évaluation dans le rapport de synthèse pour cette raison.

Study quality
Le score Jadad est utilisé pour l'évaluation de la qualité méthodologique des RCTs, en plus d'une vérification si une analyse « intention-to-treat » (ITT, tous les patients randomisés en analyse d'efficacité) a été effectuée. Lorsqu'une méta-analyse ou synthèse méthodique a été utilisée, c'est surtout la qualité des études incluses qui a été évaluée. Ce n'est donc pas la qualité de la métaanalyse / synthèse méthodique en soi qui joue un rôle dans l'évaluation GRADE, mais bien celle des RCTs incluses dans la méta-analyse / synthèse méthodique.

Score Jadad :

1	Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?	Yes	1
		No	0
1a	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.)?	Not described / NA	0
		Adequate	1
		Inadequate	-1
2	Was the study described as double-blind?	Yes	1
		No	0
2a	If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection wit hno double dummy)?.	Not described / NA	0
		Adequate	1
		Inadequate	-1
3	Was there a description of withdrawals and drop-outs	Yes	1
		No	0

(Tableau repris de 'Duke University, Center for Clinical Health Policy Research. Drug Treatments for the Prevention of Migraine. AHCPR February 1999'.)

Application dans GRADE: 1 point de qualité a été déduit lorsqu'il y avait un problème avec la question 3 du score Jadad (« was there a description of withdrawals and drop-outs »). Étant donné que la 'randomisation' était un critère d'inclusion, aucun point n'a été déduit, même si la méthode n'était pas décrite de façon adéquate. Mis à part le score Jadad, nous avons aussi vérifié si une analyse ITT avait été effectuée. Si ce n'était pas le cas, un autre point était alors déduit. Pour l'ITT, des points n'ont été déduit que si le follow-up s'élevait à moins de 80%. Aucun point supplémentaire n'a été déduit si le pourcentage de follow-up n'était pas connu.

Consistency

- Une bonne « consistency » signifie que plusieurs études obtiennent un résultat comparable ou convergent. S'il n'y a qu'une étude de disponible, « consistency » ne peut être évalué. Ceci est mentionné dans le rapport de synthèse comme « NA » (not applicable).

- « Consistency » est apprécié par le groupe bibliographique et le comité de lecture sur base de l'ensemble des études disponibles. Pour ce faire, l'on a pris en compte les critères suivants:

  - o Signification statistique
  - o Le sens de l'effet si la signification statistique n'est pas atteinte: si par exemple un effet statistiquement significatif est obtenu dans 3 études et est confirmé dans 2 autres études par un résultat dans le même sens mais non significatif statistiquement, alors ces résultats sont appelés 'consistent'.
  - o Pertinence clinique: si par exemple 3 études trouvent une différence non significative et une 4° étude trouve un résultat statistiquement significatif, mais peu pertinent cliniquement, ces résultats sont appelés convergents.

Directness

Cela concerne le pouvoir de généraliser les données vers la population réelle (validité externe). Donc, des points peuvent être déduits si la population d'étude, l'intervention en question et le groupe contrôle ou les critères de jugement en question ne sont pas pertinents.

Imprecision

Si des synthèses méthodiques ou méta-analyses sont incluses, reprenant à leur tour des études comptant moins de 40 patients par bras d'étude (pour une étude de permutation : moins de 40 patients pour l'étude complète), 1 point est alors déduit pour cause « d'imprécision ».

Appliquer le système GRADE quand il y a beaucoup d'études pour un seul critère de jugement :

Des points sont déduits uniquement si les erreurs méthodologiques contribuent fortement au résultat. Si, par exemple, 1 étude de mauvaise qualité confirme les avis de 2 grandes études de bonne qualité, aucun point n'est déduit.

1.5. Résumé des résultats d'étude

Le rapport complet comprend par question de recherche :

- Les tableaux de preuves (en anglais) des synthèses méthodiques et/ou des RCTs sur lesquels se basent les réponses
- Un bref résumé des résultats sous forme de tableau (en anglais) et de texte (français / néerlandais) avec une évaluation de la qualité des preuves trouvées selon une version adaptée du système GRADE

Le rapport de synthèse comprend par question de recherche :

- Un bref résumé des résultats sous forme de tableau (en anglais) et de texte (français / néerlandais) avec une évaluation de la qualité des preuves trouvées selon une version adaptée du système GRADE.

Toutes les conclusions ont été débattues et adaptées dans des discussions successives avec les auteurs de la recherche de la littérature et avec le comité de lecture du groupe bibliographique.

Références

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 considerations of the bibliographic group

Delineation of the subject

- The literature search was delineated to the molecules as specified by the organising committee of the RIZIV

- antiplatelets, antihypertensives and lipid lowering products registred in Belgium
- vit K-antagonists
- New anticoagulants: apixaban, dabigatran and rivaroxaban

- In consultation with the organizing comittee, the litterature search was delineated to the following subjects. This was done to avoid an overlap with the Consensus Conference of 2009 on prevention of cardiovascualr events.

- CV risk reduction in patients without AF, with a previous stroke/TIA
- CV risk reduction in patients with non-valvular AF, with or without previous stroke/TIA

- If studies in this population are not available, we refer to Clinical Evidence (see add. 1 of this document).

- The focus on drugs in this document does not mean that a global approach of cardiovascular risk factors (obesity, smoking, diabetes) is irrelevant, on the contrary. Hereby we refer to a recent document of the WHO[1].

- Acute interventions (for instance thrombolysis) are not discussed in this document. This also applies to the treatment of the rhythm problem in the patient with AF.

Definitions

- The word 'prevention' could suggest that the medical problem (in this case: stroke) could be prevented completely. Of course, this is not possible. Actually, one means to prevent a cardiovascular event. This is why we left the terms of 'primary' and 'secondary' prevention and we report 'cardiovascular risk reduction'.
- The terms 'primary' prevention and 'secondary' prevention are source of discussion. When do we talk about a real event? If one is confronted with ischaemic brain damage on CT in a patient without clinical signs, do we speak about secondary prevention?
- The trials use different inclusion criteria for 'previous stroke'.
- We would like to avoid the terms primary and secondary prevention. We will explain the event previously experienced by the patient and the event the studied intervention aims to avoid.

Characteristics of the incuded trials

- Duration of at least 6 m.

- In most of the trials, patients with severe comorbidity or excess of beeding risk were excluded and the studied population was followed very strictly. A potential superiority in this ideal study conditions should be checked in a real-life situation

- The reported endpoints in the trials are often composite and differ significantly between trials. There is a lack of data on 'functional outcomes', which could have given us an idea of the impact of stroke on

the daily life of the patient. Because residual lesions of stroke cause a wide range of consequences, from independent functionioning tot total dependence, we experience this lack of functional outcomes as a shortcoming.

- The older trials report only limited outcomes and give only limited information on adverse events.

- The trials with the newer anticoagulants are so-called non-inferiority trials. Even the experienced reader is not familiar with this complex methodology.

- The trials that compared medical treatment with surgery plus medical treatment were performed in the 90'ies. Since then, medical therapy has evolved (e.g. more general use of statins). Therefore, the advantage of surgery will probably be lower in the current situation..

- Pharmacovigilance is indicated for the newer anticoagulants. Special attention is wanted for frail elderly, often polymedicated patients.

Evaluation of the studies

- The level of evidence according to the GRADE method must be understood in the methodogical context of the GRADE system. If a certain drug gets a higher 'level of evidence', this does not necessarily mean that this drug is more effective than others. The number of trials for a certain comparison e.g. is no criterium in the GRADE-evaluation. One trial of good quality can lead to a 'high quality of evidence' label while for other comparisons several trials can be available, which can lead to a 'moderate quality of evidence' if several of these studies have methodological shortcomings.

Referenties

1. Global Atlas on Cardiovascular Disease Prevention and Control. Mendis S, Puska P, Norrving B editors. World Health Organization, Geneva 2011.
http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf

3. Summary of guidelines

3.1. Criteria for guideline selection

In order to be included, the guideline had to be of recent date (no more than 5 years old) and had to report levels of evidence and/or grades of recommendation.
Guidelines only covering the acute phase of stroke or TIA treatment were also excluded.
The following guidelines fulfilled these criteria:

Atrial Fibrillation

European Society of Cardiology	Guidelines for the management of atrial fibrillation. European Heart Journal (2010) 31, 2369-2429. Doi:10.1093/eurheart/ehq278
European Stroke Organization	Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008, update january 2009, eso-stroke.org Guideline covers ischemic stroke and transient ischemic attact (TIA).
Canadian Cardiovascular Society	Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter. Canadian Journal of Cardiology 27 (2011) 74-90.
American College of Cardiology /American Heart Association	ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation Circulation 2006, 114:e257-e354 most recent update: 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline) : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011, 123:104-123
American College of Chest Physicians	Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition) Chest 2012;141;531S-575S

Secondary Prevention of Stroke

SIGN	Management of patients with stroke of TIA: Assesment, investigation, immediate management and secondary prevention. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2008. 103 p. (SIGN publication; no. 108)
CBO	Richtlijn Diagnostiek, behandeling en zorg voor patiënten met een beroerte. 2008 Nederlandse Vereniging voor Neurologie
Catalan Agency for Health Technology Assessment and Research	Development group of the stroke prevention Guideline. Iberoamerican Cochrane Centre, coordinator. Clinical Practice Guideline for Primary and Secondary Prevention of Stroke. Madrid: Quality Plan for the National Health System of the Ministry of Health and Consumer Affairs; Catalan Agency for Health Technology Assessment and Research; 2008. Clinical Practice Guideline: AATRM Number 2006/15. Edition: 1/March/2009
American Heart Association/American Stroke Association Council on Stroke	Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke. Stroke 2006, 37:577-617 doi: 10.1161/01.STR.0000199147.30016.74
National Stroke Foundation Australia	National Stroke Foundation. Clinical Guidelines for Stroke Management. 2010. Melbourne Australia. www.strokefoundation.com.au
European Stroke Organization	Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008, update january 2009, eso-stroke.org Guideline covers ischemic stroke and transient ischemic attact (TIA).

Carotid artery stenosis

European Society of Cardiology	Guidelines on the diagnosis and treatment of peripheral artery diseases. 2011 European Heart Journal (2011) 32, 2851–2906, doi:10.1093/eurheartj/ehr211
CBO	Richtlijn Diagnostiek, behandeling en zorg voor patiënten met een beroerte. 2008 Nederlandse Vereniging voor Neurologie
American Heart Association/American Stroke Association Council on Stroke	Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack : A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke. Stroke 2006, 37:577-617 doi: 10.1161/01.STR.0000199147.30016.74
European Stroke Organization	Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008, update january 2009, eso-stroke.org

3.2. Atrial Fibrillation

3.2.1. Levels of evidence / grades of recommendation

<table>
<tr><td>European Society of Cardiology</td><td>Levels of evidence

A: Data derived from multiple randomized clinical trials or meta-analyses.
B: Data derived from a single randomized clinical trail of large non-randomized studies.
C: Consensus of opinion of the experts and/or small studies, retrospectivestudies, registries.

Classes of recommendations

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td></tr>
<tr><td>European Stroke Organization</td><td>Levels of evidence

Class 1: An adequately powered, prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:
a. randomization concealment
b. primary outcome(s) is/are clearly defined
c. exclusion/inclusion criteria are clearly defined
d. adequate accounting for dropouts and crossovers with numbers sufficiently low to have a minimal potential for bias; and
e. relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class 2: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a-e above or a randomized, controlled trial in a representative population that lacks one criterion a-e

Class 3: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class 4: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Grades of recommendation

Level A — Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing Class I study or at least two consistent, convincing Class II studies.
Level B — Established as probable useful/predictive or not useful/predictive for a diagnostic measure or established as probable effective, ineffective or harmful for a therapeutic intervention; requires at</td></tr>
</table>

		least one convincing Class II study or overwhelming Class III evidence.
	Level C	Established as possible useful/predictive or not useful/predictive for a diagnostic measure or established as possible effective, ineffective or harmful for a therapeutic intervention; requires at least two Class III studies.
	Good Clinical Practice (GCP) points	Recommended best practice based on the experience of the guideline development group. Usually based on Class IV evidence indicating large clinical uncertainty, such GCP points can be useful for health workers
Canadian Cardiovascular Society	**Levels of evidence** High: Future research unlikely to change confidence in estimate of effect; eg, multiple well-designed, well-conducted clinical trials Moderate: Further research likely to have an important impact on confidence in estimate of effect and may change the estimate; eg, limited clinical trials, inconsistency of results or study limitations Low: Further research very likely to have a significant impact on the estimate of effect and is likely to change the estimate; eg,small number of clinical studies or cohort observations Very Low:The estimate of effect is very uncertain; eg, case studies, consensus opinion **Factors determining the strength of recommendations** Quality of evidence :The higher the quality of evidence, the greater the probability that a strong recommendation is indicated. Difference between desirable:The greater the difference between desirable and undesirable effects, the greater the probability that a strong recommendation is indicated; Values and preferences: The greater the variation or uncertainty in values and preferences, the higher the probability that a conditional recommendation is indicated. Cost: The higher the cost, the lower the likelihood that a strong recommendation is indicated.	
American College of Cardiology / American Heart Association	**Levels of evidence** A: Data derived from multiple randomized clinical trials or meta-analyses. B: Data derived from a single randomized clinical trail or non-randomized studies. C: Consensus of opinion of the experts and/or small studies, case studies or standard or care **Classes of recommendations** Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy. Class IIb: Usefulness/efficacy is less well established by evidence/opinion. Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	
American College of Chest Physicians	**Levels of Evidence** High (A): RCT and observational studies with very large effects Moderate (B): Downgraded RCTs or upgraded observational studies Low (C): Observational studies and RCTs with major limitations	

	Grades of recommendation Strong (1): Desirable effects clearly outweigh undesirable effects, or vice versa Weak (2): Desirable effects closely balanced with undesirable effects

3.2.2. Included populations – risk stratification

European Society of Cardiology (ESC)	- Patients with atrial fibrillation (paroxysmal, persistant and permanent) - CHA_2DS_2-VASc score [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)]. 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.), and female sex. Valvular heart disease is also considered as 'high risk'. - HAS BLED (hypertension, abnormal liver or renal function, history of stroke or bleeding, labile INRs, elderly age (65 years), and concomitant use of drugs that promote bleeding or excess alcohol) risk stratification for bleeding
European Stroke Organization	- Patients wit atrial fibrillation - Risk factors: aged >75y, high blood pressure, left ventricular dysfunction, or diabetes mellitus
Canadian Cardiovascular Society	- Patients wit atrial fibrillation (paroxysmal, persistant and permanent) and atrial flutter - $CHADS_2$-score - HAS BLED risk stratification for bleeding
American College of Cardiology Foundation/American Heart Association	- Patients with atrial fibrillation (paroxysmal, persistant and permanent). Distinctionbetween atrial flutter and atrial fibrillation - Risk factors: Less Validated or weaker: female, 65-74y, coronary artery disease, thyrotoxicosis Moderate: ≥75y, hypertension, heart failure, LVE fraction <35%, diabetes High-Risk: previous stroke, TIA or embolism, mitral stenosis, prosthetic heart valve - Other than dose intensity, advanced age, and hypertension, factors associated with higher rates of intracerebral hemorrhage during anticoagulant therapy include associated cerebrovascular disease and possibly concomitant antiplatelet therapy, tobacco or alcohol consumption, ethnicity, genotype, and certain vascular abnormalities detected by brain imaging, such as amyloid angiopathy, leukoaraiosis, or microbleeds.
American College of Chest Physicians	- Patients with atrial fibrillation (persistent, permanent and paroxysmal) and atrial flutter. - These recommendations apply to patients with persistent or paroxysmal AF and not to patients with a single brief episode of AF due to a reversible cause, such as an acute illness. - $CHADS_2$-score: congestive heart failure, hypertension, age ≥75y, diabetes mellitus, prior stroke or TIA - No risk stratification for bleeding

3.2.3. Recommendations

European Society of Cardiology	Antithrombotic management: CHA_2DS_2-VASc score≥ 2: oral anticoagulant (1A) CHA_2DS_2-VASc score = 1: oral anticoagulant (preferred) (1A) or aspirin (75-325mg) (1B) CHA_2DS_2-VASc score = 0: nothing (preferred) or aspirin (75-325mg) (1B) Oral anticoagulant: Vitamine K antagonist dose adjusted to achieve a INR of 2.0 – 3.0 (1A) Dabigatran may be considered as an alternative to adjusted dose VKA therapy. Selection of antitrombotic therapy should be considered irrespective of the patern of AF (paroxysmal, persistent, or permanent) (2A) Combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g.inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding. After cardioversion: Long term anticoagulation depends on risk of stroke. (2a, B)
European Stroke Organization	Antithrombotic management: Aspirin may be recommended for patients with non-valvular AF who are younger than 65 years and free of vascular risk factors **(Class I, Level A)** Unless contraindicated, either aspirin or an oral anticoagulant (international normalized ratio [INR] 2.0-3.0) is recommended for patients with non-valvular AF who are aged 65-75 years and free of vascular risk factors **(Class I, Level A)** Unless contraindicated, an oral anticoagulant (INR 2.0–3.0) is recommended for patients with non-valvular AF who are aged >75, or who are younger but have risk factors such as high blood pressure, left ventricular dysfunction, or diabetes mellitus **(Class I, Level A)** Oral anticoagulation is not recommended in patients with co-morbid conditions such as falls, poor compliance, uncontrolled epilepsy, or gastrointestinal bleeding **(Class III, Level C)**. Increasing age alone is not a contraindication to oral anticoagulation **(Class I, Level A)** It is recommended that patients with AF who are unable to receive oral anticoagulants should be offered aspirin **(Class I, Level A)** It is recommended that patients with AF who have mechanical prosthetic heart valves should receive long-term anticoagulation with a target INR based on the prosthesis type, but not less than INR 2–3 **(Class II, Level B)**
Canadian Cardiovascular Society	Antithrombotic management: Very low risk of stroke ($CHADS_2$ = 0) : *aspirin* (75-325 mg/d) (Strong Recommendation, High-Quality Evidence). No antithrombotic may be appropriate in selected young patients with no stroke risk factors Low risk of stroke ($CHADS_2$ = 1) : *OAC* therapy (either warfarin [INR 2 to 3] or Dabigatran)

	(Strong Recommendation, High-Quality Evidence). Based on individual risk-benefit considerations, aspirin is a reasonable alternative for some (Conditional Recommendation, Moderate-Quality Evidence). Moderate risk of stroke ($CHADS_2$ = 2) : *OAC* therapy (either warfarin [INR 2-3] or Dabigatran) (Strong Recommendation, High-Quality Evidence). When OAC therapy is indicated, most patients should receive dabigatran in preference to warfarin. In general, the dose of *dabigatran 150 mg* by mouth twice a day is preferable to a dose of *110 mg* by mouth twice a day (Conditional Recommendation, High-Quality Evidence). After cardioversion: Long term anticoagulation depends on risk of stroke. (Strong Recommendation, Moderate Quality Evidence)
American College of Cardiology Foundation/American Heart Association	Antithrombotic management: Antithrombotic therapy is recommended for all patients with AF, except those with lone AF (younger than 60y with no clinical history or echocardiographic sings of cardiopulmonary disease) or contraindications. (Level of Evidence: A, class 1) The selection of the antithrombotic agent should be based upon the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient. (Level of Evidence: A, class 1) No risk factors: aspirine 81-325mg daily (level A, class 1) One moderate risk factor: aspirin 81-325mg daily or warfarin (INR 2-3) (level A, class 2a) Any high risk factor or more than 1 moderate risk factor: warfarin (INR 2-3) (level A, class 1) It is reasonable to select antithrombotic therapy using the same criteria irrespective of the pattern (i.e., paroxysmal, persistent, or permanent) of AF. (Level of Evidence: B, Class 2a) After cardioversion: Duration of anticoagulation after cardioversion depends both on the likelihood that AF will recur in an individual patient with or without symptoms and on the intrinsic risk of thromboembolism (Level of Evidence: C, class 2a) .
American College of Chest Physicians	Antithrombotic management: For patients with non-valvular AF, including paroxysmal AF: *low risk of stroke ($CHADS_2$-score=0) we suggest no therapy rather than antithrombotic therapy for patients choosing antithrombotic therapy, we suggest aspirin rather than oral anticoagulation or combination therapy with aspirin and clopidogrel (Grade 2B) *intermediate risk of stroke ($CHADS_2$-score=1) we recommend oral anticoagulation rather than no therapy (Grade 1B) we suggest oral anticoagulation rather than aspirin or combination therapy with aspirin and clopidogrel (Grade 2B) *high risk of stroke ($CHADS_2$-score≥2) we recommend oral anticoagulation rather than no therapy (Grade 1A), aspirin (Grade 1B) or combination therapy with aspirin and clopidogrel (Grade 1B)

	Where we recommend or suggest in favor of oral anticoagulation, we suggest dabigatran 150mg bid rather than adjusted-dose vitamin K antagonist therapy (Grade 2B)

3.3. Secondary prevention of stroke

3.3.1. Levels of evidence / grades of recommendation

SIGN	**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, eg case reports, case series 4 Expert opinion **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+
CBO	**Levels of evidence** A1 Systematic review of at least 2 independently conducted studies level A2 A2 Randomised double blind controlled trial of good quality and size B Comparative research, but not with all the characteristics mentioned under A2 (This also includes case-control studies, cohort study) C non-comparative study D expert opinion **Levels of conclusions** 1 Conclusion based of level A1 evidence or at least two independently conducted studies level A2 2 1 level A2 study or at least two independently conducted studies level B 3 1 level B or C study 4 Expert opinion

Catalan Agency for Health Technology Assessment and Research	**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, eg case reports, case series 4 Expert opinion **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 Clinical Practice: Recommended practice based on clinical experience and the consensus of the elaborating team.
American Heart Association/American Stroke Association Council on Stroke	**Levels of evidence** A Data derived from multiple randomized clinical trials or meta-analyses. B Data derived from a single randomized clinical trail or non-randomized studies. C Consensus of opinion of the experts and/or small studies, case studies or standard or care **Classes of recommendations** Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. Class IIa : Weight of evidence/opinion is in favour of usefulness/efficacy. Class IIb: Usefulness/efficacy is less well established by evidence/opinion. Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.
National Stroke Foundation Australia	**Grades of recommendation** A: Body of evidence can be trusted to guide practice B: Body of evidence can be trusted to guide practice in most situations

	C: Body of evidence provides some support for recommendation(s) but care should be taken in its application D: Body of evidence is weak and recommendation must be applied with caution Good Clinical Practice: Recommended practice based on clinical experience and expert opinion **Levels of evidence** 1 A systematic review of level 2 studies 2 A Randomized controlled trial 3-1 A pseudorandomised controlled trial (i.e. alternate allocation or som other method) 3-2 A comparative study with concurrent controls: Non-randomised experimental trial, cohort study, case-control study, interrupted time series with a control group^ 3-3 A comparative study without concurrent controls: Historical control study, two or more single arm study, interrupted time series without a parallel control group 4 Case series with either post-test or pre-test/post-test outcomes
European Stroke Organization	**Levels of evidence** Class 1: An adequately powered, prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required: a. randomization concealment b. primary outcome(s) is/are clearly defined c. exclusion/inclusion criteria are clearly defined d. adequate accounting for dropouts and crossovers with numbers sufficiently low to have a minimal potential for bias; and e. relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences Class 2: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a-e above or a randomized, controlled trial in a representative population that lacks one criterion a-e Class 3: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment Class 4: Evidence from uncontrolled studies, case series, case reports, or expert opinion **Grades of recommendation** Level A — Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing Class I study or at least two consistent, convincing Class II studies.

	Level B	Established as probable useful/predictive or not useful/predictive for a diagnostic measure or established as probable effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing Class II study or overwhelming Class III evidence.
	Level C	Established as possible useful/predictive or not useful/predictive for a diagnostic measure or established as possible effective, ineffective or harmful for a therapeutic intervention; requires at least two Class III studies.
	Good Clinical Practice (GCP) points	Recommended best practice based on the experience of the guideline development group. Usually based on Class IV evidence indicating large clinical uncertainty, such GCP points can be useful for health workers

3.3.2. Definitions and patients covered

SIGN	Stroke: A focal neurological deficit (loss of function affecting a specific region of the nervous system) due to disruption of its blood supply (The World Health Organization (WHO) definition) Transient ischaemic attack (TIA): Historically defined as a neurological deficit caused by interruption in blood supply to the brain (or retina), in which all symptoms resolve within 24 hours. Stroke and TIA have identical symptoms and represent a continuum, with only an arbitrary time limit distinguishing them. Proposals to change the definition recognise that most TIAs resolve fully within 30-60 minutes.Permanent damage to brain tissue occurs in at least half of TIAs. This guideline covers the treatment, monitoring and prevention of recurrent stroke in patients with ischaemic stroke, transient ischaemic attack (TIA), primary intracerebral haemorrhage (PICH) and asymptomatic carotid disease. Management of patients with subarachnoid haemorrhage has not been addressed.
CBO	Stroke: Sudden onset of a focal disorder in the brains, there is no other cause than a vascular disorder. The guideline covers s all stroke patients with or without transient symptoms. Among stroke, this guideline does not include a subarachnoid or subdural hemorrhage
Catalan Agency for Health Technology Assessment and Research	Cerebrovascular disease or stroke: circulatory brain disorder that transitorily or permanently disrupts the functioning of one or more parts of the brain. There are several types of stroke, which, depending on the nature of the lesion produced, can cause cerebral ischemia or cerebral hemorrhage. TIA is a brief episode of neurologic dysfunction, with clinical symptoms that last less than an hour and with no evidence of stroke in neuroimaging techniques. The guideline covers stroke (ischemic and hemorrhagic) and transient ischemic attack [TIA].
American Heart Association/American Stroke Association Council on Stroke	Stroke: symptoms lasting >24 hours or imaging of an acute clinically relevant brain lesion in patients with rapidly vanishing symptoms. TIA: Brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of infarction. Guideline covers prevention of ischemic stroke among survivors of ischemic stroke or TIA. Hemorrhagic stroke: guideline covers only anticoagulation management after

	cerebral hemorrhage.
National Stroke Foundation Australia	Stroke: sudden and unexpected damage to brain cells that causes symptoms that last for more than 24 hours in the parts of the body controlled by those cells. Stroke happens when the blood supply to part of the brain is suddenly disrupted, either by blockage of an artery or by bleeding within the brain. TIA: Stroke-like symptoms that last less than 24 hours. Exclusion of subarachnoid hemorrhage.
European Stroke Organization (1)	Guideline covers Ischemic stroke and TIA. Exclusion of intracerebral hemorrhage and subarachnoid hemorrhage.

3.3.3. Recommendations

SIGN	<u>Secondary prevention</u> <u>Antithrombotic treatment:</u> Low-dose aspirin (75 mg daily) and dipyridamole (200 mg modified release twice daily) should be prescribed after ischaemic stroke or TIA for secondary prevention of vascular events (A)**.** Clopidogrel (75mg daily) monotherapy should be considered as an alternative to combination aspirin and dipyridamole after ischaemic stroke or TIA for secondary prevention of vascular events. The combination of aspirin and clopidogrel is not recommended for long term secondary prevention of ischaemic stroke or TIA (A). Anticoagulation is not recommended for preventing recurrent stroke in patients with non-cardioembolic ischaemic stroke (A). Patients with ischaemic stroke or TIA who are in atrial fibrillation should be offered warfarin with target INR 2.0-3.0 (A). In the absence of contraindications and patient preference for alternative treatment, warfarin should be offered routinely to elderly patients (>75 years) with ischaemic stroke or TIA who are in atrial fibrillation (B). <u>Statins</u> A statin should be prescribed to patients who have had an ischaemic stroke, irrespective of cholesterol level (A). Atorvastatin (80 mg) should be considered for patients with TIA or ischaemic stroke (A). Other statins (such as simvastatin 40 mg) may also be considered as they reduce the risk of major vascular events (A). Statin therapy after haemorrhagic stroke is not routinely recommended unless the risk of further vascular events outweighs the risk of further haemorrhage (A). <u>Antihypertensives</u> All patients with a previous stroke or TIA should be considered for treatment with an ACE inhibitor (for example, perindopril) and thiazide (for example, indapamide) regardless of blood pressure, unless contraindicated (A).
CBO	<u>Secondary Prevention</u> <u>Antithrombotic treatment:</u> After a TIA or non-disabling ischemic stroke (with no cardiac source of embolism shown), patients are eligible for treatment with the combination of aspirin (30-100 mg) and dipyridamole (2 dd 200 mg modified release) (based on level 1 conclusion). <u>Statins:</u> For patients who have a history of TIA or stroke treatment with a statin is recommended to prevent recurrent stroke and in particular new vascular disease. The guideline Cardiovascular Risk management can be followed, which recommends to start treatment with simvastatin 40 mg or pravastatin 40 mg, and an LDL value is pursued of <100mg/dl. For the specific indication "Stroke Prevention ‘’ no proof exists for this LDL-limit. There is insufficient evidence for the efficacy and safety of the use of high dose atorvastatin (80 mg Instead of 10-20 mg) with the aim of preventing recurrent stroke (no grade of recommendation) (based on level 2 conclusions).

	Antihypertensive drugs: For patients with hypertension who have a history of TIA or stroke a antihypertensive therapy is initiated or intensified, with a target ≤ 130 / ≤ 80 mmHg, unless an absolute contraindication exists. For patients with a history of TIA or stroke but do not meet the criteria for hypertension, antihypertensive therapy may be considered, for example if there are other important risk factors. The choice of antihypertensive treatment is guided by effective blood pressure reduction. The choice of the different classes of antihypertensive agents can be based on individual patient characteristics (such as comorbidity and age). However, monotherapy with beta-blocker or ACE inhibitor appears to be less effective. Conversely, diuretics proved effective (based on level 2 conclusions).
Catalan Agency for Health Technology Assessment and Research	Secondary Prevention Antithrombotic treatment: The combination of aspirin and sustained release dipiridamol results in increased efficacy versus aspirin monotherapy for the prevention of recurrent stroke or other vascular episodes (A,1+).Anticoagulant treatment is not more effective than antiaggregants at reducing the recurrence of non-cardioembolic stroke and is associated with an increased risk of bleeding episodes (A, 1++). In patients with non-cardioembolic ischemic stroke or transient ischemic attack, antiaggregation with aspirin (100-300 mg/d), combined aspirin and sustained release dipiridamol (50 and 400 mg/d), triflusal (600 mg/d) or clopidrogel (75 mg/d) is recommended (A, 1++). Long term use of combined aspirin and clopidogrel is not recommended due to the increased risk of bleeding complications (A, 1++). Statins: It is recommended to treat patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology with atorvastatin (80 mg/d), regardless of their basal LDL-cholesterol levels (A). Treatment with other statins (simvastatin 40 mg) is also indicated in patients with ischemic stroke or prior transient ischemic attack of atherothrombotic etiology, regardless of their basal LDL-cholesterol levels (1++,B). These patients should maintain LDL-cholesterol levels below 100 mg/dl (Good Clinical Practice). The combination of statins with other hypolipemiant drugs to reach LDLcholesterol target values should be avoided (Good Clinical Practice). Antihypertensive drugs: In patients with a history of stroke or transient ischemic attack and high or even normal blood pressure values it is recommended to initiate treatment with antihypertensive drugs, preferably with the combination of an angiotensin converting enzyme inhibitor and a diuretic (4 mg/d of perindopril and 2.5 mg/d of indapamide) (1++,A). Depending on the patient's tolerance or concomitant pathologies, monotherapy treatment with diuretics, angiotensin converting enzyme inhibitors or angiotensin II antagonists should be considered (B). Once a patient who has had an ischemic stroke or transient ischemic attack is stabilised, blood pressure values should be gradually decreased with the aim of maintaining levels below 130/80 mmHg, and preferably below 120/80 mmHg (B).
American Heart Association/American Stroke Association Council on Stroke	Secondary prevention Antithrombotic treatment: For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I, Level of Evidence A). Aspirin (50 to 325mg/d), the combination of aspirin and extended release dipyridamole, and clopidogrel are all acceptable options for initial therapy (Class IIa, Level of Evidence A). Compared with aspirin alone, both the combination of aspirin and extended-release dipyridamole and clopidogrel are

	safe. The combination of aspirin and extended-release dipyridamole is suggested instead of aspirin alone (Class IIa, Level of Evidence A), and clopidogrel may be considered instead of aspirin alone (Class IIb, Level of Evidence B) on the basis of direct-comparison trials. The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for ischemic stroke or TIA patients (Class III, Level of Evidence A). For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Statines: Statin agents are recommended, with a target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease is an LDL-C of <100 mg/dL and LDL-C of <70 mg/dL for very-high-risk persons with multiple risk factors (Class I, Level of Evidence A). Patients with ischemic stroke or TIA presumed to be due to an atherosclerotic origin but with no preexisting indications for statins (normal cholesterol levels, no comorbid coronary artery disease, or no evidence of atherosclerosis) are reasonable candidates for treatment with a statin agent to reduce the risk of vascular events (Class IIa, Level of Evidence B). Antihypertensive drugs: Antihypertensive treatment is recommended in (Class I, Level of Evidence A). Because this benefit extends to persons with and without a history of hypertension, this recommendation should be considered for all ischemic stroke and TIA patients (Class IIa, Level of Evidence B). The optimal drug regimen remains uncertain; however, the available data support the use of diuretics and the combination of diuretics and an ACEI (Class I, Level of Evidence A).
National Stroke Foundation Australia	Secondary prevention Antithrombotic treatment: Long-term antiplatelet therapy should be prescribed to all people with ischaemic stroke or TIA who are not prescribed anticoagulation therapy (A). Low-dose aspirin and modified release dipyridamole or clopidogrel alone should be prescribed to all people with ischaemic stroke or TIA, taking into consideration patient co-morbidities (A). Aspirine alone can be used, particularly in people who do not tolerate aspirin plus dipyridamole or clopidogrel (A). The combination of aspirin plus clopidogrel is NOT recommended for the secondary prevention of cerebrovascular disease in people who do not have acute coronary disease or recent coronary stent (A). Statines: Therapy with a statin should be used for all patients with ischemic stroke or TIA (A). Statins should not be used routinely for haemorrhagic stroke (B). Antihypertensive drugs: All stroke and TIA patients, whether normotensive or hypertensive, should receive blood pressure lowering therapy, unless contraindicated by symptomatic hypotension (A).
European Stroke Organization	Secondary Prevention Antithrombotic treatment: It is recommended that patients not requiring anticoagulation should receive antiplatelet therapy (Class I, Level A). Where possible, combined aspirin and dipyridamole, or clopidogrel alone, should be given. Alternatively, aspirin alone, or triflusal alone, may be used (Class I, Level A) The combination of aspirin and clopidogrel is not recommended in patients with recent ischaemic stroke, except in patients with specific indications (e.g. unstable angina or non-Q-wave MI, or recent stenting); treatment should be given for up to 9 months after the event (Class I, Level A).

	Oral anticoagulation (INR 2.0–3.0) is recommended after ischaemic stroke associated with AF (Class I, Level A). Oral anticoagulation is not recommended in patients with co-morbid conditions such as falls, poor compliance, uncontrolled epilepsy, or gastrointestinal bleeding (Class III, Level C). Increasing age alone is not a contraindication to oral anticoagulation (Class I, Level A). It is recommended that patients with cardioembolic stroke unrelated to AF should receive anticoagulants (INR 2.0-3.0) if the risk of recurrence is high (Class III, Level C).It is recommended that anticoagulation should not be used after non-cardio-embolic ischaemic stroke, except in some specific situations, such as aortic atheromas, fusiform aneurysms of the basilar artery, cervical artery dissection, or patent foramen ovale in the presence of proven deep vein thrombosis (DVT) or atrial septal aneurysm (Class IV, GCP). It is recommended that combined low dose aspirin and dipyridamole should be given if oral anticoagulation is contraindicated (Class IV, GCP) <u>Statines:</u> Statin therapy is recommended in subjects with non-cardioembolic stroke (Class I, Level A) <u>Antihypertensive drugs:</u> Blood pressure lowering is recommended after the acute phase, including in patients with normal blood pressure (Class I, Level A)

3.4. Carotid artery stenosis

3.4.1. Levels of evidence / grades of recommendation

European Society of Cardiology	**Levels of evidence** Level A: Data derived from multiple randomized clinical trials or meta analyses. Level B: Data derived from a single randomized clinical trial or large non randomized studies. Level C : Consensus of opinion of the experts and/or small studies, retrospective studies, registries. **Classes of recommendations** Class 1: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. 'recommended' or 'indicated' Class 2: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. Class 2a: Weight of evidence/opinion is in favour of usefulness/efficacy 'should be considered' Class 2b: Usefulness/efficacy is less well established by evidence/opinion. 'may be considered' Class 3: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. 'not recommended'
CBO	**Levels of evidence** A1: Systematic review of at least 2 independently conducted studies level A2 A2: Randomised double blind controlled trial of good quality and size B: Comparative research, but not with all the characteristics mentioned under A2 (This also includes case-control studies, cohort study) C: non-comparative study D: expert opinion **Levels of conclusions** 1. Conclusion based of level A1 evidence or at least two independently conducted studies level A2 2. 1 level A2 study or at least two independently conducted studies level B 3. 1 level B or C study 4. Expert opinion
American Heart Association/American Stroke Association Council on Stroke	**Levels of evidence** A: Data derived from multiple randomized clinical trials or meta-analyses. B: Data derived from a single randomized clinical trail or non-randomized studies. C: Consensus of opinion of the experts and/or small studies, case studies or standard or care **Classes of recommendations** Class I: Evidence and/or general agreement that a given treatment or

<table>
<tr><td></td><td>procedure is beneficial, useful, effective.
Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</td></tr>
<tr><td>European Stroke Organisation</td><td>Levels of evidence

Class 1: An adequately powered, prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:
a. randomization concealment
b. primary outcome(s) is/are clearly defined
c. exclusion/inclusion criteria are clearly defined
d. adequate accounting for dropouts and crossovers with numbers sufficiently low to have a minimal potential for bias; and
e. relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class 2: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a-e above or a randomized, controlled trial in a representative population that lacks one criterion a-e

Class 3: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class 4: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Grades of recommendation

<table>
<tr><td>Level A</td><td>Established as useful/predictive or not useful/predictive for a diagnostic measure or established as effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing Class I study or at least two consistent, convincing Class II studies.</td></tr>
<tr><td>Level B</td><td>Established as probable useful/predictive or not useful/predictive for a diagnostic measure or established as probable effective, ineffective or harmful for a therapeutic intervention; requires at least one convincing Class II study or overwhelming Class III evidence.</td></tr>
<tr><td>Level C</td><td>Established as possible useful/predictive or not useful/predictive for a diagnostic measure or established as possible effective, ineffective or harmful for a therapeutic intervention; requires at least two Class III studies.</td></tr>
<tr><td>Good Clinical Practice (GCP) points</td><td>Recommended best practice based on the experience of the guideline development group. Usually based on Class IV evidence indicating large clinical uncertainty, such GCP points can be useful for health workers</td></tr>
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</td></tr>
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3.4.2. Definitions

European Society of Cardiology	Guideline covers treatment of extracranial carotid and vertebral disease. The term carotid artery stenosis refers to a stenosis of the extracranial portion of the internal carotid artery, and the degree of stenosis is according to the NASCET criteria. Carotid artery stenosis is considered symptomatic in the presence of TIA or stroke affecting the corresponding territory within the previous 6 months.
CBO	Carotid artery stenosis is considered symptomatic in the presence of TIA or stroke affecting the corresponding territory within the previous 6 months. Degree of stenosis according to NASCET criteria.
American Heart Association/American Stroke Association Council on Stroke	The term carotid artery stenosis refers to a stenosis of the extracranial portion of the internal carotid artery, and the degree of stenosis is according to the NASCET criteria. Carotid artery stenosis is considered symptomatic in the presence of TIA or stroke affecting the corresponding territory within the previous 6 months.
European Stroke Organisation	Degree of stenosis according to NASCET criteria.

3.4.3. Recommendations

European Society of Cardiology	<u>Medical therapy:</u> All patients with carotid artery stenosis should be treated with long-term statin therapy (Class 1, level C for asymptomatic stenosis, class 1, level B for symptomatic stenosis). Low-dose aspirin (or clopidogrel in case of aspirin intolerance) should be administered to all patients with carotid artery disease irrespective of symptoms (Class 1, level B for asymptomatic stenosis, Class 1, level A for symptomatic stenosis). Dual antiplatelet therapy with aspirin and clopidogrel is recommended for patients undergoing CAS <u>Surgery:</u> <u>Symptomatic carotid stenosis:</u> Best Medical Treatment (BMT) vs invasive techniques: Carotid artery stenosis < 50%: BMT Carotid artery stenosis 50-69%: revascularization should be considered + BMT (2a, A) Carotid artery stenosis 70-99%: revascularization is recommended + BMT (1, A) Occluded carotid artery: BMT <u>Asymptomatic carotid stenosis:</u> Carotid artery stenosis <60%: BMT Carotid artery stenosis 60-99%: revascularization + BMT should be considered when life expectancy >5y, perioperative stroke and death rate <3% and favourable anatomy. (2a, A) Occluded carotid artery: BMT
CBO	<u>Medical therapy:</u> No specific recommendations for carotid stenosis <u>Surgery:</u> <u>Symptomatic carotid stenosis:</u> In patients with ischemic stroke, TIA or retinal ischemia and carotid stenosis of 70-99% carotid endarterectomy is effective in preventing recurrent stroke. (level 1, A1-A2) In men with ischemic stroke or TIA with 50-70% stenosis carotid endarterectomy is useful in preventing recurrent stroke.(level 1, A1-A2). Surgery is useless after 12 weeks. <u>Asymptomatic carotid stenosis:</u> In an asymptomatic carotid stenosis carotid endarterectomy is not indicated.

	In an asymptomatic stenosis of more than 70% in men younger than 75 years, a carotid endarterectomy can be considered if the surgical risk of a disabling stroke or death is lower than 3%. (level 1, A1-A2)
American Heart Association/American Stroke Association Council on Stroke	Medical therapy: Stroke or TIA patients who undergo interventional procedures also need to be treated with maximal medical therapies. Surgery: Symptomatic carotid stenosis: For patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, CEA by a surgeon with a perioperative morbidity and mortality of <6% (Class I, Level of Evidence A) is recommended. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended, depending on patient-specific factors such as age, gender, comorbidities, and severity of initial symptoms (Class I, Level of Evidence A). When the degree of stenosis is <50%, there is no indication for CEA (Class III, Level of Evidence A) Asymptomatic carotid stenosis: No recommendations.
European Stroke Organisation	Medical therapy: Low dose aspirin is recommended for patients with asymptomatic internal carotid artery (ICA) stenosis >50% to reduce their risk of vascular events (Class II, Level B) Surgery: Symptomatic carotid stenosis: CEA is recommended for patients with 70–99% stenosis (Class I, Level A). CEA should only be performed in centres with a perioperative complication rate (all strokes and death) of less than 6% (Class I, Level A) It is recommended that CEA may be indicated for certain patients with stenosis of 50–69%; males with very recent hemispheric symptoms are most likely to benefit (Class III, Level C). CEA for stenosis of 50–69% should only be performed in centres with a perioperative complication rate (all stroke and death) of less than 3% (Class I, Level A) CEA is not recommended for patients with stenosis of less than 50% (Class I, Level A) Asymptomatic carotid stenosis: Carotid surgery is not recommended for asymptomatic individuals with significant carotid stenosis (NASCET 60-99%), except in those at high risk of stroke (Class I, Level C). Carotid angioplasty, with or without stenting, is not recommended for patients with asymptomatic carotid stenosis (Class IV, GCP**)**

3.5. Conclusions from guidelines

3.5.1. Atrial fibrillation

Antithrombotic therapy for the prevention of stroke depends on risk stratification. The selection of the antithrombotic agent should be based upon the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient. Variation in guideline recommendations for antithrombotic therapy for AF results from differences in risk stratification for ischemic stroke. Generally spoken patients with 1 important risk factor (prior stroke or TIA, valvular disease, age ≥75) or 2 less important risk factors (diabetes, hypertension, female, heart failure,…) should receive oral vitamin K antagonists (INR 2-3, (no valvular disease)). Patients with 1 less important risk factor should receive either oral vitamin K antagonists or aspirin (75-325mg), with a preference in most guidelines for vitamin K antagonists. Patients with no risk factors are suitable for either aspirin or no antithrombotic therapy, with a preference in some guidelines for no antithrombotic therapy.
Dabigatran (2*150mg) Is considered an alternative in the European guideline and is preferred in the American and Canadian guideline.
In most guidelines the choice of long term antithrombotic therapy is not altered by cardioversion: choice depends on risk of stroke.

3.5.2. Secondary prevention of stroke

All patients should receive medical treatment with antithrombotic, lipid-lowering and antihypertensive drugs. Low-dose aspirin (75 mg daily) + dipyridamole (200 mg modified release twice daily) is the preferred choice for antithrombotic treatment in 4/6 guidelines. The other 2 guidelines consider clopidogrel as an equivalent choice.
Statins are the preferred lipid-lowering drugs. Most guidelines consider all statins equally effective. There is no consensus about a target LDL-level. Statins should not be used routinely for haemorrhagic stroke.
Treatment with antihypertensive drugs is indicated regardless of blood pressure. Several guidelines consider diuretics or the combination of diuretics and ACE-inhibitors as the preferred treatment.

3.5.3. Carotid artery stenosis

Most guidelines do not recommend surgery for asymptomatic carotid stenosis. Only in case of stenosis of more than 70% in men younger than 75 years and favourable anatomy a carotid endarterectomy can be considered if the surgical risk of a disabling stroke or death is lower than 3%. For symptomatic (TIA or stroke in previous 6 months) carotid artery stenosis of 50-69% surgery should be considered. Surgery is recommended for symptomatic stenosis of 70-99%. Surgery is not indicated for stenosis <50% or near occlusions.
All patients with symptomatic and asymptomatic carotid stenosis should receive long-term antiplatelet therapy (low dose aspirin) and statin therapy (European Society of Cardiology).

4. Evidence tables and conclusions: risk reduction after stroke/TIA in patients without AF

4.0. Legend of the evidence table

Ref	n / Population	Duration	Comparison	Efficacy outcomes (with indication of primary endpoint)		Harms	Methodological
Design: - RCT P / CO - MA - SR	n= -mean age - baseline data: • AF y/n • Previous stroke/TIA • CHADS score • TTR INR			Vascular events (composite endpoint, definition according to trial)		Other AE	- Jadad score RANDO: /2 BLINDING: /2 ATTRITION: /1 - FU: % - ITT: Yes/No - Other important methodological remarks? - Sponsor:
				Stroke			
				Ischemic stroke			
				Systemic embolism			
				Hemorrhagic stroke			
				Mortality			
				Vascular mortality			
				Myocardial infarction			
				Any bleeding			
				Major bleeding (definition according to trial)			
				Minor bleeding			
				Intracranial bleeding			

AE= adverse event
AF= atrial fibrillation
AR= absolute risk
ARR= absolute risk reduction
CI= Confidence Interval
CO= crossover RCT
FU= follow-up
HR= hazard ratio
ICH= intracerebral haemorrhage
IS= ischaemic stroke
ITT= intention-to-treat analysis
MA= meta-analysis
MI= myocardial infarction
N= number of patients
NR= not reported
NS= not statistically significant
NT= no statistical test
OAC= oral anticoagulants
OR= odds ratio
P= parallel RCT
PE= primary endpoint
RR= relative risk
RRR= relative risk reduction
RIND= reversible ischaemic neurological deficit
SA= subgroupanalysis
SAH= subarachnoid hemorrhage
SE= standard error
SS= statistically significant
SR= systematic review
TIA= transient ischaemic attack
TTR INR= percent time in therapeutic INR range

4.1. Antiaplatelet drugs after stroke/TIA in patients without AF

4.1.1. Antiplatelet drugs vs. placebo/control

Ref	N/n	Comparison	Outcomes	
* APTC 2002 Design: meta-analysis Search date: 9/1997	N= 21 n= 18.270	Antiplatelets vs. control - ASA 50-1500 mg - dipyridamole 400-800 mg - ticlopidine 500 mg - sulfinpyrazone - association of ASA and sulfinpyrazone - association of ASA and dipyridamole In patients with previous stroke or TIA Mean treatment duration 3 years	Serious vascular event (non-fatal AMI, non-fatal stroke or vascular mortality)	antiplatelet= 17.5% control= 21,4% OR= 0.78 (95% CI 0.73-0.85) → Benefit per 1000 patients/3y= 36 (standard error 6) p<0.0001
			Non-fatal myocardial infarction	antiplatelet= 1.7% control= 2.3% → Benefit per 1000 patients/3y= 6 (SE 2) p= 0.0009
			Non-fatal stroke recurrence	antiplatelet= 8.3% control= 10.8% → Benefit per 1000 patients/3y= 25 (SE 5) p<0.0001
			Vascular mortality	antiplatelet= 8.0% control= 8.7% → Benefit per 1000 patients/3y= 7 (SE 4) p= 0.04
			Total mortality	antiplatelet= 11.3% control= 12.8% → Benefit per 1000 patients/3y= 15 (SE 5) p= 0.002
			Major extracranial haemorrhage (haemorrhages requiring hospital admission or blood transfusion)	antiplatelet= 0.97% control= 0.47% OR= 2.0 (95% CI not reported) → estimated excess risk of bleeding= 1-2 major extracranial bleeds/1000 patients/year
			Intracranial haemorrhage	antiplatelet= 0.64% control= 0.56% OR= 1.2 (95% CI not reported)

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
AITA (28,29) Fields 1997-98	319	-Patients with carotid TIA in previous 3 m -surgically treated or not -mostly 45-65 y	37 m	ASA 1200 mg vs. control	- Jadad score: 4/5 - FU: NR - ITT: no
Reuther (30) 1978	60	Patients with cerebral ischaemia and normal angiograms or non-surgical lesions	24 m	ASA 1500 mg vs. control	- Jadad score: NR - FU: NR - ITT: NR (publication not available)
Canadian Co-op (31,32) 1978	585	Patients with threatened stroke	26 m	Sulfinpyrazone vs. ASA 1300 mg vs. ASA 1300 + sulfinpyrazone vs. control	- Jadad score: NR - FU: NR - ITT: NR (publication not available)
Toulouse-TIA (33) Guiraud-Chaumeil 1982	596	Patients with previous ischaemic vascular accident	34 m	ASA 900 mg + dipyridamole 150 mg vs. ASA 900 mg vs. control	- Jadad score: NR - FU: NR - ITT: NR (publication not available)
AICLA (34) Bousser 1983	604	- patients with previous TIA (16%) or stroke (84%) referable to the carotid or to the vertebral-basilar circulation - no atrial fibrillation - mean age: NR (50% 55-65 y)	36 m	ASA 990 mg vs. ASA 990+dipyridamole 225 mg vs. control	- Jadad score: 4/5 - FU: 82% - ITT: no
Danish Co-op (35) Sorensen 1983	203	- At leat 1 reversible cerebral ischemic attack of <72 h duration (TIA + RIND) - 3% atrial fibrillation - mean age 61 y	25 m	ASA 1000 mg vs. placebo	- Jadad score: 5/5 - FU: 100% - ITT: yes
Britton (36) 1987	505	- minor or major stroke due to cerebral infarction in the previous 3 w (not TIA) - no atrial fibrillation - mean age 68 y	24 m	ASA 1500 mg vs. control	- Jadad score: 5/5 - FU: 100% - ITT: yes
Danish low-dose (37) Boysen 1988	301	- Patients with carotid endartectomy in previous 3 m - Without incapacitating neurological deficit - Mean age 59 y	23 m	ASA 50 mg vs. control	- Jadad score: 4/5 - FU: 80% - ITT: yes
ESPS-1 (38) 1990	2.500	- TIA, RIND or stroke in previous 3 m - meam age 59 y	23 m	ASA 975+dipyridamole 225 vs. control	- Jadad score: 3/5 - FU: 74% - ITT: no
UK-TIA (39) 1991	3.249	- TIA or minor stroke in previous 3 m - 3% atrial fibrillation - mean age 60 y	50 m	ASA 300 mg vs. ASA 1200 mg vs. control	- Jadad score: 5/5 - FU: 100% - ITT: yes

Stroke (40) Acheson 1969	169	-Patients with previous TIA or stroke -Mean age 59 y	25 m	Dipyridamole 400-800 mg vs. control	- Jadad score: 3/5 - FU: 71% - ITT: no
Memphis (41) Robertson 1975	148	Patients with previous TIA or minr stroke	48 m	Sulfinpyrazone vs control	- Jadad score: NR - FU: NR - ITT: NR (publication not available)
Blakely-stroke (42) 1979	290	Patients with thrombotic stroke	38 m	Sulfinpyrazone vs control	- Jadad score: NR - FU: NR - ITT: NR (publication not available)
CATS (43) Gent 1989	1.072	-thromboembolic stroke or TIA in previous 4 m -no atrial fibrillation -mean age 61 y	28 m	Ticlopidine 500 mg vs. control	- Jadad score: 4/5 - FU: 55% - ITT: yes
Gent-stroke (44) 1985	447	-thromboembolic stroke in previous 4 m -no atrial fibrillation -mean age 67 y	20 m	Suloctidil vs control	- Jadad score: 4/5 - FU: 50% - ITT: yes
Ross Russell (45) 1985	22	patients with amaurosis fugax	3 m	Ticlopidine 500 mg vs control	- Jadad score: NR - FU: NR - ITT: NR (publication not available)
Birmingham-B (46) Roden 1981	50 x2 cross over	- patients with previous TIA - mean age 63 y	2x4 m	Sulfinpyrazone vs control	- Jadad score: 3/5 - FU: 70% - ITT: no
Charing Cross (47) Gawel 1982	55	- patients with previous stroke	18 m	Sulfinpyrazone vs control	- Jadad score: NR - FU: NR - ITT: NR (publication not available)
McKenna-III (48) Graham 1987	53	- patients with previous stroke	16 d	Ticlopidine 500 mg vs control	- Jadad score: NR - FU: NR - ITT: NR (publication not available)
SALT (49) 1991	1.360	- TIA (27%), minor ischaemic stroke (67%) or retinal artery occlusion in previous 3 m - no atrial fibrillation - mean age 75 y	32 m	ASA 75 mg vs placebo	- Jadad score: 5/5 - FU: 99% - ITT: yes
ESPS-2 (50) Diener 1996	9.900	- TIA or stroke in preceding 3 m - 6.5% atrial fibrillation - mean age 67 y	24 m	ASA 50+dipyridamole 400 mg vs. dipyridamole 400 vs. ASA 50 vs control	- Jadad score: 5/5 - FU: 99% - ITT: yes

4.1.1.bis. Conclusion: Antiplatelet drugs vs. placebo/control

Antiplatelet treatment (acetylsalicylic acid, ticlopidine, dipyridamole, sulfinpyrazone and associations) vs placebo/control (MA ATTC 2002: AITA Fields 1997-98, Reuther 1978,Canadian Co-op 1978, Toulouse-TIA Guiraud-Chaumeil 1982, AICLA Bousser 1983,Danish Co-op Sorensen 1983, Britton 1987, Danish low-dose Boysen 1988, ESPS-1 1990, UK-TIA 1991, Stroke Acheson 1969, Memphis Robertson 1975, Blakely-stroke 1979, CATS Gent 1989, Gent-stroke 1985, Ross Russell 1985, Birmingham B Roden 1981 1981, Charing Cross Gawel 1982, McKenna-III Graham 1987, SALT 1991, ESPS-2 Diener 1996)

N/n	Duration	Population	Results	
N=21, n= 18.270	mean 3 y	- patients with previous stroke or TIA - without atrial fibrillation	Serious vascular event (non-fatal AMI, non-fatal stroke or vascular mortality)	antiplatelet= 17.5% control= 21,4% OR= 0.78 (95% CI 0.73-0.85) → Benefit per 1000 patients/3y= 36 (standard error 6) p<0.0001
			Non-fatal myocardial infarction	antiplatelet= 1.7% control= 2.3% → Benefit per 1000 patients/3y= 6 (SE 2) p= 0.0009
			Non-fatal stroke recurrence	antiplatelet= 8.3% control= 10.8% → Benefit per 1000 patients/3y= 25 (SE 5) p<0.0001
			Vascular mortality	antiplatelet= 8.0% control= 8.7% → Benefit per 1000 patients/3y= 7 (SE 4) p= 0.04
			Total mortality	antiplatelet= 11.3% control= 12.8% → Benefit per 1000 patients/3y= 15 (SE 5) p= 0.002
			Major extracranial haemorrhage (haemorrhages requiring hospital admission or blood transfusion)	antiplatelet= 0.97% control= 0.47% OR= 2.0 (95% CI not reported) → estimated excess risk of bleeding= 1-2 major extracranial bleeds/1000 patients/year
			Intracranial haemorrhage	NT

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→High quality of evidence**
OK	OK	OK	OK	

- Antiplatelet agents have been examined elaborately in patients with AF and a history of stroke/TIA. Most of the trials were done with acetylsalicylic acid, with or without other antiplatelets. Antiplatelets proved to be effective in the prevention of cardiovascular events, including myocardial infarction and stroke. Treatment of 1000 patients for 3 years can prevent 36 cardiovascular events. Mortality was also significantly lower in the groups treated with antiplatelet drugs.

GRADE: high quality of evidence

- In patients treated with antiplatelet drugs, an elevated incidence of major extracranial bleedings occurred. Treatment of 1000 patients for 1 year causes 1-2 major bleedings extra, compared to control.

4.1.2. Low dose ASA vs. placebo

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
SALT Sweden 1991 Design: RCT	n= 1.360 mean age 75 y - 27% previous TIA - 67% previous minor stroke <u>Incl</u> - 50-79 y - TIA, minor ischaemic stroke or retinal artery occlusion in previous 3 m <u>Excl</u> - potential cardiac source of emboli - pervious or planned carotid surgery - other causes of the symptoms: migraine, arteritis, haematological disorders, … - severe comorbidity - contra-indications to ASA - need for long-term treatment with antiplatelet or anticoagulant drugs	Mean 32 months	Acetylsalicylic acid (ASA) 75 mg/d vs placebo	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: /1 - FU: 99% - treatment discontinuation 20% - ITT: yes - Sponsor: Swedish National Association against Heart and Chest Diseases, Swedish Medical Research Agency
				Stroke (minor or major) or total mortality (PE)	ASA= 20% pla= 25% → **RRR= 18% (95% CI 0.67-0.99)**	
				Stroke (fatal or non-fatal)	ASA= 14% pla= 16% → NS	
				Stroke or ≥2 TIAs within 1 week necessitating change of therapy	ASA= 15% pla= 19% → **RR= 0.80 (95% CI 0.63-1.01); p=0.03**	
				AMI	ASA= 8% pla= 10% → NS	
				First event of stroke, AMI and vascular mortality	RR= 0.83 (95% CI 0.70-1.00) in favour of ASA	
				Harms		
				Bleeding outcomes		
				Haemorrhagic stroke	ASA= 22% pla= 18% → SS; p= 0.02	
				Any bleeding	ASA= 7.2% pla= 3.2% → SS; p= 0.001	
				Severe bleeding	ASA= 3% pla= 1.3% → SS; p= 0.04	
				AE's		
				Any adverse event	ASA= 4.6% pla= 6.1% NT	

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Diener 1996 ESPS-2 Design: RCT P	n= 6.602 -mean age: 66.7y -mean CHADS score: NR -TTR INR: NR -6.5% AF <u>Incl</u> -TIA or stroke in preceding 3m <u>Excl</u> -gastrointestinal bleeding or peptic ulcer -hypersensitivity or intolerance to study medication -bleeding disturbances -any condition requiring continued use of ASA or anticoagulants -any life-threatening condition	2y	Acetylsalic ylic (ASA) 50mg vs dipyridamole (DP) 400mg vs ASA 50mg + DP 400mg vs placebo	**Efficacy**		- Jadad score: 5/5 RANDO: 2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 99% - ITT: yes -comparison ASA vs DP: NT - Sponsor: Boehringer Ingelheim
				Stroke (ischemic or hemorrhagic) =PE	ASA: 12.5% DP: 12.8% ASA+DP: 9.5% Placebo: 15.8% **ASA vs pla: SS RRR=18.1% (p=0.013)** **DP vs pla: SS RRR=16.3% (p=0.039)** **ASA+DP vs pla: SS RRR=37% (p<0.001)** **ASA+DP vs ASA: SS RRR=23.1% (p=0.006)** **ASA+DP vs DP: SS RRR=24.7% (p=0.002)**	
				Mortality	ASA: 11.37% DP: 11.4% ASA+DP: 11.2% Placebo: 12.2% ASA vs pla: RRR=10.9% (p=0.204) DP vs pla: RRR=7.3% (p=0.453) ASA+DP vs pla: RRR=8.5% (p=0.324) ASA+DP vs ASA: RRR=-2.7% (p=0.777) ASA+DP vs DP: RRR=1.3% (p=0.815) ⇨ NS difference amongst the groups	
				TIA =SE	ASA: 12.5% DP: 13.2% ASA+DP: 10.4% Placebo: 16.5% **ASA vs pla: SS RRR=21.9% (p<0.01)** **DP vs pla: SS RRR=18.3% (p<0.01)** **ASA+DP vs pla: SS RRR=35.9% (p<0.001)** ASA+DP vs ASA: RRR=16.5% ASA+DP vs DP: RRR=20.1%	
				Myocardial infarction	ASA: 2.4% DP: 2.9% ASA+DP: 2.1% Placebo: 2.8% ASA vs pla: 13.2% DP vs pla: -6.2% ASA+DP vs pla: 22.3% ASA+DP vs ASA: 10.5% ASA+DP vs DP: 24.1%	

					⇨ NS difference amongst the groups	
				Harms		
				Bleeding outcomes		
				Intracranial	NR	
				Decrease in Hb ≥ 2g/dl	NR	
				Fatal bleeding	NR	
				Nonmajor clinically relevant bleeding	NR	
				GI-bleeding	NR	
				Any bleeding	ASA: 8.2% DP: 4.7% ASA+DP: 8.7% Placebo: 4.5% **Bleeding is SS more frequent in ASA and in combination ASA+DP**	
				AE's		
				Any adverse event	ASA: 60% DP: 62.5% ASA+DP: 64% Placebo: 56.6% ⇨ NS	
				Gastrointestinal event	ASA: 30.4% DP: 30.5% ASA+DP: 32.8% Placebo: 28.2% ⇨ NS	
				Headache	ASA: 33.1% DP: 37.2% ASA+DP: 38.2% Placebo: 32.4% ⇨ NS	

Remarks

The UK-TIA trial (Farrell 1991, ASA 1200 g vs ASA 300 mg vs pla) is not included in this analysis because of lack of separate reporting of efficacy outcomes with low-dose (300 mg/d) aspirin.

4.1.2.bis. Conclusion: Low dose ASA vs. placebo

Acetylsalicylic acid (ASA) 50-75 mg/d vs placebo (SALT 1991, Diener ESPS-2 1996)						
N/n	**Duration**	**Population**	**Results**			
N= 2, n=7.962	2-3 y	- patients with recent TIA or stroke - without atrial fibrillation - mean age 70 y	Stroke	Reported in 2/2 trials. NS in smallest trial: ASA 14% vs pla 16% SS in largest trial: ASA 12.5% vs pla 15.8% (p=0.013)		
			Mortality	Reported in 1/2 trials ASA 11.4% vs pla 12.2% NS		
			Stroke or total mortality	Reported in 1/2 trials ASA 20% vs pla 25%: SS in favour of ASA		
			Myocardial infarc tion	Reported in 2/2 trials NS		
			Hemaorrhagic stroke	Reported in 1/2 trials ASA 22% vs pla 18% SS		
			Any bleeding	Reported in 2/2 trials ASA 7-8% according to study pla 3-4% according to study SS in both trials		
			Gastrointestinal event	Reported in 1/2 trials NS		
GRADE assessment						
Quality		**Consistency**	**Directness**	**Imprecision**	**→High quality of evidence**	
OK		OK	OK	OK		

- Acetylsalicylic acid 50-75 mg/d is more efficacious than placebo for the prevention of a new stroke in patients with AF and a history of stroke. Total mortality and the incidence of AMI were unaffected by the treatment.

GRADE: high quality of evidence

- Acetylsalicylic acid was associated with a higher incidence of bleeding, compared to placebo.

4.1.3. Comparison of antiplatelet drugs

4.1.3.1.Clopidogrel or ticlopidine versus ASA

Ref	N/n	Comparison	Outcomes	
			Efficacy in previous TIA/stroke patients	
Sudlow 2009 (Cochrane)* Design: meta-analysis Search date: 12 July 2009	N=5 N=11978 (N= 10, n= 26865 in entire meta-analysis)	thienopyridine vs acetylsalicylic acid ticlopidine 500 mg/d (N=4) clopidogrel 75 mg/d (N=1) ASA 100-13600 mg/d	Stroke, MI or vascular death	Reported in 4/5 studies, 11649 participants OR=0.94 (95% CI: 0.85-1.03) ⇨ NS
			Ischemic/unknown stroke	Reported in 3/5 studies, 9829 participants **OR=0.85 (95% CI: 0.75-0.97)** ⇨ **SS in favour of thienopyridines**
			Hemorrhagic stroke	Reported in 3/5 studies, 9829 participants OR=0.96 (95% CI: 0.60-1.55) ⇨ NS
			All strokes	Reported in 5/5 studies, 11978 participants OR=0.94 (95% CI: 0.85-1.03 ⇨ NS
			Harms in all high vascular risk patients	
			Mortality (death from any cause)	OR=0.96 (95%CI:0.87-1.06) ⇨ NS
			Intracranial bleeding (symptomatic)	OR=0.89 (95%CI:0.59-1.35) ⇨ NS
			Extracranial bleeding	OR=1.00 (95%CI:0.91-1.09) ⇨ NS
			Gastrointestinal bleeding	**OR=0.71 (95%CI:0.59-0.86)** ⇨ **SS in favour of thienopyridine**
			Indigestion/nausea/vomiting	**OR=0.84 (95%CI:0.78-0.90)** ⇨ **SS in favour of thienopyridine**
			Neutropenia	**OR=1.61 (95%CI:1.01-2.55)** ⇨ **SS in favour of acetylsalicylic acid**
			Thrombocytopenia	OR=1.04 (95%CI:0.0.61-1.76) ⇨ NS
			Skin rash	**OR=1.47 (95%CI:1.32-1.64)** ⇨ **SS in favour of acetylsalicylic acid**
			Diarrhoea	**OR=1.63 (95%CI:1.45-1.83)** ⇨ **SS in favour of acetylsalicylic acid**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
AAASPS Gorelick 2003 RCT	1809	-patients with non-cardioembolic ischemia stroke (within 3m) -mean age: 61y -47% male -100% black -TIA excluded	19m	Ticlopidine 2x250mg vs ASA 2x325mg	- Jadad score: 5/5 - FU: 86% - ITT: NR
CAPRIE 1996 RCT	6431 (19185 total)	-patients with recent ischemic stroke (within 6m), MI (<35d) or atherosclerotic peripheral arterial disease	23m	Clopidogrel 75mg Vs ASA 325mg	- Jadad score: 5/5 - FU: 99% - ITT: yes
Japanese-B Toghi 1987 RCT	340	-patients with recent TIA (within 3m) -in Japan	17m	Ticlopidine 2x100mg Vs ASA 500mg	- Jadad score:3/5 - FU: 50% - ITT: NR
Li 2000 RCT	165 (329 total)	-patients with high vascular risk -in China	6-18m	Ticlopidine 500mg Vs ASA 100mg	- Jadad score: 2/5 - FU: 91% - ITT: no
TASS Hass 1989 RCT	3069	-patients with previous TIA, RIND or minor ischemic stroke due to presumed atherothromboembolism (mean time from event to treatment: 21d) -mean age: 63y -64% male -80% white	24-72m (mean: 40m)	Ticlopidine 2x250mg Vs ASA 2x650mg	- Jadad score: 4/5 - FU: 97% - ITT: NR

Remarks

- This meta-analysis compared thienopyridine derivatives with acetylsalicylic acid for preventing stroke and other serious vascular events in high vascular risk patients. We are interested in the subgroup of patients who had previous TIA or ischemic stroke. For this purpose, we only include the following trials: AAASPS, CAPRIE, TASS, Japanese-B and Li 2000.
- The results of this subgroup are similar to the overall results on each outcome for all high vascular risk patients.
- This meta-analysis does not distinguish between different types of thienopyridine derivatives; only for some adverse effects (neturopenia, thrombocytopenia, skin rash, diarrhea) in high risk vascular patients the thienopyridine subgroups (ticlopidine and clopidogrel) are reported separately.

4.1.3.1.bis. Conclusion: Clopidogrel or ticlopidine vs. ASA

Thienopyridine derivatives (ticlopidine, clopidogrel) vs acetylsalicylic acid (Gorelick 2003, Li 2000, CAPRIE 1996, Hass 1989, Toghi 1987)				
N/n	**Duration**	**Population**	**Results**	
N= 5 n= 11978	Mean 1.5y per patient	-recent ischemic stroke -recent TIA or RIND = high vascular risk	All strokes (ischemic and hemorrhagic)	Reported in 5/5 studies, 11978 participants OR=0.94 (95% CI: 0.85-1.03 ⇨ NS
			Ischemic/ unknown stroke	Reported in 3/5 studies, 9829 participants **OR=0.85 (95% CI: 0.75-0.97)** ⇨ **SS in favour of thienopyridines**
			Hemorrhagic stroke	Reported in 3/5 studies, 9829 participants OR=0.96 (95% CI: 0.60-1.55) ⇨ NS (
			Stroke, MI or vascular death	Reported in 4/5 studies, 11649 participants OR=0.94 (95% CI: 0.85-1.03) ⇨ NS

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	→ **Moderate quality of evidence**
OK	-1	OK	OK	

- Thienopyridines are statistically significantly better than acetylsalicylic acid for the prevention of ischemic stroke in patients with a previous stroke or TIA; although the clinical benefit is rather limited. No difference was found between both groups as to the prevention of hemorrhagic stroke. For the total stroke incidence and the composite endpoint of stroke, AMI or vascular mortality, no significant difference was found between thienopyridines and ASA in secondary prevention

GRADE: moderate quality of evidence

- This meta-analysis reports no information on adverse events.

4.1.3.2. Clopidogrel vs. ASA

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
CAPRIE 1996 Design: RCT P	n= 6431 (n total= 19185) -mean age subgroup: 64.6y -63.5% male in subgroup -mean CHADS score: NR -TTR INR: NR <u>Incl</u> -focal neurological deficit likely to be of atherothrombotic origin -onset ≥1w and ≤6m before randomisation -neurological signs persisting ≥1w from stroke onset <u>Excl</u> -age <21y -carotid endarterectomy after stroke -limited life expectancy -uncontrolled hypertension -contraindications to study drugs	1-3y (mean: 1.91y)	clopidogrel 75mg vs aspirin 325mg	**Efficacy subgroup stroke**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 99% - ITT: yes - Other important methodological remarks? ° We only studied subgroup stroke/TIA in this summary; CAPRIE trial also included other subgroups: MI, atherosclerotic peripheral arterial disease °CAPRIE was powered to detect a realistic treatment effect in the whole study cohort but not in each of the three clinical subgroups ((°Some patients in subgroup had AF (4 in each treatment group))) - Sponsor: Sanofi, Bristol-Myers Squibb
				Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	5.20% per year clopidogrel vs 5.65% per year ASA	
				Ischemic stroke	NR	
				Hemorrhagic stroke	NR	
				Myocardial infarction	0.73% per year clopidogrel vs 0.85% per year ASA	
				Other vascular death	1.22% per year clopidogrel vs 1.20% per year ASA	
				Mortality (fatal stroke, fatal MI, other vascular death)	1.68% per year clopidogrel vs 1.70% per year ASA	
				Stroke, MI, other vascular death	7.15% per year clopidogrel vs 7.71% per year ASA => RR=7.3% per year (95% CI: -5.7-18.7) p=0.26	
				Harms CAPRIE		
				Bleeding outcomes		
				Intracranial	0.35% clopidogrel vs 0.49% ASA (p≥0.05)	
				Any bleeding	9.27% clopidogrel vs 9.28% ASA (p≥0.05)	
				Decrease in Hb ≥ 2g/dl	NR	
				Fatal bleeding	NR	
				Nonmajor clinically relevant bleeding	NR	
				GI-bleeding	**1.99% clopidogrel vs 2.66% ASA (p<0.05)**	
				AE's		
				Rash	**6.02% clopidogrel vs 4.61% ASA (p<0.05)**	
				Diarrhea	**4.46% clopidogrel vs 3.36% ASA (p<0.05)**	
				Indigestion/nausea/ vomiting	**15.01% clopidogrel vs 17.59% ASA (p<0.05)**	
				Abnormal liver function	**2.97% clopidogrel vs 3.15% ASA (p<0.05)**	

Conclusion:

Recurrent stroke and stroke deaths were most common within the stroke subgroup. For patients with stroke, the average event rate per year in the clopidogrel group was 7.15% compared with 7.71% in the aspirin group, a relative-risk reduction of 7.3% (-5.7 to 18.7) in favour of clopidogrel (p=0.26)

4.1.3.2.bis. Conclusion: Clopidogrel vs. ASA

Clopidogrel 75 mg/d vs acetylsalicylic acid 325 mg/d (CAPRIE 1996)				
N/n	**Duration**	**Population**	**Results**	
N=1 n= 6431 subgroup with recent ischaemic stroke	1-3y (mean: 1.91y)	-focal neurological deficit likely to be of atherothrombotic origin -onset ≥1w and ≤6m before randomisation -neurological signs persisting ≥1w from stroke onset -mean age subgroup: 64.6y -63.5% male in subgroup	Stroke, MI, other vascular death (PE)	7.15% per year clopidogrel vs 7.71% per year ASA NS
			Ischemic stroke	NR
			Hemorrhagic stroke	NR
			Myocardial infarction	0.73% per year clopidogrel vs 0.85% per year ASA NS
			Other vascular death	1.22% per year clopidogrel vs 1.20% per year ASA NS
			Mortality (fatal stroke, fatal MI, other vascular death)	1.68% per year clopidogrel vs 1.70% per year ASA
			Stroke (ischemic or hemorrhagic)	5.20% per year clopidogrel vs 5.65% per year ASA NS
GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
-1 for subgroup analysis	NA	OK	OK	

- This conclusion is based on the results of the CAPRIE-trial. This trial included 19.185 patients with recent ischemic stroke, recent myocardial infarction or symptomatic peripheral arterial disease. In the global study population, a limited benefit was found for clopidogrel 75 mg/d compared to ASA 325 mg/d for the composite endpoint ischemic stroke, AMI or vascular mortality (5.32% events/y vs. 5.83% events/y).
In the subgroup of 6.431 patients with recent ischemic stroke, clopidogrel was not superior to ASA, neither for the primary composite endpoint nor for the secondary singular endpoints.

GRADE: moderate quality of evidence

- Information on adverse avents is only available for the total study population with elevated cardiovascular risk. ASA did not cause more bleedings than clopidogrel, with the exception of gastro-intestinal bleeding. Clopidogrel was associated with an elevated incidence of rash and diarrhea. Nausea and abnormal liver function tests occurred more frequently with clopidigrel.

4.1.3.3. Clopidogrel plus ASA vs. clopidogrel

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Diener 2004 Design: RCT	n= 7599 -mean age: 66 <u>Inclusion</u> -Ischaemic stroke (79%) or TIA (21%) ≤3months -at least 1 additional risk factors ≤ 3years (previous ischemic stroke, previous myocardial infarction, angina pectoris, diabetes mellitus or symptomatic peripheral arterial disease) <u>Exclusion</u> -age <40 -increased bleeding risk -severe comorbid conditions -CI for aspirin or clopidogrel	1,5y	Aspirin 75mg + clopidogrel 75mg vs placebo+ clopidogrel 75mg	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION:1 /1 - FU: 96% - ITT: yes - Other important methodological remarks? - - Sponsor: Sanofi-Synthelabo Research and Bristol Myers Squibb
				Ischaemic stroke or Myocardial infarction or vascular death or rehospitalisation for acute ischaemia (PE)	Aspirin+clopidogrel 15.7% vs 16.7% clopidogrel NS: ARR= 1.0% (95% CI -0.6 to 2.7) RRR = 6.4% (95% CI -4.6 to 16.3) p=0.244	
				Stroke (any)	Aspirin+clopidogrel 9% vs 9% clopidogrel NS: ARR= 0.2% (95% CI -1.1 to 1.5)RRR = 2.0% (95% CI -13.8 to 15.6) p=0.790	
				Ischemic stroke	Aspirin+clopidogrel 8% vs 9% clopidogrel NS: ARR= 0.62% (95% CI -0.6 to 1.9) RRR = 7.1% (95% CI -8.5 to 20.4) p=0.353	
				Vascular death	Aspirin+clopidogrel 3% vs 3% clopidogrel NS: ARR= -0.08% (95% CI -0.9 to 0.7) RRR = -2.4% (95% CI -31.5 to 20.3) p=0.854	
				Death (all causes)	Aspirin+clopidogrel 5% vs 5% clopidogrel NS: ARR= -0.01% (95% CI -1.0 to 1.0) RRR = 0.1% (95% CI -21.5 to 17.8) p=0.992	
				Myocardial infarction	Aspirin+clopidogrel 2% vs 2% clopidogrelNS: ARR= -0.13% (95% CI -0.7 to 0.5) RRR = -7.7% (95% CI -49.8 to 22.6) p=0.660	
				Harms		
				Bleeding outcomes (safety evaluation on the treated population) % of patients with bleeding events		
				Primary intracranial haemorrhage	Aspirin+clopidogrel 3% vs 1% clopidogrel **SS**: ARR = 0.4% (95% CI 0.04 to 0.76) p<0.029 (graphic representation)	

				Life –threatening bleeding	Aspirin+clopidogrel 3% vs 1% clopidogrel **SS**: ARR = 1.26% (95% CI 0.64 to 1.88) p<0.0001	
				Major bleeding	Aspirin+clopidogrel 2% vs 1% clopidogrel **SS**: ARR = 1.36% (95% CI 0.86 to 1.86) p<0.0001	
				Fatal bleeding	Aspirin+clopidogrel 0.4% vs 0.3% clopidogrel NS: ARR = 0.13% (95% CI -0.14 to 0.40)	
				Nonmajor clinically relevant bleeding (minor)	Aspirin+clopidogrel 3% vs 1% clopidogrel **SS**: ARR = 2.16% (95% CI 1.51 to 2.81) p<0.0001	
				GI-bleeding	Aspirin+clopidogrel 1.4% vs 0.6% clopidogrel NT	
				AE's		

Life –threatening bleeding defined as any fatal bleeding event, drop in Hb of ≥50g/L; significant hypotension with need for inotropes, symptomatic intracranial haemorrhage, or transfusion of ≥4 units of red-blood cells.
Major bleeding defined as significantly disabling, intraocular bleeding leading to significant loss of vision; or transfusion of ≥3 units of red-blood cells.

4.1.3.3.bis. Conclusion: Clopidogrel plus ASA vs. clopidogrel

<table>
<tr><td colspan="6">Clopidogrel 75 mg/d + acetylsalicylic acid 75 mg/d vs clopidogrel 75 mg/d (Diener 2004)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="11">N=1, n= 7599</td><td rowspan="11">1.5 y</td><td rowspan="11">-Ischaemic stroke (79%) or TIA (21%) ≤3months

-at least 1 additional risk factor

- mean age 66 y</td><td colspan="3">Efficacy</td></tr>
<tr><td>Ischaemic stroke or Myocardial infarction or vascular death or rehospitalisation for acute ischaemia (PE)</td><td colspan="2">Aspirin+clopidogrel 15.7% vs 16.7% clopidogrel
NS:
ARR= 1.0% (95% CI -0.6 to 2.7)
RRR = 6.4% (95% CI -4.6 to 16.3) p=0.244</td></tr>
<tr><td>Stroke (any)</td><td colspan="2">NS</td></tr>
<tr><td>Ischemic stroke</td><td colspan="2">NS</td></tr>
<tr><td>Vascular mortality</td><td colspan="2">NS</td></tr>
<tr><td>Total mortality</td><td colspan="2">NS</td></tr>
<tr><td>Myocardial infarction</td><td colspan="2">NS</td></tr>
<tr><td colspan="3">Harms</td></tr>
<tr><td>Primary intracranial haemorrhage</td><td colspan="2">Aspirin+clopidogrel 3% vs 1% clopidogrel
SS: ARR = 0.4% (95% CI 0.04 to 0.76) p<0.029</td></tr>
<tr><td>Life –threatening bleeding</td><td colspan="2">Aspirin+clopidogrel 3% vs 1% clopidogrel
SS: ARR = 1.26% (95% CI 0.64 to 1.88) p<0.0001</td></tr>
<tr><td>Major bleeding</td><td colspan="2">Aspirin+clopidogrel 2% vs 1% clopidogrel
SS: ARR = 1.36% (95% CI 0.86 to 1.86) p<0.0001</td></tr>
<tr><td>Minor bleeding</td><td colspan="2">Aspirin+clopidogrel 3% vs 1% clopidogrel
SS: ARR = 2.16% (95% CI 1.51 to 2.81) p<0.0001</td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><td>Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td colspan="2">→High quality of evidence</td></tr>
<tr><td>OK</td><td>OK</td><td>OK</td><td>OK</td><td colspan="2"></td></tr>
</table>

- In patients with recent ischemic stroke or TIA, and with elevated cardiovascular risk, the association of ASA 75 mg/d to a treatment with clopidogrel 75 mg/d does not lead to an decrease in cardiovascular events, compared to monotherapy with clopodogrel. Neither for the composite primary endpoint (ischemic stroke, AMI, vascular mortality or rehospitalisation for acute ischaemia), nor for the separate endpoints, significant differences were found between both groups.

GRADE: high quality of evidence

- In patients treated with the association of ASA and clopidogrel, an elevated incidence of major and major bleedings and intracranial bleedings was found.

4.1.3.4. Dipyridamole plus ASA vs. ASA

Ref	N/n	Comparison	Outcomes	
*Verro 2008 Design: meta-analysis Search date: 2006	N= 6 n= 7.649	ASA (50-1300 mg) vs. ASA (50-1300 mg) + dipyridamole (150-400 mg) in patients with a history of non cardioembolic TIA or stroke	non-fatal stroke (both ischemic and hemorrhagic)	ASA= 9.9% ASA+DP= 7.6% **RR= 0.77 (95% CI 0.67-0.89) SS**
			combined vascular events (non-fatal stroke, non-fatal AMI and vascular mortality)	ASA= 16.7% ASA+DP= 14.2% **RR= 0.85 (95% CI 0.76-0.94) SS**
			adverse events	NR
		prespecified subset analysis: trials using exclusively immediate-release dipyridamole (N=4)	non-fatal stroke (both ischemic and hemorrhagic)	RR= 0.83 (95% CI 0.59-1.15) NS
			combined vascular events (non-fatal stroke, non-fatal AMI and vascular mortality)	RR= 0.95 (95% CI 0.75-1.19) NS
		prespecified subset analysis: trials using exclusively extended-release dipyridamole (N=2: ESPS-2 and ESPRIT)	non-fatal stroke (both ischemic and hemorrhagic)	**RR= 0.76 (95% CI 0.65-0.89) SS**
			combined vascular events (non-fatal stroke, non-fatal AMI and vascular mortality)	**RR= 0.82 (95% CI 0.73-0.92) SS**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Caneschi 1985 RCT	36	- patients with a history of stroke or TIA	2-3 y	ASA 150 mg/d vs. ASA 150 mg + IR-DP 225 mg/d	- Jadad score: 2/5 - FU: NR - ITT: NR
Guiraud-Chaumeil 1982 RCT	285	- patients with a history of stroke or TIA	3 y	ASA 990 mg/d vs. ASA 990 mg + IR-DP 150 mg/d	- Jadad score: 3/5 - FU: NR - ITT: NR
AICLA Bousser 1983 RCT	400	- patients with a history of stroke or TIA in the preceding year - mostly 65-75 y - 70% male	3 y	ASA 990 mg/d vs. ASA 990 mg + IR-DP 225 mg/d	- Jadad score: 5/5 - FU: 59% - ITT: yes
ACCSG 1985 RCT	890	- patients with a history of recent carotid territory TIA - 94% TIA in previous 3 m - mean age 63 y - 67% male	median 25 m	ASA 1300mg/d vs. ASA 1300 mg + IR-DP 300 mg/d	- Jadad score: 5/5 - FU: 96% - ITT: 'modified' ITT - 43% stopped the medication before completion of the trial
ESPS-2 1996 RCT	3.299	- patients with a history of stroke or TIA in the preceding 3 m - mean age 67 y	2 y	ASA 50 mg/d vs. ASA 50 mg + ER-DP 400 mg/d	- Jadad score: 5/5 - FU: 99% - ITT: yes
ESPRIT 2006 RCT	2.763	- patients with a history of stroke or TIA - 28% TIA, 66% minor ischaemic stroke, 6% transient monocular blindness - mean age 63 y	3.5 y	ASA 75 mg/d vs. ASA 75 mg + DP 400 mg/d (mostly ER)	- Jadad score: 3/5 - FU: 71% - ITT: yes

ASA= acetyl salicylic acid; DP= dipyridamole; IR= immediate- release; ER= extended-release

Remarks

This meta-analysis reports no information on adverse events. For information on harms: see elaborate discussion of ESPS-2 and ESPRIT trials below.

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Uchiyama 2011 (JASAP) Design: RCT, P	- n= 1.294 japanese patients - mean age : 66 -TTR INR: % NA <u>Inclusion</u> -age ≥ 50 -ischemic stroke in the previous 6 months (diagnostic criteria of cerebrovascular disease III) -at least 2 of the following risk factors: diabetes, hypertension, smoking, BMI>25, previous vascular disease, end organ damage, hyperlipidemia <u>Exclusion:</u> -brain disorders with bleeding risk -cardiogenic cerebral embolism -acute coronary syndromes <6 months - peptic ulcer <3 years -“post stroke” arterial	mean: 1.3y	Extended-Release dipyridamole (ER-DP) 200 mg plus ASA 25mg 2x/d vs ASA 81 mg 1x/d	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 70.1% - ITT: not for PE - Other important methodological remarks? non-inferiority trial - Sponsor: Boehringer Ingelheim
				Recurrent ischemic stroke (fatal or nonfatal) (PE)	ER-DP plus ASA 6.9% vs 5% ASA NS for non-inferiority: HR = 1.47 (95% CI 0.93 - 2.31)	
				Stroke (ischemic stroke, cerebral hemorrhage or subarachnoid hemorrhage)	ER-DP plus ASA 8.7% vs 6.1% ASA SS for non-inferiority: HR = 1.52 (95% CI 1.01 - 2.29)	
				TIA	ER-DP plus ASA 0.5% vs 0.5% ASA NS for non-inferiority: HR = 1.02 (95% CI 0.21 - 5.07)	
				Ischemic vascular composite end point (Ischemic stroke, TIA, myocardial infarction, unstable angina, or sudden death attributable to thromboembolism)	ER-DP plus ASA 8.7% vs 8.0% ASA NS for non-inferiority: HR = 1.16 (95% CI 0.79 – 1.69)	
				Acute coronary syndromes (acute myocardial infarction, unstable angina, sudden cardiac death)	ER-DP plus ASA 1.4% vs 2.5% ASA NS for non-inferiority: HR = 0.58 (95% CI 0.26 – 1.31)	
				Other vascular events (pulmonary embolism, retinal vascular disorder, deep vein thrombosis, peripheral artery obstruction, vascular interventions like percutaneous coronary intervention	ER-DP plus ASA 1.7% vs 0.9% ASA NS for non-inferiority: HR = 1.88 (95% CI 0.69 - 5.07)	
				Harms		
				Bleeding outcomes		
				Any bleeding	NR	
				Decrease in Hb ≥ 2g/dl	NR	
				Fatal bleeding	ER-DP plus ASA 0% vs 0.3% ASA NS for non-inferiority p= 0,2437	
				Nonmajor clinically	ER-DP plus ASA 25.3% vs 25.5% ASA	

	reconstruction -bleeding or bleeding tendencies -severe hypertension (SBP≥180 or DBP≥120)			relevant bleeding	NS for non-inferiority p= 0,9492	
				GI-bleeding		
				Major bleeding	ER-DP plus ASA 4% vs 3.8% ASA NS p= 0,8859	
				AE's		
				Total number with adverse events: ER-DP plus ASA 97.7% vs 95.6% ASA SS for non-inferiority p=0.0431 **Mortality** ER-DP plus ASA 0.6% vs 1.6% ASA NS for non-inferiority p= 0,1125 **Headache** ER-DP plus ASA 44.7% vs 29.3% ASA SS for non-inferiority p<0.0001	

Major bleed: defined as at least 1 of the following: fatal hemorrhage; retroperitoneal hemorrhage, intracranial hemorrhage, intraocular hemorrhage or spinal/intraspinal hemorrhages; bleedings requiring surgery; clinically obvious bleeding requiring≥ 4.5 units of blood transfusion or accompanied by a ≥2g/dl decrease in hemoglobin level.

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
ESPRIT 2006 Design: RCT	n= 2.763 -mean age : 63 -Qualifying event: ±28% TIA, ± 66% minor ischaemic stroke, ± 6% transient monocular blindness -TTR INR: % NA <u>Inclusion</u> -TIA or minor ischaemic stroke (grade ≤3 on modified Rankin scale) of presumed arterial origin -Transient monocular blindness <u>Exclusion</u> -possible cardiac source of embolism, -cerebral ischaemia associated with high-grade carotid stenosis, -any blood coagulation disorder, -any contraindication for aspirin or dipyridamole, -limited life expectancy -age>75 years -leukoaraiosis	Mean follow-up: 3.5y	Acetylsalicylic acid (ASA) (30-325mg, median 75 mg, 50% ≤50 mg)) + dipyridamole (2x200mg) vs ASA (30-325mg)	**Efficacy**		- Jadad score 3/5 RANDO: 2/2 BLINDING: 0/2 (open label) ATTRITION:1 /1 - FU: 71% - ITT: yes - Other important methodological remarks? Auditing of outcome events blinded but not the treatment - Sponsor: Academic trial
				First event - Death from all vascular causes, non-fatal stroke, non fatal MI or major bleeding complication (PE)	**DP plus ASA 12.69% vs 15.70% ASA** **SS: HR =0.80 (95% CI 0.66 – 0.98)** **ARR= 1%/y ➔ NNT =104 per year**	
				Mortality	DP plus ASA 6.82% vs 7.78% ASA NS: HR =0.88 (95% CI 0.67 – 1.17)	
				Death from all vascular causes	DP plus ASA 3.23% vs 4.36% ASA NS: HR =0.75 (95% CI 0.51– 1.10)	
				Death from all vascular causes, non-fatal stroke	**DP plus 9.68% vs 12.43% ASA** **SS: HR =0.78 (95% CI 0.62– 0.97)**	
				Death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction	**DP plus 10.93% vs 13.95% ASA** **SS: HR =0.78 (95% CI 0.63– 0.97)**	
				All major ischaemic events: non-haemorrhagic death from vascular causes, non-fatal ischaemic stroke, non-fatal myocardial infarction	DP plus ASA 10.27% vs 12.64% ASA NS: HR =0.81 (95% CI 0.65– 1.01)	
				First event - Ischemic stroke	DP plus ASA 7.04% vs 8.43% ASA NS: HR =0.84 (95% CI 0.64 – 1.10)	
				First cardiac event	DP plus ASA 3.15% vs 4.36% ASA NS: HR =0.73 (95% CI 0.49 – 1.08)	
				Harms		
				Bleeding outcomes		
				Major bleeding complication	DP plus ASA 2.57% vs 3.85% ASA NS: HR =0.67 (95% CI 0.44 – 1.03)	
				Intracranial (fatal and non-fatal)	DP plus ASA 0.88% vs 1.53% ASA NT	

				Fatal bleeding	DP plus ASA 0.37% vs 0.29% ASA NT	
				Minor bleeding	DP plus ASA 12.55% vs 12.21% ASA NS:HR =1.03 (95% CI 0.84 – 1.25)	
				AE's		
				% of patients who discontinued treatment NT DP plus ASA 34% (mainly because of AE's – 26% for headache) vs 13% ASA (mainly because of a medical reason – new TIA, stroke…)		

The outcome event of major bleeding complication included all intracranial bleeding, any fatal bleeding, or any bleeding requiring hospital admission.

Our primary aim was to randomise patients in a three-arm randomisation scheme (anticoagulation therapy vs aspirin+dipyridamole vs aspirin), but a two-arm randomisation scheme (aspirin+dipyridamole vs aspirin) was permitted if there was a contraindication for anticoagulation therapy (age >75 years or leukoaraiosis on a brain scan), if a patient refused to participate because he or she did not want to use anticoagulation therapy, if the physician did not feel comfortable with prescribing anticoagulation therapy, or if regular assessment of INR values was impossible.

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Diener 1996 ESPS-2 Design: RCT P	n= 6.602 -mean age: 66.7y -mean CHADS score: NR -TTR INR: NR -6.5% AF <u>Incl</u> -TIA or stroke in preceding 3m <u>Excl</u> -gastrointestinal bleeding or peptic ulcer -hypersensitivity or intolerance to study medication -bleeding disturbances -any condition requiring continued use of ASA or anticoagulants -any life-threatening condition	2y	Acetylsalicyclic (ASA) 50mg vs dipyridamole (DP) 400mg vs ASA 50mg + DP 400mg vs placebo	**Efficacy**		- Jadad score: 5/5 RANDO: 2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 99% - ITT: yes -comparison ASA vs DP: NT - Sponsor: Boehringer Ingelheim
				Stroke (ischemic or hemorrhagic) =PE	ASA: 12.5% DP: 12.8% ASA+DP: 9.5% Placebo: 15.8% **ASA vs pla: SS RRR=18.1% (p=0.013)** **DP vs pla: SS RRR=16.3% (p=0.039)** **ASA+DP vs pla: SS RRR=37% (p<0.001)** **ASA+DP vs ASA: SS RRR=23.1% (p=0.006)** **ASA+DP vs DP: SS RRR=24.7% (p=0.002)**	
				Mortality	ASA: 11.37% DP: 11.4% ASA+DP: 11.2% Placebo: 12.2% ASA vs pla: RRR=10.9% (p=0.204) DP vs pla: RRR=7.3% (p=0.453) ASA+DP vs pla: RRR=8.5% (p=0.324) ASA+DP vs ASA: RRR=-2.7% (p=0.777) ASA+DP vs DP: RRR=1.3% (p=0.815) NS difference amongst the groups	
				TIA =SE	ASA: 12.5% DP: 13.2% ASA+DP: 10.4% Placebo: 16.5% **ASA vs pla: SS RRR=21.9% (p<0.01)** **DP vs pla: SS RRR=18.3% (p<0.01)** **ASA+DP vs pla: SS RRR=35.9% (p<0.001)** ASA+DP vs ASA: RRR=16.5% ASA+DP vs DP: RRR=20.1%	
				Myocardial infarction	ASA: 2.4% DP: 2.9% ASA+DP: 2.1% Placebo: 2.8% ASA vs pla: 13.2%	

					DP vs pla: -6.2% ASA+DP vs pla: 22.3% ASA+DP vs ASA: 10.5% ASA+DP vs DP: 24.1% NS difference amongst the groups	
				Harms		
				Bleeding outcomes		
				Intracranial	NR	
				Decrease in Hb ≥ 2g/dl	NR	
				Fatal bleeding	NR	
				Nonmajor clinically relevant bleeding	NR	
				GI-bleeding	NR	
				Any bleeding	ASA: 8.2% DP: 4.7% ASA+DP: 8.7% Placebo: 4.5% **Bleeding is SS more frequent in ASA and in combination ASA+DP**	
				AE's		
				Any adverse event	ASA: 60% DP: 62.5% ASA+DP: 64% Placebo: 56.6% NS	
				Gastrointestinal event	ASA: 30.4% DP: 30.5% ASA+DP: 32.8% Placebo: 28.2% NS	
				Headache	ASA: 33.1% DP: 37.2% ASA+DP: 38.2% Placebo: 32.4% NS	

4.1.3.4.bis. Conclusion: Dipyridamol plus ASA vs. ASA

<table>
<tr><td colspan="6">Acetylsalicylic acid 30-1300 mg/d + dipyridamole 150-400 mg/d vs acetylsalicylic acid 30-1300 mg/d (MA Verro 2008: Caneschi 1985, Guiraud-Chaumeil 1982, AICLA Bousser 1983, ACCSG 1985, ESPS-s 1996, ESPRIT 2006 + Uchiyama JASAP 2011)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th colspan="3">Results</th></tr>
<tr><td rowspan="9">N=7, n= 8943</td><td rowspan="9">1.3-3.5 y</td><td rowspan="9">- patients with a history of recent minor stroke or TIA
- no atrial fibrillation
- mean age 65 y</td><td colspan="3">Efficacy</td></tr>
<tr><td>Non-fatal stroke (both ischemic and hemorrhagic)</td><td colspan="2">- Reported in 6/7 trials.
- NS in 5 trials, SS in favour of association in 1 large trial (ESPS-2)
- Pooled event rate 9.9% vs. 7.6%
- Pooled RR= 0.77 (95% CI 0.67-0.89) SS in favour of association</td></tr>
<tr><td>Recurrent ischemic stroke (fatal or non fatal)</td><td colspan="2">- Reported in 1/7 trials
- Event rate 6.9% vs. 5%
- NS for non-inferiority: HR = 1.47 (95% CI 0.93 - 2.31)</td></tr>
<tr><td>TIA</td><td colspan="2">- Reported in 1/7 trials
- NS for noninferiority</td></tr>
<tr><td>Combined vascular events (definition according to trial)</td><td colspan="2">- Reported in 6/7 trials
- NS in 3 trials, SS in favour of association in 2 trials, NS for non-inferiority in 1 recent Japanese trial.
- Pooled event rates for 5 trials: 16.7% vs 14.2%
- Pooled RR for 5 trials= 0.85 (95% CI 0.76-0.94) SS in favour of association</td></tr>
<tr><td colspan="3">Harms</td></tr>
<tr><td>Any bleeding</td><td colspan="2">NS</td></tr>
<tr><td>Major bleeding</td><td colspan="2">NS</td></tr>
<tr><td>Minor bleeding</td><td colspan="2">NS</td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><td>Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td colspan="2">→Moderate quality of evidence</td></tr>
<tr><td>-1 for heterogeneity</td><td>OK</td><td>OK</td><td>OK</td><td colspan="2"></td></tr>
</table>

- The association of dipyridamole and ASA is more effective than ASA (median dosis 75 mg/d) alone for the prevention of a new stroke in patients with a history of stroke or TIA. The total incidence of cardiovascular events was also lower in the group treated with the association. For both of these outcomes, the absolute risk reduction was about 2%. These results could not be confirmed in a recent Japanese trial; in this trial no significant difference was found between the association and ASA in monotherapy (50 mg/d).

GRADE: moderate quality of evidence

- No significant differences could be found between the association and monotherapy for the total bleeding incidence.

4.1.3.5. Dipyridamole plus ASA vs. clopidogrel

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Sacco 2008 Design: RCT	n= 20.332 -mean age: 66 -mean CHADS score: NR -TTR INR (%): NA <u>Inclusion</u> -recent ischemic stroke or confirmed ischemic TIA (within <90days) - age ≥ 55 After protocol amendment: -age≥ 50 -recent ischemic stroke or confirmed ischemic TIA (within 90 to 120 days) if at least 2 additional vascular risk factors <u>Exclusion</u> -contraindications to antiplatelet agents	2,5y (mean duration of follow-up)	ASA 25mg+ER-DP 200mg 2x/d vs clopidogrel 75mg (1x/day) (and telmisartan 80mg vs placebo)	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 85.5% - ITT: yes - Other important methodological remarks: Design modified during study, underpowered - Telmisartan vs placebo: different publication - Sponsor: Boerhinger Ingelheim
				Stroke (first recurrence) (PE)	ASA+ER-DP 9.0% vs 8.8% clopidogrel NS for non-inferiority: HR = 1.1 (95% CI 0.92 to 1.11)	
				Stroke, Myocardial infarction or vascular death	ASA+ER-DP 13.1% vs 13.1% clopidogrel NS for non-inferiority: HR = 0.99 (95% CI 0.92 to 1.07)	
				Ischemic stroke (first)	ASA+ER-DP 7.7% vs 7.9% clopidogrel NS for non-inferiority: HR = 0.97 (95% CI 0.88 to 1.07)	
				Mortality (any cause)	ASA+ER-DP 7.3% vs 7.4% clopidogrel NS for non-inferiority: HR = 0.97 (95% CI 0.87 to 1.07)	
				Mortality (vascular causes)	ASA+ER-DP 4.3% vs 4.5% clopidogrel NS for non-inferiority: HR = 0.94 (95% CI 0.82 to 1.07)	
				Myocardial infarction	ASA+ER-DP 1.7% vs 1.9% clopidogrel NS for non-inferiority: HR = 0.90 (95% CI 0.73 to 1.10)	
				Congestive heart failure (new or worsening)	**ASA+ER-DP 1.4% vs 1.8% clopidogrel** **SS** for non-inferiority**: HR = 0.78 (95% CI 0.62 to 0.96) p=0.02**	
				Other vascular events	ASA+ER-DP 5.2% vs 5.1% clopidogrel NS for non-inferiority: HR = 1.03 (95% CI 0.91 to 1.16)	
				First recurrence of stroke or major hemorrhagic event	ASA+ER-DP 11.7% vs 11.4% clopidogrel NS for non-inferiority: HR = 1.03 (95% CI 0.95 to 1.11)	
				Harms		
				Bleeding outcomes		
				Intracranial	**ASA+ER-DP 1.4% vs 1.0% clopidogrel** **SS** for non-inferiority**: HR = 1.42 (95% CI 1.11 to 1.83) p=0.006**	

				Any bleeding	ASA+ER-DP 5.3% vs 4.9% clopidogrel NS for non-inferiority: HR = 1.08 (95% CI 0.96 to 1.22)	
				Major hemorrhagic event	ASA+ER-DP 4.1% vs 3.6% clopidogrel NS for non-inferiority : HR = 1.15 (95% CI 1.00 to 1.32)	
				Life threatening hemorrhagic event	ASA+ER-DP 1.3% vs 1.1% clopidogrel (NT)	
				Non-life-threatening hemorrhagic event	ASA+ER-DP 2.9% vs 2.5% clopidogrel (NT)	
				Thrombocytopenia or neutropenia	ASA+ER-DP 0.1% vs 0.1% clopidogrel NS for non-inferiority: HR = 0.89 (95% CI 0.32 to 2.44)	
				AE's		
				Patients with AE's leading to discontinuation: ASA+ER-DP 16.4% vs 10.6% clopidogrel (NT) **Headache** ASA+ER-DP 5.9% vs 0.9% clopidogrel (NT)		

Major hemorrhagic event was defined as a hemorrhagic event that resulted in clinically significant disability, symptomatic intracranial hemorrhage, intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or the equivalent amount of whole blood, or the need for hospitalization.
Life-threatening hemorrhagic events were defined as those that were fatal or that required use of inotropic medication to maintain blood pressure, surgical intervention, or transfusion of 4 or more units of red cells or the equivalent amount of whole blood.
Non–life-threatening hemorrhagic events were defined as those classified as major hemorrhagic events but not as life-threatening

4.1.3.5.bis. Conclusion: Dipyridamole plus ASA vs. clopidogrel

2x/d (dipyridamole extended-release 200 mg+ acetylsalicylic acid 25 mg) vs clopidogrel 75 mg/d (Sacco 2008)				
N/n	**Duration**	**Population**	**Results**	
N=1 n=20.332	2.5y (mean)	-recent ischemic stroke or TIA (<120 days) -mean age: 66 -2.6% congestive heart failure	Stroke	ASA+ER-DP 9.0% vs 8.8% clopidogrel NS for non-inferiority:
			Ischemic stroke	ASA+ER-DP 7.7% vs 7.9% clopidogrel NS for non-inferiority
			Myocardial infarction	ASA+ER-DP 1.7% vs 1.9% clopidogrel NS for non-inferiority
			Congestive heart failure (CHF new or worsening)	**ASA+ER-DP 1.4% vs 1.8% clopidogrel** **SS** for non-inferiority**: HR = 0.78 (95% CI 0.62 to 0.96) p=0.02**
			Intracranial	**ASA+ER-DP 1.4% vs 1.0% clopidogrel** **SS** for non-inferiority**: HR = 1.42 (95% CI 1.11 to 1.83) p=0.006**
			Major hemorrhagic event	ASA+ER-DP 4.1% vs 3.6% clopidogrel NS for non-inferiority
			Stroke, Myocardial infarction or vascular death	ASA+ER-DP 13.1% vs 13.1% clopidogrel NS for non-inferiority
			Mortality (vascular causes)	ASA+ER-DP 4.3% vs 4.5% clopidogrel NS for non-inferiority
			Mortality (any cause)	ASA+ER-DP 7.3% vs 7.4% clopidogrel NS for non-inferiority

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→ Moderate quality of evidence**
-1 for modification of design during study	NA	OK	OK	

- The association of dipyridamole and ASA is not superior to clopidogrel for the prevention of strokes (total and ischemic) and myocardial infarctions in patients with a recent history of stroke or TIA. No statistical differences were found between both treatments, neither for total or vascular mortality nor for the composite endpoint of stroke, AMI and/or vascular mortality. The incidence of cardiac failure was slightly, but significantly, elevated in the group treated with clopidigrel.

GRADE: moderate quality of evidence

- No signifcant differences were found between both treatment groups as to major bleedings. Although, in patients treated with the association of dipyridamole and ASA, the indicence of intracranial bleedings was significantly higher compared to clopidigrel.

4.1.3.6. Clopidogrel vs. ticlopidine

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Uchiyama 2009 Design: RCT	n= 1.869 Japanese patients Phase IIIa: n=714 Phase IIIb: n= 1155 -mean age : 65 -TTR INR: NA <u>Inclusion criteria</u> - age: 20–80 y - previous stroke > 8 days (confirmed by CT or MRI; non cardiogenic) <u>Exclusion criteria</u> - TIA since the most recent stroke - Serious impairment that would hinder detection of recurrent stroke - Bleeding disorders, risk of bleeding, or history of intracranial hemorrhage - Severe renal, hepatic or heart disease - Uncontrolled hypertension -Diabetic retinopathy (Phase IIIb only) -History of elevated liver tests	Phase IIIa: 0.5y Phase IIIb: 1y	Clopidogrel 75mg/d vs Ticlopidine 200mg/d	**Efficacy (n=1862)**		- Jadad score 5/5 RANDO: 2/2 BLINDING: /22 ATTRITION:1/1 - FU: 70% - ITT: yes - Other important methodological remarks: - Combined analysis of 2 Phase III studies - Primary endpoint = safety; but no statistical test on bleeding parameters - Sponsor: Sanofi-Aventis
				Cerebral infarction, Myocardial infarction, Vascular death (SE)	2.6% Clopidogrel vs Ticlopidine 2.5% NS: HR = 0.918 (95% CI 0.518 to 1.626) p=0.769	
				Cerebral infarction	2.6% Clopidogrel vs Ticlopidine 2.5% NT	
				Other vascular event	1.1% Clopidogrel vs Ticlopidine 1.2% NT	
				All vascular events	3.6% Clopidogrel vs Ticlopidine 3.7% NS: HR = 0.88 (95% CI 0.55 to 1.41) p=0.591	
				Safety (n=1869)		
				Symptoms considered to be study-related and abnormal laboratory changes (PE)	**35.0% Clopidogrel vs Ticlopidine 48.7%** **SS: HR = 0.610 (95% CI 0.529 to 0.703) p<0.001**	
				Hepatic dysfunction	**13.4% Clopidogrel vs Ticlopidine 25.6%** **SS: HR = 0.455 (95% CI 0.367to 0.565) p<0.001**	
				Leukopenia	**1.8% Clopidogrel vs Ticlopidine 4.5%** **SS: HR = 0.402(95% CI 0.231to 0.700) p<0.001**	
				Neutropenia	**0.6% Clopidogrel vs Ticlopidine 2.4%** **SS: HR = 0.082 (95% CI 0.082to 0.575) p<0.001**	
				Skin and subcutaneous disorders	**More frequent in ticlopidine group (graphic representation) p<0.05**	
				Gastrointestinal disorders	**More frequent in ticlopidine group (graphic representation) p<0.05**	
				Major hemorrhage	No significant difference in the frequency (graphic representation)	
				Deaths	0.2% Clopidogrel vs Ticlopidine 0.2% NT	
				AE's		
				Discontinuation for AE's: 14.2% Clopidogrel vs Ticlopidine 19.9% NT		

4.1.3.6.bis. Conclusion: Clopidogrel vs. ticlopidine

Clopidogrel 75 mg/d vs ticlopidine 200 mg/d (Uchiyama 2009)				
N/n	**Duration**	**Population**	**Results**	
N=1 (2 phases) n=1869 Japanese	Phase IIIa: 0.5y Phase IIIb: 1y	-previous stroke (>8 days) -mean age: 65	Cerebral infarction	2.6% clopidogrel vs ticlopidine 2.5% NT
			Other vascular event	1.1% clopidogrel vs ticlopidine 1.2% NT
			Major hemorrhage	No significant difference in the frequency (graphic representation)
			Cerebral infarction, Myocardial infarction, Vascular death	2.6% clopidogrel vs ticlopidine 2.5% NS
			Deaths	0.2% clopidogrel vs ticlopidine 0.2% NT
			Symptoms considered to be study-related and abnormal laboratory changes (PE)	**35.0% clopidogrel vs ticlopidine 48.7% SS: HR = 0.610 (95% CI 0.529 to 0.703) p<0.001**
			Hepatic dysfunction	**13.4% clopidogrel vs ticlopidine 25.6% SS: HR = 0.455 (95% CI 0.367to 0.565) p<0.001**

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→ Moderate quality of evidence**
OK	NA	-1 (limited clinical outcomes)	OK	

- In patients with previous stroke, no statistically significant differences could be found between clopidogrel and ticlopidine as to the incidence of stroke, other cardiovascular events and mortality.

GRADE: moderate quality of evidence

- The incidence of major bleedings was not significantly different between both treatment groups. In patients treated with ticlopidine, more adverse events were reported: abnormal blood results (neutropenia, leukopenia, thrombocytopenia) and hepatic dysfunction.

4.1.4. Dose comparison: high- vs. low dose ASA

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Dutch TIA 1991 Design: RCT	n= 3.131 - mean age: NR 53% > 65 y - prior TIA: 32% - prior minor ischemic stroke: 68% <u>Incl</u> - TIA or minor ischemic stroke in previous 3 m <u>Excl</u> - contraindications to ASA - cerebral ischemia due to other causes: AF, cardiac valve disease, AMI, disorders of blood coagulation	2.6 y	Acetylsalicylic acid (ASA) 30 mg/d vs ASA 325 mg/d	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: 0/1 - FU: NR 82% still using trial medication at 3 y - ITT: yes - Sponsor: NR
				Combined event of vascular mortality, nonfatal stroke or nonfatal AMI (PE)	ASA 30 mg= 14.7% ASA 283 mg= 15.2% hazard ratio= 0.91 (95% CI 0.76-1.09) → NS	
				Total mortality	ASA 30 mg= 10.3% ASA 283 mg= 9.6% hazard ratio= 1.01 (95% CI 0.81-1.26) → NS	
				Vascular mortality	hazard ratio= 0.92 (95% CI 0.71-1.22) → NS	
				Vascular mortality or nonfatal stroke	hazard ratio= 0.86 (95% CI 0.71-1.05) → NS	
				Stroke	NR	
				Myocardial infarction	NR	
				Harms		
				Bleeding outcomes		
				Major bleeding (requiring hospitalization)	ASA 30 mg= 2.6% ASA 283 mg= 3.2% → NS	
				Intracerebral bleeding	NR	
				Minor bleeding	ASA 30 mg= 3.2% ASA 283 mg= 5.3% hazard ratio= 0.58 (95% CI 0.41-0.83) → SS in favour of low dose	
				Fatal bleeding	NR	
				Minor GI-bleeding	NS	
				Any bleeding	NR	
				AE's		
				Gastric discomfort	NS	
				Any AE	NS	

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
UK-TIA 1991 Design: RCT	n= 2.435 - mean age 60 y - previous TIA 70% - previous minor stroke 22% - 3% atrial fibrillation <u>Incl</u> - recent TIA or minor ischaemic stroke in previous 3 m <u>Excl</u> - < 40 y - previous major disabling stroke - attacks due to other causes: migraine, cardiac arrhythmia, … - contra-indications to ASA - need for regular ASA - AMI in previous 3 m	Mean 4 y (1-7 y)	acetylsalicylic acid (ASA) 2x600 mg/d vs ASA 300 mg/d vs pla	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 100% - ITT: yes - Change to predefined primary outcome during trial - Sponsor: Medical research Council, Beecham, Glaxo, Eli Lilly and the Aspirin Foundation
				Major stroke, myocardial infarction and vascular death (PE)	20% in both groups NS	
				Ischemic stroke	NT	
				Hemorrhagic stroke	NT	
				Mortality	NT	
				Myocardial infarction	NT	
				Harms		
				Bleeding outcomes		
				Intracranial	NR	
				Any bleeding	NR	
				GI-bleeding	- ASA 300 vs pla: OR=2.57 (95% CI 1.20-5.53) → SS more frequent with ASA ASA 300 vs ASA 1200: NS	
				AE's		
				upper GI symptoms	- ASA 300 vs pla: OR= 1.32 (95%CI 1.06-1.65) - ASA 1200 vs pla: OR= 1.54 (95% CI 1.25-1.89) → SS more frequent with ASA → dose comparison: NT	

4.1.4.bis. Conclusion: Dose comparison: high- vs. low-dose ASA

High-dose acetylsalicylic acid vs low-dose (UK-TIA 1991: 1200 vs 300 mg/d; Dutch TIA 1991: 325 vs 30 mg/d)				
N/n	**Duration**	**Population**	**Results**	
N=2, n=5566	2-4 y	- patients with recent minor stroke or TIA - without atrial fibrillation - mean age 60 y	Combined vascular events (stroke, mortality and AMI, definition according to trial)	Reported in 2/2 trials No significant differences between high-dose and low-dose.
			Total mortality	Reported in 1/2 trials NS
			Stroke	Reported in 1/2 trials, but no statistical test
			Myocardial infarction	Reported in 1/2 trials, but no statistical test
			Any bleeding	Reported in 0/2 trials
			Major bleeding	Reported in 1/2 trials NS
			Intracranial bleeding	NR
			Minor bleeding	Reported in 1/2 trials NS
			GI bleeding	Reported in 2/2 trials NS

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Low quality of evidence**
-2 for heterogeneity and incomplete reporting of results	OK	OK	OK	

- Only 2 trials examined the difference between ASA in high and low dose in patients with previous stroke or TIA. The 2 available trials examined very divergent doses (1200 vs. 300 mg/d and 325 vs. 30 mg/d). Neither of both studies could find a difference in efficacy between high- and low-dose ASA.

GRADE: low quality of evidence

- No significant differences were found between high- and low-dose ASA as to the incidence of major and minor bleedings. There is no statistical test for other adverse events.

Clinical Evidence concludes, based on trials with persons with high cardiovascular risk in general:

Clinical guide
Aspirin 75 mg daily seems as effective as doses of 325 mg daily and higher. Observational studies suggested that lower doses of aspirin (less than 75 mg/day) may be associated with a lower risk of haemorrhage than moderate doses (75–325 mg), but RCTs did not confirm this. There seems no significant difference in effectiveness or safety between aspirin doses of 75 mg daily and 325 mg daily. Hence, dosing considerations should include an evaluation of a person's individual clinical status, and an overall benefit-versus-risk assessment.

4.2. Oral anticoagulants in patients with previous stroke/TIA without AF

4.2.1. Oral anticoagulants vs. control

Ref	N/n	Comparison	Outcomes	
* Cochrane review Sandercock Design: meta-analysis Search date: 2008	N= 11 n= 2.487	Anticoagulants (parenteral, oral) vs. Open control / placebo For the prevention of recurrent vascular events in patients -with previous, presumed non-cardioembolic ischemic stroke or TIA - in sinus rythm (mainly patients not in atrial fibrillation) "Prolonged" treatment (≥1 m)	Death or dependency (N=2, n= 326)	OR=0.83 (95%CI 0.52-1.34) NS
			Non fatal stroke, myocardial infarction or vascular death (N=4, n=575)	OR=0.96 (95%CI 0.68-1.37) NS
			Death from any causes (N=10, n=1333)	OR=0.95 (95%CI 0.73-1.24) NS
			Death from vascular causes (N=9, n=1214)	OR=0.86 (95%CI 0.66-1.13) NS
			Recurrent ischaemic stroke (N=10, n=2368)	OR=0.85 (95%CI 0.66-1.09) NS
			Recurrent fatal ischaemic stroke (N=7, n=1132)	OR=0.51 (95%CI 0.26-1.02) NS
			Fatal intracranial haemorrhage (N=9, n=1214)	**OR=2.54 (95%CI 1.19-5.45)** **SS more frequent with anticoagulants** **➔11 additional fatal intracranial haemorrhages per year for every 1000 patients given anticoagulant**
			Major extracranial haemorrhage (N=7, n=1183)	**OR=3.43 (95%CI 1.94-6.08)** **SS more frequent with anticoagulants** **➔25 additional major extracranial haemorrhages per year for every 1000 patients given anticoagulant**
			Fatal extracranial haemorrhage (N=7, n=1094)	**OR=4.86 (95%CI 1.40-16.88)** **SS more frequent with anticoagulants**
			Myocardial infarction (N=7, n=795)	OR=1.02 (95%CI 0.62-1.70) NS
			Other embolic events (N=3, n=515)	OR=0.83 (95%CI 0.38-1.78) NS
			Non-fatal stroke, intracranial haemorrhage, or vascular death (N=8, n=1251)	OR=0.88 (95%CI 0.69-1.13) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Baker 1964 RCT	60	-any TIA (time since TIA unknown:probably within days ; no CT) - severe hypertension, peptic ulcer, bleeding risk, age > 80years excluded - mean age 62 y	Mean follow-up: 3.25y	Unnamed anticoagulant (adequate AC 80% of time) vs no treatment Primary outcome: Death + cause of death	- Jadad score: 2/5 - FU: 85% (2 lost to follow-up and AC stopped in 7) - ITT: NR -Randomisation: sealed envelopes (opaque?sequentially numbered?)
Bradshaw 1975 CT	49	-Carotid TIA/Minor stroke (84%<28days ; no CT; Lumbar Puncture in all but 4;carotid arteriogram) - age > 65years, diabetes, myxoedema, diastolic BP>104mm Hg, heart disease, peripheral vascular disease excluded - mean age 52 y	Mean duration of intervention: 1.5y Mean follow-up: 3.55y	Anticoagulant (22 warfarine, 2 phenindione-adequacy of AC unknown) vs no treatment Primary outcome: Death + cause of death	- Jadad score: 1/5 - FU: 65% (AC stopped in 17) - ITT: NR
Enger 1965 CT	111	-Non-embolic stroke, TIA stroke (mean=20days ; no CT;carotid arteriogram) -age > 75years,diastolic BP>120mm Hg, peptic ulcer, poor life expectancy excluded - mean age 62.6 y	Mean duration of intervention: 1.9y Mean follow-up: 3.2y	Phenindione (adequate AC 77% of time) vs placebo Primary outcome: Death + cause of death	- Jadad score: 2/5 - FU: (data unavailable for 5, AC stopped in 11 and placebo withdrawn in 7) - ITT: NR
Howard 1963 RCT	30	-Non-embolic stroke (time since stroke unknown:probably within days ; no CT) -systolic BP>200mm Hg, recent MI, bleeding risk excluded - mean age 71 y	Follow-up: 1 y	Dicumarol (adequacy of AC unknown) vs placebo Primary outcome: Death	- Jadad score: 2/5 - FU: 100% (no discontinuation in AC group) - ITT: NR -unknown method of randomization
LHSPS Fortini 1999 RCT	1095	-Non-embolic ischaemic stroke (>21 to 210 days; confirmed by CT) - mean age: NR	Follow-up: 2y	Unfractionated heparin 12500IU/d + usual therapy vs usual therapy Primary outcome: Cumulated stroke recurrence	- Jadad score: 1/5 - FU: ? - ITT: NR No details on the methods of randomisation were available for SWAT 1998 and LHSPS 1999 but from the abstract our judgement was that they were probably truly randomised.
McDevitt 1959 RCT	215	Non-embolic stroke (time since stroke < 7 days to 2 months; no CT; 100% LP) -severe hepatic or renal disease, bleeding risk, active peptic ulcer, BP>180/110mm Hg, prolonged depression of consciousness unlikely to survive, excluded - mean age 68.7 y	Intervention duration: 4 days to 62 months Mean follow-up: 2.75y	Dicumarol or warfarin (adequate AC 44% of total follow-up) vs placebo Primary outcome: Death + cause of death	- Jadad score: 3/5 - FU:89% - ITT: NR -Randomization: sealed opaque envelopes (sequentially numbered?)

Nat-Coop Baker 1962 RCT	440	-Presumed Non-embolic stroke (90%) or TIA (10%) (time since stroke < 2 months; no CT; 100% LP) -gastrointestinal/urinary bleeding, bleeding disorder, serious disease excluded - mean age: NR (84%>55y)	Mean duration of intervention: unknown Mean follow-up: 1,1y	Heparin 50mg 4-hourly iv then dicumarol (adequacy of control not specified) vs placebo Primary outcome: Death + cause of death	- Jadad score: 2/5 - FU:73% (data unavailable for 22, AC stopped in 96) - ITT: NR -Randomization: sealed envelopes (opaque?sequentially numbered?)
SWAT Stewart 1998 RCT	178	- Patients with non-embolic TIA or mild stroke within 180 days of last event and without carotid stenosis > 70% - mean age: NR	Follow-up: 2y	Aspirin 2*650mg/day vs warfarin (INR 2.0 to 3.0) vs warfarin+ Aspirin 1*80mg/day Primary outcome: Death + cause of death	- Jadad score: 2/5 - FU:NR - ITT: NR Rem: Only aspirin and aspirin + warfarin groups included in this review No details on the methods of randomisation were available for SWAT 1998 and LHSPS 1999 but from the abstract our judgement was that they were probably truly randomised.
Thygesen 1964 RCT	68	-Predominantly non-embolic stroke (time since stroke :6 weeks; no CT; LP and arteriography in most) -no major exclusions - mean age: 60.5y	Mean duration of intervention: unknown Mean follow-up: 1.6y	Phenindione vs placebo Primary outcome: Death + cause of death	- Jadad score: 2/5 - FU:100 % - ITT NR Rem : ,more cardiac disease in treated group at baseline
VA Study Baker 1961 RCT	189	-Presumed non-embolic TIA (24%) or stroke (76%) (time since TIA/stroke < 1 month; no CT) - severe hypertension, bleeding risk, coma excluded - mean age: NR	Mean duration of intervention: unknown Mean follow-up: 0.9y	Coumadin or dicumarol (adequate control 80% of time) vs no treatment Primary outcome: Death + cause of death	- Jadad score: 1/5 - FU:66 % - ITT: NR -Randomization: numbered sealed envelopes (opaque?) Rem : more cardiac problems in controls (48% vs 33%) at baseline
Wallace 1964 RCT	52	-Non-embolic stroke (time since stroke > 14 days; no CT; 100% LP) -acute peptic ulcer, recent bleed, renal/liver disease excluded -mean age: 75.7 -inpatients only	Until hospital discharge Mean follow-up: 0.8y	Phenindione or warfarin (adequacy of AC unclear) vs no treatment Primary outcome: Death	- Jadad score: 1/5 - FU:100% (inpatients only) - ITT: NR - unknown method of randomization

4.2.1.bis. Conclusion: Oral anticoagulants vs. control

Anticoagulants vs control (Baker 1964, Bradshaw 1975, Enger 1965, Howard 1963, Fortini 1999, McDevitt 1959, Nat-Coop Baker 1962, Stewart 1998, Thygesen 1964, Baker 1961, Wallace 1964)				
N/n	**Duration**	**Population**	**Results**	
N= 11 n= 2487	Mean follow up: 2y	-patients with previous non-cardioembolic ischemic stroke or TIA -mean age: 64.6y	Death from any causes	OR= 0.95 (95% CI: 0.73-1.24) => NS
			Recurrent ischemic stroke	OR= 0.85 (95% CI: 0.66-1.09) => NS
			Fatal intracranial hemorrhage	**OR= 2.54 (95% CI: 1.19-5.45)** **=> SS more frequent with anticoagulants**
			Fatal extracranial stroke	**OR= 4.86 (95% CI: 1.40-16.88)** **=> SS more frequent with anticoagulants**
			Myocardial infarction	OR= 1.02 (95% CI: 0.62-1.70) => NS

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→ Very low quality of evidence**
-2 Lack of information on included trials (randomisation method, follow-up, ITT,…)	-1 Conflicting results	OK	OK	

- In patients with previous stroke or TIA and without AF, no significant difference can be found between oral anticoagulants and control as to total mortality, recurrence of ischemic stroke or myocardial infarction.

GRADE: very low quality of evidence

- In patients treated with oral anticoagulants, the incidence of fatal bleedings was significantly higher.

4.2.2. Oral anticoagulants vs. ASA

Ref	N/n	Comparison	Outcomes	
* Cochrane review Algra 2011 Design: meta-analysis Search date: sept 2004	N= 5 n= 4.076	Oral anticoagulants (OAC) vs. antiplatelet therapy (ASA 30-1000 mg) for preventing further vascular events after TIA or minor stroke of presumed arterial origin. Long-term treatment (>6 m)	**High-intensity anticoagulation (INR 3.0-4.5) (N=1, n=1.316)**	
			Composite outcome: vascular death, non-fatal stroke, non-fatal AMI or major bleeding	RR= 2.30 (95% CI 1.15-3.35) due to excess of bleeding in OAC group **SS**
			Total mortality	RR= 2.38 (95% CI 1.31-4.32) **SS in favour of ASA**
			Vascular mortality	RR= 2.23 (95% CI 1.10-4.51) **SS in favour of ASA**
			Recurrent ischaemic stroke	RR= 1.02 (95% CI 0.49-2.13) NS
			Recurrent ischaemic stroke or intracranial bleeding	RR= 2.30 (95% CI 1.37-3.85) **SS in favour of ASA**
			Major bleeding	RR= 9.02 (95% CI 3.91-20.84) **SS in favour of ASA**
			Fatal intracranial or extracranial bleeding	RR= 17.37 (95% CI 2.32-130.11) **SS in favour of ASA**
			Intracranial bleeding (fatal or non-fatal)	RR= 9.19 (95% CI 2.80-30.16) **SS in favour of ASA**
			Medium-intensity anticoagulation (INR 2.1-3.6) (N=3, n=493)	
			Total mortality	RR= 1.30 (95% CI 0.51-3.35) NS
			Vascular mortality	RR= 1.67 (95% CI 0.55-5.06) NS
			Recurrent ischaemic stroke	RR= 0.96 (95% CI 0.38-2.42) NS
			Recurrent ischaemic stroke or intracranial bleeding	RR= 0.82 (95% CI 0.37-1.82) NS
			Major bleeding	RR= 1.19 (95% CI 0.59-2.41) NS
			Fatal intracranial or extracranial bleeding	RR= 1.05 (95% CI 0.14-7.60) NS
			Intracranial bleeding (fatal or non-fatal)	RR= 1.05 (95% CI 0.14-7.60) NS
			Low-intensity anticoagulation (INR 1.4-2.8) (N=1, n=2.206)	
			Total mortality	RR= 0.89 (0.60-1.30) NS
			Vascular mortality	NR
			Recurrent ischaemic stroke	NR
			Recurrent ischaemic stroke or intracranial bleeding	NR
			Major bleeding	RR= 1.27 (95% CI 0.79-2.03) NS
			Fatal intracranial or extracranial bleeding	RR= 1.40 (95% CI 0.45-4.40) NS
			Intracranial bleeding (fatal or non-fatal)	NR

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Garde 1983 RCT	241	- carotid symptoms or homonymous anopsia (104 TIA) - time since stroke < 14d - mean age 60 y, 64% male	20 m	warfarin (thrombotest 7-15%) vs. ASA 1000 mg/d	- Jadad score: 2/5 - FU: 86% - ITT: no
Olsson 1980 RCT	135	- TIA or RIND (= Reversible Ischaemic Neurological Deficit) - time since TIA/RIND <2-3 m - mean age 66 y; 69% male	12 m	(1) run-in with Coumadin 2 m for all patients (2) coumadin (thrombotest 7-15%) vs. ASA (1000 mg/d) + dipyridamole (150 mg/d)	- Jadad score: 2/5 - FU: 90% - ITT: yes
SPIRIT 1997 RCT	1.316	- cerebral ischemia of non-cardiac origin or transient monocular blindness - time since stroke < 6m - mean age 63y; 65% male	14 m (trial was stopped at first interim analysis)	phenprocoumon (INR 3.0-4.5) vs. ASA 30 mg (95%), 75 mg (2%), 100 mg (3%)	- Jadad score: 4/5 - FU: 86% - ITT: yes
SWAT Stewart 1998 RCT (abstract)	178	- non-cardiogenic TIA or mild stroke - time since stroke < 180 d - mean age 68y; 58% male	NR	warfarin (INR 2.0-3.0) vs. ASA 1300 mg vs. warfarin (INR 2.0-3.0) + ASA 80 mg	- Jadad score: 2/5 - FU: NR - ITT: NR
WARSS Mohr 2001 RCT	2.206	- ischemic stroke of of non-cardiac origin - time since stroke: <30 d - mean age 63y; 59% male	2 years	warfarin (INR 1.4-2.8) vs. ASA 325 mg/d	- Jadad score: 5/5 - FU: 98.5% - ITT: yes

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
ESPRIT 2007 Design: RCT	n=1.068 -mean age: 61y -mean CHADS score: NR -mean INR: 2.57 (SD: 0.86) <u>Incl</u> -TIA (incl transient monocular blindness) or minor stroke (grade ≤3 on modified Rankin scale) of presumed arterial origin <u>Excl</u> -possible cardiac source of embolism -high-grade carotid stenosis -any blood coagulation disorder -leukoaraiosis -any contraindication for study drugs -reduced life expectancy -intracerebral hemorrhage -age >75y	4.6y	Oral antico (target INR 2-3) vs Aspirin 30-325 mg (57% 30 mg/d)	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 0/2 ATTRITION: 1/1 - FU: 96% - ITT: yes - Other important methodological remarks? °Treatment allocation not blinded but auditing committee for outcome events was masked - Sponsor: Non-profit organisations and Boehringer Ingelheim (but complete scientific freedom)
				First event - Death from all vascular causes, non-fatal stroke, non fatal MI or major bleeding complication (PE)	Antico: 19% ASA: 18% HR=1.02 (95% CI: 0.77-1.35) → NS	
				Mortality	Antico: 11% vs. ASA: 8% HR=1.36 (95% CI: 0.92-2.01) → NS	
				Death from vascular causes	Antico: 6% ASA: 5% HR=1.31 (95% CI: 0.77-2.23) → NS	
				Death from vascular causes or non-fatal stroke	Antico: 13% ASA: 15% HR=0.90 (95% CI: 0.65-1.24) → NS	
				Death from vascular causes or non-fatal stroke or non-fatal MI	Antico: 15% ASA: 17% HR=0.85 (95% CI: 0.63-1.15) → NS	
				All major ischaemic events: non-haemorrhagic death from vascular causes, non-fatal ischaemic stroke, non-fatal MI	Antico: 12% vs. ASA: 16% HR=0.73 (95% CI: 0.52-1.01) → NS	
				First event - Ischemic stroke	Antico: 8% vs. ASA: 10% HR=0.76 (95% CI: 0.51-1.15) → NS	
				First cardiac event	Antico: 5% vs. ASA: 6% HR=0.77 (95% CI: 0.46-1.29) → NS	
				Harms		
				Bleeding outcomes		
				Major bleeding complication	Antico: 8% ASA: 3% **HR=2.56 (95% CI: 1.48-4.43) SS**	
				Intracranial bleeding	Antico: 3% ASA: 2% → NT	
				Fatal bleeding	Antico: 2% ASA: 1% HR=2.80 (95% CI: 0.90-8.80) → NS	
				AE's		
				see Major bleeding complications		

4.2.2.bis. Conclusion: oral anticoagulants vs. ASA

Oral anticoagulants vs acetylsalicylic acid (Olsson 1980, Garde 1983, SPIRIT 1997, Stewart 1998, Mohr 2001, ESPRIT 2007)				
N/n	**Duration**	**Population**	**Results**	
N= 6 n= 5.144	Mean 21m	TIA or minor stroke of presumed arterial origin	**High-intensity anticoagulation (INR 3.0-4.5) (N=1, n=1316)**	
			Mortality	RR= 2.38 (95% CI 1.31-4.32) **SS in favour of ASA**
			Vascular mortality	RR= 2.23 (95% CI 1.10-4.51) **SS in favour of ASA**
			Recurrent ischemic stroke	RR= 1.02 (95% CI 0.49-2.13) NS
			Recurrent ischemic stroke or intracranial bleeding	RR= 2.30 (95% CI 1.37-3.85) **SS in favour of ASA**
			Major bleeding	RR= 9.02 (95% CI 3.91-20.84) **SS in favour of ASA**
			Fatal intracranial or extracranial bleeding	RR= 17.37 (95% CI 2.32-130.11) **SS in favour of ASA**
			Intracranial bleeding (fatal or non-fatal)	RR= 9.19 (95% CI 2.80-30.16) **SS in favour of ASA**
			Medium-intensity anticoagulation (INR 2.1-3.6) (N=4, n=1561)	
			Mortality	RR= 1.30 (95% CI 0.51-3.35) NS HR= 1.36 (95% CI: 0.92-2.01) NS
			Vascular mortality	RR= 1.67 (95% CI 0.55-5.06) NS HR= 1.31 (95% CI: 0.77-2.23) NS
			Recurrent ischemic stroke	RR= 0.96 (95% CI 0.38-2.42) NS
			Recurrent ischemic stroke or intracranial bleeding	RR= 0.82 (95% CI 0.37-1.82) NS
			Major bleeding	RR= 0.86 (95% CI: 0.36-2.07) NS **HR= 2.56 (95% CI: 1.48-4.43) SS in favour of ASA**
			Fatal intracranial or extracranial bleeding	RR= 1.05 (95% CI 0.14-7.60) NS HR= 2.80 (95% CI: 0.90-8.80) NS
			Intracranial bleeding (fatal or non-fatal)	RR= 1.05 (95% CI 0.14-7.60) NS
			Low-intensity anticoagulation (INR 1.4-2.8) (N=1, n=2206)	
			Mortality	RR= 0.89 (95% CI 0.60-1.30) NS
			Vascular mortality	NR
			Recurrent ischemic stroke	NR
			Recurrent ischemic stroke or intracranial bleeding	NR
			Major bleeding	RR= 1.27 (95% CI 0.79-2.03) NS
			Fatal intracranial or extracranial bleeding	RR= 1.40 (95% CI 0.45-4.40) NS
			Intracranial bleeding (fatal or non-fatal)	NR

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→High quality of evidence**
OK	OK	OK	OK	

- Long-term treatment with ASA seems superior to oral anticoagulants (INR>3) on most outcomes, including the prevetion of stroke, for patients without AF. In patients with a lower intensity anticoagulation the difference between both groups is not statistically significant.

GRADE: high quality of evidence

- In case of an INR >3, significantly more major bleedings occur with oral anticoagulants, compared to ASA. Even in the group with intermediate INR, more major bleedings occur compared to ASA.

4.3. Antihypertensive drugs in patients with previous stroke/TIA without AF

4.3.1. Antihypertensive drugs versus placebo

4.3.1.1. Antihypertensives as a group versus placebo

Ref	N/n	Comparison	Outcomes	
* SR Rashid 2003 Design: meta-analysis Search date: Not reported	N= 7 n=15.527	Antihypertensive treatment vs control (placebo or no treatment) For the prevention of recurrent vascular events in patients: -with previous ischemic stroke, TIA or primary intracerebral hemorrhage (average time from stroke : 3 weeks to 14 months) -with hypertension (mean: 64% of patients) Follow-up interval : 2-5y Mean age: 64	Stroke (fatal and non-fatal) (N=7, n=15527)	**9% Antihypertensive vs control 11%** **OR=0.76 (95%CI 0.63-0.92) p=0.005** **SS less frequent with antihypertensive treatment**
			Fatal stroke (N=7, n=15527)	OR=0.76 (95%CI 0.56-1.03) p=0.08 NS
			Non-fatal stroke (N=7, n=15527)	**OR=0.79 (95%CI 0.65-0.95) p=0.01** **SS less frequent with antihypertensive treatment**
			Myocardial infarction (N=6, n=15428)	**3% Antihypertensive vs control 4%** **OR=0.79 (95%CI 0.63-0.98) p=0.03** **SS less frequent with antihypertensive treatment**
			Vascular events (stroke, MI or vascular death) (N=6, n=15428)	**13% Antihypertensive vs control 16%** **OR=0.79 (95%CI 0.66-0.95) p=0.01** **SS less frequent with antihypertensive treatment**
			Vascular death	OR=0.86 (95%CI 0.70-1.06) p=0.16 NS
			Death	OR=0.91 (95%CI 0.79-1.05) p=0.18 NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration (year)	Comparison	Methodology
Carter 1970 RCT	99	-100% ischemic stroke (time from stroke: >0.5 months) -100% hypertension (baseline BP :?) - 58% male - mean age ? y	2-5	Thiazide diuretic mg_methyldopa (750 mg) vs control	- Jadad score: 2/5 Randomisation: process not given; concealment of allocation unclear - FU: NR - ITT: NR (publication not available in Belgium)
HSCSG 1974 RCT	452	-96% ischemic stroke/intracerebral hemorrhage; 4% TIA (time from stroke: <12 months) -100% hypertension (baseline BP :167/100) - 60% male - mean age 59 y	2.8	Deserpidine (1 mg) and methylclothiazide (10 mg) vs placebo	- Jadad score: 4/5 - FU: NR - ITT: NR (publication not available in Belgium)
Dutch TIA 1993 RCT	1473	-66% ischemic stroke; 34% TIA (time from stroke: <3 months) -29% hypertension(baseline BP:157/91) - 64% male - mean age 66 y	2.6	Atenolol (50 mg) vs placebo	- Jadad score: 4/5 - FU: 97 - ITT: yes
PATS 1995 RCT	5665	-71% ischemic stroke; 14%intracerebral hemorrhage; 12% TIA ; 2%SAH (time from stroke: 14 months) -84% hypertension (baseline BP:154/93) - 72% male - mean age 60 y	2	Indapamide (2.5 mg) vs placebo	- Jadad score: 4/5 - FU: NR - ITT: NR (Chinese publication, not available in Belgium
Eriksson 1995 RCT	720	-67% ischemic stroke/intracerebral hemorrhage; 20% TIA (time from stroke<0.75 months) -100% hypertension (baseline BP:161/88) - 60% male - mean age 70 y	2.5	Atenolol (? mg) vs placebo	- Jadad score: 5/5 - FU: 83% - ITT: yes
HOPE 2000 RCT	1013	-100% “stroke”/ TIA (time from stroke>1month) Data related to whole trial and not just subgroup of patients with prior cerebrovascular disease -47% hypertension (baseline BP:139/79) - 73% male - mean age 66 y	5	Ramipril vs placebo Primary outcome:composite of myocardial infarction, stroke, or death from cardiovascular causes	- Jadad score: 4/5 - FU: NR (subgroup analysis) - ITT: NR (subgroup analysis)

PROGRESS 2001 RCT	2561	-70% ischemic stroke; 11%ICH; 23% TIA (time from stroke=0.5-60months) -40% hypertension (baseline BP:144/84) - 68% male - mean age 65 y	4.1	Perindopril 4 mg vs Placebo	- Jadad score: 5/5 - FU: 99% - ITT: yes
	3544	-71% ischemic stroke11%ICH; 22% TIA (time from stroke=0.5-60months) -54% hypertension (baseline BP:149/87) - 71% male - mean age 63 y	4.1	Perindopril 4 mg + indapamide 2.5 mg vs double-placebo	

IS= Ischemic stroke; TIA= Transient Ischemic attack; ICH= intracerebral hemorrhage; SAH= Subarachnoid hemorrhage

4.3.1.1.bis.Conclusion: Antihypertensives as a group vs. placebo

<table>
<tr><td colspan="5">Antihypertensive treatment (thiazide, deserpidine, atenolol, indapamide, ramipril, perindopril+indapamide) vs control (MA Rashid 2003: Carter 1970, HSCSG 1974, Dutch TIA 1993, PATS 1995, Eriksson 1995, HOPE 2000, PROGRESS 2001)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th colspan="2">Results</th></tr>
<tr><td rowspan="8">N= 7
n= 15.527</td><td rowspan="8">2-5 y</td><td rowspan="8">-patients with previous ischemic stroke, TIA or primary intra-cerebral hemorrhage (average time from stroke : 3 weeks to 14 months)

-with hypertension (mean: 64% of patients)

Mean age: 64</td><td>Stroke</td><td>- Reported in 7/7 trials
- NS in 4/7 trials, SS in favour of antihypertensive treatment in 3/7 trials
- pooled event rate: 9% vs. 11%
- pooled OR=0.76 (95%CI 0.63-0.92) SS in favour of antihypertensive treatment</td></tr>
<tr><td>Fatal stroke</td><td>Reported in 7/7 trials
NS</td></tr>
<tr><td>Non-fatal stroke</td><td>- Reported in 7/7 trials
- pooled OR=0.79 (95%CI 0.65-0.95) SS in favour of antihypertensive treatment</td></tr>
<tr><td>Myocardial infarction</td><td>- Reported in 6/7 trials
- NS in 6/7 trials, SS in favour of ACE-I+diuretic in PROGRESS trial
- pooled event rate: 3% vs. 4%
- pooled OR=0.79 (95%CI 0.63-0.98) SS in favour of antihypertensive treatment</td></tr>
<tr><td>Vascular events (stroke, MI or vascular mortality)</td><td>- Reported in 6/7 trials
- NS in 4/6 trails, SS in favour of ACE-I (HOPE trial) or of ACE-I+diuretic (PROGRESS trial)
- pooled event rate: 13% vs. 16%
- pooled OR= 0.79 (95% CI 0.66-0.95) SS in favour of antihypertensive treatment</td></tr>
<tr><td>Vascular mortality</td><td>NS</td></tr>
<tr><td>Total mortality</td><td>NS</td></tr>
<tr><td>Adverse events</td><td>NR</td></tr>
<tr><td colspan="5">GRADE assessment</td></tr>
<tr><td>Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td>→Moderate quality of evidence</td></tr>
<tr><td>-1 for heterogeneity</td><td>OK</td><td>OK</td><td>OK</td><td></td></tr>
</table>

- In patients with previous stroke or TIA (ischaemic or hemorrhagic), antihypertensive treatment is associated with a lower incidence of new stroke, myocardial infarction and cardiovascular events. When analyzing trials separately, only a trend was found and statistical significance could not be reached.

GRADE: moderate quality of evidence

- This meta-analysis reports no harms.

4.3.1.2. ACE-I vs. placebo

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
PROGRESS collaborative group 2001 Design: RCT P	n= 6015 - Mean age 64y Mean BP at baseline: 147/86 mm Hg - Mean CHADS-score: NR Incl - history of stroke or TIA <5yclinically stable for ≥2w after most recent vascular event Excl - Definite indication for treatment with ACE inhibitor (eg. Heart failure) - Definite contraindication for ACE inhibitor (eg previous intolerance) Subgroups 'hypertensive subgroup' - Mean BP at baseline: 159/94 mm Hg 'non-hypertensive subgroup' - Mean BP at baseline: 136/79mm Hg Assigned to combination therapy - Mean age 64y - Age >70y: 22% - Mean BP at baseline: 149/87mm Hg - SBP >160mmHg: 25% Assigned to monotherapy - Mean age: 65y - Age>70y: 31%	Mean 3.9y	Perindopril 4mg +2.5 (2) mg indapamide vs placebo or Perindopril 4mg vs placebo Choice of combination/ monotherapy by physician before inclusion in study	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 99% - ITT: yes - Other important methodological remarks: - 4week run-in perindopril (open-label) - classification as hypertensive if BP>160/90 at inclusion - classification as (non-) hypertensive irrespective of any use of antihypertensive treatment - Choice between combination or monotherapy made by physician (prior to study entry) - no p-values reported for subgroup analyses - Sponsor: Servier
				Fatal or nonfatal stroke (ischaemic or haemorraghic) (PE)	Perindopril 4mg +/- indapamide: 10% Placebo: 14% **SS: RRR 28% (95%CI 17 to 38), p<0.0001**	
					Prespecified SA: Hypertensive patients Perindopril 4mg +/- indapamide: 11.1% Placebo: 16.2% **SS: RRR 32% (95%CI 17 to 44)**	
					Prespecified SA: Non-hypertensive patients Perindopril 4mg +/- indapamide: 9.1% Placebo: 11.5% **SS: RRR 27% (95%CI 8 to 42)**	
					Prespecified SA: Combination therapy Perindopril 4mg +indapamide: 8.5% Placebo: 12.7% **SS: RRR 43% (95%CI 30 to 54)**	
					Prespecified SA: Single drug therapy Perindopril 4mg : 12.3% Placebo: 12.9% NS: RRR 5% (95%CI -19 to 23)	
				Fatal or disabling stroke	Perindopril 4mg +/- indapamide: 4% Placebo: 5.9% **SS: RRR 33% (95%CI 15 to 46)**	
				Ischaemic stroke	Perindopril 4mg +/- indapamide: 8.1% Placebo: 10.4% **SS: RRR 24% (95%CI 10 to 35)**	
				Cerebral haemorrhage	Perindopril 4mg +/- indapamide: 1.2% Placebo: 2.4% **SS: RRR 50% (95%CI 26 to 67)**	
				Total major vascular events (non-fatal stroke, non-fatal myocardial infarction, death due to any vascular cause,	Perindopril 4mg +/- indapamide: 15% Placebo: 20% **SS: RRR 26% (95%CI 16 to 34)**	
					Prespecified SA: Hypertensive patients Perindopril 4mg +/- indapamide: 16.4% Placebo: 22.8%	

	- Mean BP at baseline: 144/84 mm Hg - SBP>160 mm Hg: 17%			including unexplained sudden death)	**SS: RRR 29% (95%CI 16 to 40)**	
					<u>Prespecified SA: Non-hypertensive patients</u> Perindopril 4mg +/- indapamide: 13.3% Placebo: 17% **SS: RRR 24% (95%CI 9 to 37)**	
					<u>Prespecified SA: Combination therapy</u> Perindopril 4mg +indapamide: 19.7% Placebo: 31.3% **SS: RRR 40% (95%CI 29 to 49)**	
					<u>Prespecified SA: Single drug therapy</u> Perindopril 4mg : 17.7% Placebo: 18.5% NS: RRR 4% (95%CI -15 to 23)	
				Mortality	Perindopril 4mg +/- indapamide: 5.9% Placebo: 6.5% NS: RRR 9% (95%CI -12 to 20)	
				Vascular mortality	Perindopril 4mg +/- indapamide: 10% Placebo: 10.4% NS: RRR 4% (95%CI -12 to 18)	
				Hospital admissions	Perindopril 4mg +/- indapamide: 41% Placebo: 44% **SS: RRR 9% (95%CI 1 to 15)**	
				Blood pressure	Perindopril 4mg +/- indapamide vs Placebo Average 9.0/4.0 mm Hg (SE 0.3/0.2) reduction	
					<u>Prespecified SA: Combination therapy</u> Perindopril 4mg +indapamide vs placebo Average 12.3/5.0 mm Hg (SE 0.5/0.3) reduction	
					<u>Prespecified SA: Single drug therapy</u> Perindopril 4mg vs placebo Average 4.9/2.8 mm Hg (SE 0.6/0.3) reduction	
				Harms		
				AE's		
				Discontinuation for cough	Perindopril 4mg +/- indapamide: 2.2% Placebo: 0.4% NT	
				Discontinuation for hypotension	Perindopril 4mg +/- indapamide: 2.1% Placebo: 0.9% NT	

				Discontinuation for heart failure requiring treatment with ACE or diuretic	Perindopril 4mg +/- indapamide: 2.2% Placebo: 2.3% NT	
				Angio-oedema	Perindopril 4mg +/- indapamide: 4 cases (1 at run-in) Placebo: 0 cases NT	

4.3.1.2.bis. Conclusion: ACE-I vs. placebo

<table>
<tr><td colspan="6">Perindopril 4mg + indapamide 2-2.5mg of perindopril 4mg vs placebo (PROGRESS Collaborative Group '01)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="20">N=1, n= 6015</td><td rowspan="20">Mean 3.9y</td><td rowspan="20">- history of stroke or TIA <5y
- clinically stable for ≥2w after most recent vascular event
- Mean age 64y
- Mean BP at baseline: 147/86 mm Hg

<u>Exlcusion</u>
- Indication for ACE-I treatment
- Contraindication for ACE-I

<u>Subgroups</u>
<u>'hypertensive'</u>
- Mean baseline BP: 159/94 mm Hg
<u>'non-hypertensive '</u>
- Mean baseline BP: 136/79mm Hg
<u>Combination therapy</u>
- Mean age 64y
- Age >70y: 22%
- Mean baseline BP: 149/87mm Hg
- SBP >160mm Hg: 25%
<u>Monotherapy</u>
- Mean age: 65y
- Age>70y: 31%
- Mean baseline BP: 144/84 mm Hg
- SBP>160 mm Hg: 17%

Choice between combination- or monotherapy by physician (before entry in study)</td><td rowspan="5">Fatal or nonfatal stroke (ischaemic or haemorraghic) (PE)</td><td>Perindopril 4mg +/- indapamide: 10%
Placebo: 14%
SS: RRR 28% (95%CI 17 to 38), p<0.0001</td></tr>
<tr><td><u>Prespecified SA: Hypertensive patients</u>
Perindopril 4mg +/- indapamide: 11.1%
Placebo: 16.2%
SS: RRR 32% (95%CI 17 to 44)</td></tr>
<tr><td><u>Prespecified SA: Non-hypertensive patients</u>
Perindopril 4mg +/- indapamide: 9.1%
Placebo: 11.5%
SS: RRR 27% (95%CI 8 to 42)</td></tr>
<tr><td><u>Prespecified SA: Combination therapy</u>
Perindopril 4mg +indapamide: 8.5%
Placebo: 12.7%
SS: RRR 43% (95%CI 30 to 54)</td></tr>
<tr><td><u>Prespecified SA: Single drug therapy</u>
Perindopril 4mg : 12.3%
Placebo: 12.9%
NS: RRR 5% (95%CI -19 to 23)</td></tr>
<tr><td rowspan="5">Total major vascular events (non-fatal stroke, non-fatal myocardial infarction, death due to any vascular cause, including unexplained sudden death)</td><td>Perindopril 4mg +/- indapamide: 15%
Placebo: 20%
SS: RRR 26% (95%CI 16 to 34)</td></tr>
<tr><td><u>Prespecified SA: Hypertensive patients</u>
Perindopril 4mg +/- indapamide: 16.4%
Placebo: 22.8%
SS: RRR 29% (95%CI 16 to 40)</td></tr>
<tr><td><u>Prespecified SA: Non-hypertensive patients</u>
Perindopril 4mg +/- indapamide: 13.3%
Placebo: 17%
SS: RRR 24% (95%CI 9 to 37)</td></tr>
<tr><td><u>Prespecified SA: Combination therapy</u>
Perindopril 4mg +indapamide: 19.7%
Placebo: 31.3%
SS: RRR 40% (95%CI 29 to 49)</td></tr>
<tr><td><u>Prespecified SA: Single drug therapy</u>
Perindopril 4mg : 17.7%
Placebo: 18.5%
NS: RRR 4% (95%CI -15 to 23)</td></tr>
<tr><td rowspan="3">Blood pressure</td><td>Perindopril 4mg +/- indapamide vs Placebo
Average 9.0/4.0 mm Hg (SE 0.3/0.2) reduction</td></tr>
<tr><td><u>Prespecified SA: Combination therapy</u>
Average 12.3/5.0 mm Hg (SE 0.5/0.3) reduction</td></tr>
<tr><td><u>Prespecified SA: Single drug therapy</u>
Average 4.9/2.8 mm Hg (SE 0.6/0.3) reduction</td></tr>
<tr><td colspan="3">AE</td></tr>
<tr><td colspan="2">Discontinuation for hypotension</td><td>Perindopril 4mg +/- indapamide: 2.1%
Placebo: 0.9%
NT</td></tr>
<tr><td colspan="2">Discontinuation for heart failure requiring treatment with ACE or diuretic</td><td>Perindopril 4mg +/- indapamide: 2.2%
Placebo: 2.3%
NT</td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><td colspan="2">Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td>→Moderate quality of evidence</td></tr>
<tr><td colspan="2">-1 for unclear study design</td><td>NA</td><td>OK</td><td>OK</td><td></td></tr>
</table>

- This trial found that antihypertensive treatment with perindopril 4 mg (with or without addition of indapamide) reduces the risk of stroke (RRR 28%). The global incidence of cardiovascular events (non-fatal stroke and MI, vascular mortality and unexplained sudden death) was also significantly lower with active treatment, compared to placebo (RRR 26%).
The choice between combination or monotherapy was made at the discretion of the treating physician before the start of the trial.
In a prespecified subgroupanalysis a significant effect on the risk of stroke (RRR 43%) or the total incidence of vascular events (RRR 40%) could only be found for the combination therapy of perindopril and indapamide. Monotherapy (perindopril alone) was not more effective than placebo.
- These data are insufficient to find out if this discrepancy is due to the examined drugs, the difference in blood pressure reduction in both groups, different population characteristics or a lack of power in the subgroupanalysis.
A study arm with indapamide alone would have been interesting to clarify the role of indapamide.
- These data do not allow us to conclude that a antihypertensive treatment should contain perindopril to be effective.
- An other predefined subgroupanalysis found a reduction in the risk of stroke and cardiovascular events in 'hypertensive patients' (mean blood pressure at baseline 159/94mmHg), as well as in 'non hypertensive patients' (mean blood pressure at baseline 136/79 mmHg). However, the definition of hypertension was based on a single measurement at the start of the trial and the cut-off value was 160/90mm Hg, which does not correspond to current clinical practice.

GRADE: moderate quality of evidence

- Adverse events: no statistical test.

4.3.1.3. Diuretics vs. placebo

Ref	N/n	Comparison	Outcomes	
* Rashid 2003 Design: meta-analysis Search date:	N= 3 n= 6.216	thiazide diuretics (mostly indapamide 2.5 mg) vs. placebo For the prevention of recurrent vascular events in patients: with previous ischemic stroke, TIA or primary intracerebral hemorrhage	Stroke (fatal and non-fatal)	**OR= 0.68 (95% CI 0.50-0.92) SS in favour of diuretics**
			Myocardial infarction	OR= 1.06 (95% CI 0.63-1.78) NS
			Vascular events (stroke, MI or vascular death)	**OR= 0.75 (95% CI 0.63-0.90) SS in favour of diuretics**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Carter 1970 RCT	99	-100% ischemic stroke (time from stroke: >0.5 months) -100% hypertension (baseline BP :?) - 58% male - mean age ? y	2-5 y	Thiazide diuretic mg±methyldopa (750 mg) vs control	- Jadad score: 2/5 Randomisation: process not given; concealment of allocation unclear - FU: NR - ITT: NR (publication not available in Belgium)
HSCSG 1974 RCT	452	-96% ischemic stroke/intracerebral hemorrhage; 4% TIA (time from stroke: <12 months) -100% hypertension (baseline BP :167/100) - 60% male - mean age 59 y	2.8 y	Deserpidine (1 mg) and methylclothiazide (10 mg) vs placebo	- Jadad score: 4/5 - FU: NR - ITT: NR (publication not available in Belgium)
PATS 1995 RCT	5665	-71% ischemic stroke; 14%intracerebral hemorrhage; 12% TIA ; 2%SAH (time from stroke: 14 months) -84% hypertension (baseline BP:154/93) - 72% male - mean age 60 y	2 y	Indapamide (2.5 mg) vs placebo	- Jadad score: 4/5 - FU: 48.5% - ITT: yes

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Liu 2010 Design: RCT re-analysis of PATS 1995	n= 5.665 Chinese patients -previous stroke (62% ischemic stroke; 12% intracerebral hemorrhage…) -63% > 6 months -mean age : 60y <u>Inclusion criteria</u> - TIA or minor stroke or major stroke (not severely disabling) ≥4 weeks. -clinically and neurologically stable -without CI or compelling indications for blood-pressure lowering treatment <u>Exclusion criteria</u> -secondary hypertension, -malignancy, -rheumatic valvular disease, heart failure, atrial fibrillation, -hyperthyroidism, -concurrent hepatic or renal diseases, -hemorrhagic disorders - insulin-dependent diabetes mellitus	Median follow-up: 2y	Placebo vs indapamide 2.5 mg	**Efficacy**		- Jadad score 4/5 RANDO: 2/2 BLINDING:2 /2 ATTRITION:1/1 - FU: 48.5% - ITT: yes - Other important methodological remarks: Early termination of the trial due to significant decrease in the occurrence of stroke in the active treatment group (predefined rules). - Sponsor: mainly academic
				Recurrent Stroke (fatal or non-fatal; first event, not TIA) (PE)	**7.8% Placebo vs 5.0% indapamide** **SS:HR =0.69 (95% CI 0.54 – 0.89) p<0.001**	
				Cardiovascular event*	**9.1% Placebo vs 7.01% indapamide** **SS:HR =0.75 (95% CI 0.62 – 0.89) p=0.002**	
				Death (all causes)	31.7/1000 patient-years Placebo vs 27.7/1000 patient-years Indapamide NS: p=0.23	
				Death (all cardiovascular)	20.1/1000 patient-years Placebo vs 16.4/1000 patient-years Indapamide NS: p=0.17	
				Myocardial infarction	4.5/1000 patient-years Placebo vs 4.9/1000 patient-years Indapamide NS: p=0.76	
				* Cardiovascular event= cardiac death, myocardial infarction, retinal hemorrhage, exudates or papilledema congestive heart failure enlarging or dissecting aortic aneurysms and the development of renal insufficiency		
				Harms		
				No information on AE's		

4.3.1.3.bis. Conclusion: Diuretics vs. placebo

Diuretics (mostly indapamide 2.5 mg/d) vs placebo (MA Rashid 2003:Carter 1970, HSCSG 1974, PATS 1995)				
N/n	**Duration**	**Population**	**Results**	
N=3, n= 6216	2 y	patients with previous stroke, TIA or primary intra-cerebral hemorrhage mean age 60y	Stroke (fatal and non-fatal)	- Reported in 3/3 trials - SS in favour of antihypertensives in 2/3 trials, NS in 1 trial - pooled OR= 0.68 (95% CI 0.50-0.92) SS in favour of diuretics
			Myocardial infarction	- Reported in 2/3 trials - NS in both trials - Pooled OR= 1.06 (95% CI 0.63-1.78) NS
			Vascular events (stroke, MI or vascular death)	- Reported in 2/3 trials - NS in 1 small trial, SS in the large-scale PATS trial - pooled OR= 0.75 (95% CI 0.63-0.90) SS in favour of diuretics
			Adverse events	NR

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→ Moderate quality of evidence**
-1 for incomplete reporting of results	OK	OK	OK	

- In patients with previous stroke/TIA (ischaemic or haemorrhagic), treatment with diuretics diminishes the incidence of new stroke and the total incidence of cardiovascular events. The incidence of AMI was not influenced. Thes results were predominantly directed by the PATS-trial, a Chinese study that compared indapamide 2.5 mg/d with placebo. This trial was stopped prematurely.

GRADE: moderate quality of evidence

- The meta-analysis and supplementary publication reported no data for adverse events.

4.3.1.4. β-blockers vs. placebo

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Eriksson '95 Design: RCT P	n= 720 - mean age 70y - Mean BP at baseline: 161/89 - mean CHADS score: NR <u>Incl</u> - >40y - Stroke or TIA ≤3weeks <u>Excl</u> - Systolic BP≤140mm Hg - Diastolic BP ≤80mm HG - Bradycardia ≤50bpm - Manifest heart failure - AV-block I-III - Previous side effects of beta blockers - Poor general condition - Life-threatening disorders - Completely dependent on help for ADL - Specific indications for beta-blockade	Mean: 30 months	Atenolol 50 mg vs placebo	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 1/2 ATTRITION: 1/1 - FU: 83% - ITT: yes - Other important methodological remarks? - sample size too small to provide adequate power (n=1900 was needed) - study participants who reached BP <140/80 (defined as hypotension) were discontinued from the study - unclear definition of endpoints (eg. 'cerebrovascular mortality') - Sponsor: ICI Pharma Ltd.
				Total mortality, non-fatal stroke, non-fatal myocardial infarction (PE)	Atenolol 50 mg: 11.8 patient years Placebo: 12.4 patient years NS: RR= 0.96 (95%CI 0.74-1.25)	
				Vascular mortality, non-fatal stroke, non-fatal myocardial infarction	Atenolol 50 mg: 10.1 patient years Placebo: 10.2 patient years NS: RR= 1.0 (95%CI 0.75-1.35)	
				Total Mortality	Atenolol 50 mg: 5.3/100 patient years Placebo: 6.6/100 patient years NS: RR= 0.79(95%CI 0.54-1.16)	
				Non-fatal stroke	Atenolol 50 mg:6.5/100 patient years Placebo: 6.4/100 patient years NS: RR= 0.98(95%CI 0.68-1.40)	
				Non-Fatal myocardial infarction	Atenolol 50 mg:1.4/100 patient years Placebo:1.6/100 patient years NS: RR=1.0 (95%CI 0.49-2.07)	
				Cerebrovascular mortality	Atenolol 50mg: 1.9 patient years Placebo: 1.9 patient years NS: RR=1.08 (95%CI 0.54-2.16)	
				Cardiac mortality	Atenolol 50mg: 1.7 patient years Placebo: 2.4 patient years NS: RR=0.66 (95%CI 0.34-1.27)	
				Cardiovascular mortality	Atenolol 50mg:3.5 patient years Placebo:4.3 patient years NS: RR= 0.84 (95%CI 0.53-1.35)	
				Blood pressure	Atenolol 50 mg: 4/3 mm Hg decrease Placebo: BP unaffected NT	
				Harms		
				NR		
				AE's		
				Withdrawal from study due to side effects (bradycardia, hypotension, congestive cardial failure, AV block or subjective discomfort)	Atenolol 50mg: 17% (13.4% subjective discomfort) Placebo: 10%	

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Dutch TIA Trial Study Group '93 Design: RCT P	n= 1473 mean age: NR Age>65y: 7% Mean BP at baseline: 158/91 mmHg Mean CHADS score: NR <u>Incl</u> - Aspirin treatment - TIA or nondisabling ischemic stroke ≤3months <u>Excl</u> - Cerebral ischemia from causes other than arterial thrombosis or arterial embolism - Contraindication against beta-blocker - Strict indication for beta-blocker	Mean: 2.6y	Atenolol 50mg vs placebo	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING:2 /2 ATTRITION: 1/1 - FU: 97% - ITT: yes - Other important methodological remarks? - sample size too small to provide adequate power (n=5560 patient years per treatment group was needed) - Dutch TIA trial also compared aspirin low dose (30mg/d) vs medium dose (283mg/d), described in a different paper - Sponsor: ICI Farma
				Mortality from vascular causes, nonfatal stroke or nonfatal myocardial infarction (PE)	Atenolol 50 mg:13.3% Placebo:12.8% NS: Crude HR=1.04 (95%CI 0.78-1.37)	
				Mortality	Atenolol 50 mg: 8.7% Placebo:7.8% NS: Crude HR=1.13 (95%CI 0.79-1.61)	
				Mortality from vascular causes	Atenolol 50 mg:5.6% Placebo:4.5% NS: Crude HR=1.28 (95%CI 0.81-2.02)	
				Mortality from vascular causes + nonfatal stroke	Atenolol 50 mg:11.1% Placebo:10.9% NS: Crude HR=1.01 (95%CI 0.74-1.37)	
				Fatal stroke	Atenolol 50 mg:1.5% Placebo: 1.9% NS: Crude HR=1.40 (95%CI 0.56-3.47)	
				Fatal and nonfatal stroke	Atenolol 50 mg:7.1% Placebo:8.4% NS: Crude HR=0.84 (95%CI 0.58-1.22)	
				Cardiac death	Atenolol 50 mg:3.8% Placebo: 3.2% NS: Crude HR=1.20 (95%CI 0.70-2.07)	
				Cadiac death, nonfatal MI	Atenolol 50 mg:6.1% Placebo:0.54% NS: Crude HR=1.15 (95%CI 0.75-1.77)	
				Blood pressure at 4 months	Atenolol 50 mg: -8.0 mm Hg systolic Placebo: -2.2 mm Hg systolic **SS: Systolic MD = 5.8mm Hg (95%CI 2.9-8.6)** **Diastolic MD= 2.9 mm Hg (95% CI 1.5-4.4)**	
				Harms		
				AE's		
				Any adverse effect	Atenolol 50 mg: 21.0% Placebo: 13.9% **SS: RR=1.50 (95%CI 1.20-1.89)**	
				Hypotension	Atenolol 50 mg: 1.9% Placebo: 0.5% NT	
				Bradycardia	Atenolol 50 mg:2.7% Placebo:0.4% NT	

4.3.1.4.bis. Conclusion: β-blockers vs. placebo

<table>
<tr><td colspan="6">Atenolol 50mg vs placebo (Dutch TIA Trial Study Group '93, Eriksson '95)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="8">N=2,

n=2139</td><td rowspan="8">Mean 2.6y</td><td rowspan="8">- Recent TIA or stroke≤3m
- Mean BP 160/90
- 1 study did not report age (93%<65y), other study mean age 71y

Exclusion
- Contra-indication for beta-blocker
- Strict indication for beta blocker</td><td>Mortality from vascular causes, nonfatal stroke or nonfatal myocardial infarction</td><td colspan="2">Reported in 1/2 trials
Crude HR=1.04 (95%CI 0.78-1.37)
⇨ NS</td></tr>
<tr><td>Total mortality, non-fatal stroke, non-fatal myocardial infarction</td><td colspan="2">Reported in 1/2 trials
RR= 0.96 (95%CI 0.74-1.25)
⇨ NS</td></tr>
<tr><td>Mortality</td><td colspan="2">Reported in 2/2 trials
⇨ NS</td></tr>
<tr><td>Mortality from vascular causes</td><td colspan="2">Reported in 2/2 trials
⇨ NS</td></tr>
<tr><td>Fatal stroke</td><td colspan="2">Reported in 2/2 trials
⇨ NS</td></tr>
<tr><td>Cardiac death</td><td colspan="2">Reported in 2/2 trials
NS</td></tr>
<tr><td>Blood pressure</td><td colspan="2">Reported in 2/2 trials
1 trial MD=5.8/2.9mmHg
⇨ SS
1 trial MD=4/3mmHg (NT)</td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><td>Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td colspan="2">→ Moderate quality of evidence</td></tr>
<tr><td>-1 for inadequate power and unclear reporting of endpoints</td><td>OK</td><td>OK</td><td>OK</td><td colspan="2"></td></tr>
</table>

- Two (older) trials examine the comparison of atenolol 50 mg/d with placebo in patients with a recent history of stroke or TIA. Treatment with atenolol did not reduce the incidence of recurrent stroke or other cardiovascular events. These trials were underpowered. The trials also examined the effect of atenolol as a molecule (vasodilatory properties) and the reduction in blood pressure was regarded as an epiphenomenon. In 1 trial, participants who reached a blood pressure of <140/80 were even removed from the study.

GRADE: moderate quality of evidence

- The limited information on adverse events reported in this trial does not allow to draw conclusions.

4.3.1.5. ARA vs. placebo

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Yusuf 2008 PRoFESS Design: RCT P	n= 20,332 - mean age: 66y - mean BP at entry: 144/84 mm Hg - CHADS: NR <u>Incl</u> - recent ischemic stroke (less than 90 days or 90-120 days if ≥2 additional risk factors) <u>Excl</u> - primary hemorrhagic stroke - severe disability after qualifying stroke - contraindications to one of the study antiplatelet agents - prestrike dementia - stroke due to surgical procedure - brain tumor - uncontrolled hypertension >180/110 mm Hg - systolic BP <120 mm Hg - severe renal insufficiency - Severe hepatic	Mean: 2.5 y	Telmisartan 80 mg vs placebo	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 1/2 ATTRITION: 1/1 - FU: 99,4% - ITT: yes - Other important methodological remarks? - Inclusion protocol modified after 6.000 patients to include 50-54y and less recent stroke if ≥risk factors - This study also compared (acetylsalicylic acid + extended-release dipyridamole) with clopidogrel, not reported in this article - Sponsor: Boehringer Ingelheim
				Recurrent stroke (any type) (PE)	Telmisartan 80mg: 8.7% Placebo: 9.2% NS: HR 0.95 (95%CI 0.86 – 1.04), p=0.23	
				Major cardiovascular events (death from cardiovascular causes, recurrent stroke, myocardial infarction, new or worsening heart failure)	Telmisartan 80mg: 13.5% Placebo: 14.4% NS: HR 0.95 (95%CI 0.87 – 1.01), p=0.11	
				New-onset diabetes	Telmisartan 80 mg: 1.7% Placebo: 2.1% NS: HR 0.82 (95%CI 0.65 – 1.04), p=0.10	
				Mortality	Telmisartan 80 mg: 7.4% Placebo: 7.3% NS: HR 1.03 (95%CI 0.93 – 1.14), p=0.55	
				Mean blood pressure during follow up	Telmisartan 3.8/2.0mm Hg lower than placebo NT	
				Harms		
				Bleeding outcomes		
				Intracranial	Telmisartan 80 mg: 1.1% Placebo: 1.4% NS: HR 0.81 (95%CI 0.63-1.05)	
				Major bleeding	Telmisartan 80 mg: 3.8% Placebo:3.9% NS	
				AE's		
				Total AE leading to discontinuation	Telmisartan 80 mg: 14.3% Placebo: 11.1% **SS: p<0.001**	
				Hypotensive symptoms leading to discontinuation	Telmisartan 80 mg: 3.9% Placebo: 1.8% **SS: p<0.001**	

	dysfunction - Current active peptic ulcer disease - Severe coronary artery disease - History of thrombocytopenia - Hemostatic disorder - Use of (other) antithombotics or antiplatelets			Hypotensive symptoms	Telmisartan 80 mg: 3.9% Placebo: 1.8% **SS: p<0.001**	

4.3.1.5.bis. Conclusion: ARA vs. placebo

Telmisartan 80mg vs placebo (Yusuf 2008 PRoFESS)				
N/n	**Duration**	**Population**	**Results**	
N=1, n=20,332	Mean 2.5y	- recent ischemic stroke (<90 d or 90-120 d if ≥2 additional risk factors) - mean age: 66y - mean BP at entry: 144/84 mm Hg Exclusion - primary hemorrhagic stroke - severe disability after qualifying stroke - uncontrolled hypertension - severe renal insufficiency - Severe hepatic dysfunction - Severe coronary artery disease	Recurrent stroke (any type) (PE)	HR 0.95 (95%CI 0.86 – 1.04) ⇨ NS
			Major cardiovascular events (death from cardiovascular causes, recurrent stroke, myocardial infarction, new or worsening heart failure)	HR 0.95 (95%CI 0.87 – 1.01) ⇨ NS
			Mortality	Telmisartan 80 mg: 7.4% Placebo: 7.3% HR 1.03 (95%CI 0.93 – 1.14) ⇨ NS
			Mean blood pressure during follow up	Telmisartan 3.8/2.0mm Hg lower than placebo NT
			Harms	
			Intracranial bleeding	HR 0.81 (95%CI 0.63-1.05) ⇨ NS
			Major bleeding	Telmisartan 80 mg: 3.8% Placebo:3.9% ⇨ NS
			AE	
			Total AE leading to discontinuation	Telmisartan 80 mg: 14.3% Placebo: 11.1% ⇨ **SS**
			Hypotensive symptoms leading to discontinuation	Telmisartan 80 mg: 3.9% Placebo: 1.8% ⇨ **SS**

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→High quality of evidence**
OK	NA	OK	OK	

- In patients with a recent ischaemic stroke, telmisartan 80 mg/d could not diminish the incidence of recurrent stroke or other cardiovascular events. Patients included in this trial had a blood pressure of 144/84 mm Hg at entry; it was only weakly influenced by telmisartan: mean 3.2/2.0 mm Hg lower than with placebo.

GRADE: high quality of evidence

- Termination of treatment due to hypotension occurred significantly more often with telmisartan than with placebo (3.9 vs 1.8%).

4.3.2. Antihypertensives compared

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Schrader 2005 (MOSES) Design: RCT P	n= 1405 mean age 68y <u>Incl</u> - history of cerebrovascular events: TIA, PRIND, ischemic stroke, cerebral hemorrhage (documented by CT or MRI) within past 24 m - AND treatment requiring hypertension <u>Excl</u> - Internal carotid artery occlusion or stenosis >70% - Heart failure NYHA grade III-IV - Age>85y at time of CV event - Patient on anticoagulants for cardiac arrhythmia - High-grade aortic or mitral valve stenosis - Unstable angina pectoris	Mean: 2.5y	Eprosartan 600mg vs nitrendipine 10 mg Dose increase if necessary, combination therapy if necessary. Target RR: <140/90 mm Hg	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 96% - ITT: 'modified' ITT - Other important methodological remarks: - unbalanced composite endpoint (TIA included). - All recurrent events included Sponsor: Solvay Pharmaceuticals GmbH and Aventis Pharma Germany
				Total mortality and all cardiovascular and cerebrovascular events (including TIA), including all recurrent events (PE)	Eprosartan 600mg: 13.3/100 patient years Nitrendipine 10 mg: 16.7/100 patient years **SS: IDR=0.79 (95%CI 0.66-0.96), p=0.014**	
				Total cerebrovascular events (fatal and non fatal)	Eprosartan 600mg: 6.56/100 patient years Nitrendipine 10 mg: 8.78/100 patient years **SS: IDR= 0.75 (95%CI 0.58-0.97), p=0.026**	
				First occurrence of cerebrovascular event	Eprosartan 600mg:80 Nitrendipine 10 mg: 89 NS: HR=0.88 (95%CI 0.65-1.20), p=0.425	
				Total cardiovascular events (fatal and non fatal)	Eprosartan 600mg: 4.95/100 patient years Nitrendipine 10 mg: 6.62/100 patient years NS: 0.75 (95%CI 0.55-1.02), p= 0.061	
				First occurrence of cardiovascular event	Eprosartan 600mg: 60 Nitrendipine 10 mg: 84 **SS: HR=0.69 (95%CI 0.50-0.97), p=0.031**	
				Mortality	Eprosartan 600mg: 57 Nitrendipine 10 mg: 52 SS: HR=1.07 (95%CI 0.73-1.56), p=0.725	
				Blood pressure	Eprosartan 600mg: 137.5/80.8 mmHg (SD 16.7/8.9) Nitrendipine 10 mg: 136.0/80.2 mmHg (SD 15.6/8.8) 'Similar' blood pressure control in both treatment arms (NT)	
				Harms		
				AE's		
				dizziness/hypotension	12.9% vs 10.6%, NT ('comparable')	
				pneumonia	10.8% vs 11.4%), NT	
				metabolic disorder	(5.5% vs 5.9%), NT	

4.3.2.bis. Conclusion: Antihypertensives compared

<table>
<tr><td colspan="5">Eprosartan 600 mg (+/- dose increase or combination therapy) vs nitrendipine 10 mg (+/- dose increase or combination therapy) (Schrader 2005=MOSES)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="2">Results</td></tr>
<tr><td rowspan="10">N=1, n=1405</td><td rowspan="10">Mean: 2.5y</td><td rowspan="10">- history of cerebrovascular events:<24 m
- treatment requiring hypertension
- mean age 68y
<u>Excl</u>
- Internal carotid artery stenosis >70%
- Heart failure NYHA grade III-IV
- Age>85y at time of CV event
- Anticoagulants for cardiac arrhythmia
- High-grade aortic or mitral valve stenosis
- Unstable angina pectoris</td><td>Total mortality and all cardiovascular and cerebrovascular events (including TIA), including all recurrent events (PE)</td><td>Eprosartan 600mg: 13.3/100 patient years
Nitrendipine 10 mg: 16.7/100 patient years
SS: IDR=0.79 (95%CI 0.66-0.96), p=0.014</td></tr>
<tr><td>Total cerebrovascular events</td><td>Eprosartan 600mg: 6.56/100 patient years
Nitrendipine 10 mg: 8.78/100 patient years
SS: IDR= 0.75 (95%CI 0.58-0.97), p=0.026</td></tr>
<tr><td>First occurrence of cerebrovascular event</td><td>Eprosartan 600mg:80
Nitrendipine 10 mg: 89
NS: HR=0.88 (95%CI 0.65-1.20), p=0.425</td></tr>
<tr><td>Total cardiovascular events (fatal and non fatal)</td><td>Eprosartan 600mg: 4.95/100 patient years
Nitrendipine 10 mg: 6.62/100 patient years
NS: 0.75 (95%CI 0.55-1.02), p= 0.061</td></tr>
<tr><td>First occurrence of cardiovascular event</td><td>Eprosartan 600mg: 60
Nitrendipine 10 mg: 84
SS: HR=0.69 (95%CI 0.50-0.97), p=0.031</td></tr>
<tr><td>Mortality</td><td>Eprosartan 600mg: 57
Nitrendipine 10 mg: 52
NS: HR=1.07 (95%CI 0.73-1.56), p=0.725</td></tr>
<tr><td>Blood pressure</td><td>137.5/80.8 mmHg (SD 16.7/8.9)
vs 136.0/80.2 mmHg (SD 15.6/8.8)
‘Similar’ blood pressure control (NT)</td></tr>
<tr><td colspan="2">AE’s</td></tr>
<tr><td>dizziness/hypotension</td><td>12.9% vs 10.6% (NT : ‘comparable’)</td></tr>
<tr><td colspan="5">GRADE assessment</td></tr>
<tr><td>Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td>→ Moderate quality of evidence</td></tr>
<tr><td>OK</td><td>NA</td><td>-1 for unbalanced composite endpoint</td><td>OK</td><td></td></tr>
</table>

- This RCT compares a blood pressure-lowering treatment with eprosartan to a treatment with nintrendipin. The composite primary endpoint includes mortality, all cerebrovascular events (TIA included) and cardiovascular events, with inclusion of the recurrent events. The authors state that eprosartan is superior for this primary endpoint.
However, no significant differences can be found for ‘mortality’ or ‘first occurrence of cardiovascular event’. Maybe the results for the primary outcome can be explained by the more common occurrence of TIA.
- On base of this single trial it is impossible to draw any conclusion about the possible superiority of eprosartan for the prevention of stroke or a decrease in total mortality.

GRADE: Moderate quality of evidence

- This trial reports no outcomes as to adverse events.

4.4. Cholesterol lowering treatment after stroke/TIA in a patient without AF

4.4.1. Statins vs. placebo

Ref	n / Population	Duration	Comparison	Outcomes (first event)		Methodological
SPARCL 2006 + subgroup analysis CE 28 Sillisen 2008 Design: RCT	n= 4731 -increased risk of stroke -mean age: 63 -Entry event: 70% stroke; 30% TIA -62% systemic hypertension -TTR INR: % NA <u>Inclusion</u> - >18 years - ischemic or hemorrhagic stroke or TIA 1 to 6 months before randomization. (if hemorrhagic stroke patients were included when at risk for ischemic stroke or coronary heart disease) - Rankin score ≤ 3 - 2.6 ≤ LDL cholesterol ≤ 4.9 mmol/l <u>Exclusion</u> - history of CHD - significant peripheral vascular disease - atrial fibrillation, - prosthetic heart valves, - clinically significant mitral stenosis - sinus node dysfunction - uncontrolled	Median follow-up: 4.9y	Atorvastatin 80 mg vs placebo	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION:1/1 - FU: 96% - ITT: yes - Other important methodological remarks? proof of prespecified analysis of subgroup (not clear in the design of study) - Sponsor:Pfizer
				Stroke (fatal or non-fatal) (PE)	**Atorvastatine 11.2% vs 13.1% placebo p= 0.05** **SS: Pre-specified adjusted HR = 0.84** **(95% CI 0.71-0.99) p=0.03**	
				With Carotid Stenosis (CT) (n=1007)	**Atorvastatine 11.2% vs 16.1% placebo** **SS: Pre-specified adjusted HR = 0.67** **(95% CI 0.47-0.94) p= 0.0197**	
				Without CS (n=3724)	Atorvastatine 11.2% vs 12.3% placebo NS: Pre-specified adjusted HR = 0.90 (95% CI 0.74-1.08) p=0.2413	
				Nonfatal stroke (PE)	Atorvastatine 10.4% vs 11.8% placebo p= 0.14 NS: Pre-specified adjusted HR = 0.87 (95% CI 0.73-1.03) p=0.11	
				With CS (n=1007)	Atorvastatine 11.2% vs 14.0% placebo NS: Pre-specified adjusted HR = 0.77 (95% CI 0.54-1.10) p=0.1449	
				Without CS (n=3724)	Atorvastatine 10.3% vs 11.2% placebo NS: Pre-specified adjusted HR = 0.89 (95% CI 0.74-1.09) p=0.2654	
				Fatal stroke (PE)	**Atorvastatine 1.0% vs 1.7% placebo p= 0.04** **SS: Pre-specified adjusted HR = 0.57** **(95% CI 0.35-0.95) p=0.03**	
				With CS (n=1007)	**Atorvastatine 0% vs 2.9% placebo** NT	
				Without CS (n=3724)	Atorvastatine 1.3% vs 1.4% placebo NS: Pre-specified adjusted HR = 0.91 (95% CI 0. 52-1.59) p=0.7385	
				Stroke or TIA	**Atorvastatine 15.9% vs 20.1% placebo p<0.001** **SS: Pre-specified adjusted HR = 0.77** **(95% CI 0.67-0.88) p<0.001**	
				With CS (n=1007)	**Atorvastatine 16.0% vs 23.0% placebo** **SS: Pre-specified adjusted HR = 0.66** **(95% CI 0.50-0.89) p=0.0053**	
				Without CS (n=3724)	**Atorvastatine 15.8% vs 19.3% placebo**	

	hypertension - other cardiac sources of embolism, - subarachnoid hemorrhage - carotid revascularization <30days - hepatic dysfunction - severe renal dysfunction - use of any drugs affecting lipids levels or immunosuppressive agents, azole antifungals, or drugs associated with rhabdomyolysis in combination with statins				**SS: Pre-specified adjusted HR = 0.80** **(95% CI 0.69-0.94) p=0.0049**	
				TIA	**Atorvastatine 6.5% vs 8.8% placebo p=0.004** **SS: Pre-specified adjusted HR = 0.74** **(95% CI 0.60-0.91) p=0.004**	
				Major coronary event	**Atorvastatine 3.4% vs 5.1% placebo p=0.006** **SS: Pre-specified adjusted HR = 0.65** **(95% CI 0.49-0.87) p=0.003**	
				With CS (n=1007)	Atorvastatine 3.9% vs 6.4% placebo NS: Pre-specified adjusted HR = 0.57 (95% CI 0.32-1.00) p=0.0503	
				Without CS (n=3724)	**Atorvastatine 3.3% vs 4.7% placebo** **SS: Pre-specified adjusted HR = 0.69** **(95% CI 0.50-0.96) p=0.0257**	
				Death from cardiac causes	Atorvastatine 1.7% vs 1.6% placebo p=0.90 NS: Pre-specified adjusted HR = 1.00 (95% CI 0.64-1.56) p=1.00	
				Non fatal myocardial infarction	**Atorvastatine 1.8% vs 3.5% placebo p=0.001** **SS: Pre-specified adjusted HR = 0.51** **(95% CI 0.35-0.74) p<0.001**	
				Major cardiovascular event	**Atorvastatine 14.1% vs 17.2% placebo p=0.005** **SS: Pre-specified adjusted HR = 0.80** **(95% CI 0.69-0.92) p=0.002**	
				With CS (n=1007)	**Atorvastatine 14.2% vs 21.0% placebo** **SS: Pre-specified adjusted HR = 0.64** **(95% CI 0.47-0.86) p= 0.0035**	
				Without CS (n=3724)	Atorvastatine 14.1% vs 16.1% placebo NS: Pre-specified adjusted HR = 0.85 (95% CI 0.72-1.00) p=0.0561	
				Any cardiovascular event	**Atorvastatine 22.4% vs 29.0% placebo p<0.001** **SS: Pre-specified adjusted HR = 0.74** **(95% CI 0.66-0.83) p<0.001**	
				With CS (n=1007)	**Atorvastatine 24.1% vs 37.7% placebo** **SS: Pre-specified adjusted HR = 0.58** **(95% CI 0.46-0.73) p<0.0001**	
				Without CS (n=3724)	**Atorvastatine 21.5% vs 26.5% placebo** **SS: Pre-specified adjusted HR = 0.79** **(95% CI 0.69-0.90) p=0.0004**	
				Death	Atorvastatine 9.1% vs 8.9% placebo p=0.77 NS: Pre-specified adjusted HR = 1.00 (95% CI 0.82-1.21) p=0.98	
				Death from cardiovascular disease	Atorvastatine 3.3% vs 4.1% placebo p=0.14 NS: Pre-specified adjusted HR = 0.78	

					(95% CI 0.58-1.06) p=0.11	
				Harms		
				AE's		
				Any serious adverse event	Atorvastatine 41.8% vs 41.2% placebo: NS (in text)	
				Any adverse event	Atorvastatine 93.0% vs 91.1% placebo NT	
				Rhabdomyolysis	Atorvastatine 0.1% vs 0.1% placebo NT	
				Alanine or aspartate aminotransferase >3X Upper limit normal range at 2 consecutives measures	**Atorvastatine 2.2% vs 0.5% placebo** **SS: p<0.001**	
				With CS (n=1007)	Atorvastatine 0.6% vs 0.2% placebo (NT)	

Subgroup analysis: carotid stenosis (average degree of stenosis: 51% ±29%)
The group with carotid artery stenosis had greater benefit when all cerebro- and cardiovascular events were combined. In this subgroup, treatment with atorvastatin was associated with a 33% reduction in the risk of any stroke (HR= 0.67, 95% CI: 0.47-0.94) and a 43% reduction in risk of major coronary events (HR= 0.57, 95% CI: 0.32-1.00)
Consistent with the overall results of the SPARCL intention to treat population, intense lipid lowering with atorvastatin reduced the risk of cerebro- and cardiovascular events in patients with and without carotid stenosis. The carotid stenosis group may have greater benefit but this substudy was not powered to show a statistical significant difference in the primary end point (stroke) of the SPARCL trial.

4.4.1.bis. Conclusion: Statins vs. placebo

Atorvastatin 80mg vs placebo (SPARCL 2006)				
N/n	**Duration**	**Population**	**Results**	
N= 1 n= 4731	median follow-up: 4.9y	-patients with previous stroke or TIA -mean age: 63y -AF excluded	Stroke (fatal or non-fatal)	**Atorvastatin 11.2% vs 13.1% placebo (p=0.05)** **HR= 0.84 (95% CI: 0.71-0.99) => SS**
			TIA	**Atorvastatin 6.5% vs 8.8% placebo (p=0.004)** **HR= 0.74 (95% CI: 0.60-0.91) => SS**
			Major coronary event	**Atorvastatin 3.4% vs 5.1% placebo (p=0.006)** **HR= 0.65 (95% CI: 0.49-0.87) => SS**
			Myocardial infarction (non-fatal)	**Atorvastatin 1.8% vs 3.5% placebo (p=0.001)** **HR= 0.51 (95% CI: 0.35-0.74) => SS**
			Mortality	Atorvastatin 9.1% vs 8.9% placebo (p=0.77) HR= 1.00 (95% CI: 0.82-1.21) => NS
			Any adverse event	Atorvastatin 93.0% vs 91.1% placebo => NT
			Elevated liver enzymes	**Atorvastatin 2.2% vs 0.5% placebo (p<0.001) => SS**
GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→High quality of evidence**
OK	OK	OK	OK	

- In patients with previous stroke or TIA, treatment with atorvastatin is associated with a lower incidence of recurrent stroke, TIA or myocardial infarction. However, the mortality was not significantly different.

GRADE: high quality of evidence

- This trial does not report a significance test for the total incidence of adverse events. Treatment with atorvastatin was associated with a higher incidence of elevated liver enzymes.

5. Surgery + medical treatment vs. medical treatment alone

5.0. Legend of the evidence tables

Ref	n / Population	Duration	Comparison	Efficacy outcomes (with indication of primary endpoint)		Harms	Methodological
Design: - RCT P / CO - MA - SR	n= -mean age - baseline data: • AF y/n • Previous stroke/TIA • CHADS score • TTR INR			Vascular events (composite endpoint, definition according to trial)		Other AE	- Jadad score RANDO: /2 BLINDING: /2 ATTRITION: /1 - FU: % - ITT: Yes/No - Other important methodological remarks? - Sponsor:
				Stroke			
				Ischemic stroke			
				Systemic embolism			
				Hemorrhagic stroke			
				Mortality			
				Vascular mortality			
				Myocardial infarction			
				Any bleeding			
				Major bleeding (definition according to trial)			
				Minor bleeding			
				Intracranial bleeding			

AE= adverse event
AF= atrial fibrillation
AR= absolute risk
ARR= absolute risk reduction
CI= Confidence Interval
CO= crossover RCT
FU= follow-up
HR= hazard ratio
ICH= intracerebral haemorrhage
IS= ischaemic stroke
ITT= intention-to-treat analysis
MA= meta-analysis
MI= myocardial infarction
N= number of patients
NR= not reported
NS= not statistically significant
NT= no statistical test
OAC= oral anticoagulants
OR= odds ratio
P= parallel RCT
PE= primary endpoint
RR= relative risk
RRR= relative risk reduction
RIND= reversible ischaemic neurological deficit
SA= subgroupanalysis
SAH= subarachnoid hemorrhage
SE= standard error
SS= statistically significant
SR= systematic review
TIA= transient ischaemic attack

5.1. Carotid endarterecomy + medical treatment vs. medical treatment alone in case of asymptomatic carotid stenosis

Ref	N/n	Comparison	Outcomes	Results
*Chambers BR. 2005 Cochrane Systematic review Design: systematic review and meta-analysis Search date: may 2004	N= 3 n= 5.223	Carotid endarterectomy plus medical therapy vs medical treatment In patients with asyptomatic carotid stenosis (>50% stenosis)	Perioperative stroke or death or any subsequent stroke (3/3)	**RR 0.69 (95%CI 0.57-0.83) SS in favour of surgery** **VA: 1% ARR over 4y** **ACAS: 3% ARR over 2.7y** **ACST: 3.1% ARR over 3.4y**
			Perioperative stroke or death or subsequent ipsilateral stroke (3/3) over 3-4 years	**RR 0.71 (95%CI 0.55-0.90) SS in favour of surgery**
			Any stroke or death (3/3)	RR 0.92 (95%CI 0.83-1.02) NS
			Perioperative stroke or death (2/3)	**RR 6.49 (95%CI 2.53-16.61) SS in favour of medical treatment**
			Subgroup analysis (post hoc) for the outcome perioperative stroke or death or subsequent carotid stroke (ACAS and ACST)	
			Gender : Men (2/3) Female (2/3)	 **RR 0.49 (95%CI 0.36-0.66) SS in favour of surgery** RR 0.96 (95%CI 0.64-1.44) NS
			Age: Younger (<68y or <75y) Older	 **RR 0.50 (95%CI 0.37-0.68) SS in favour of surgery** RR 0.91 (95%CI 0.61-1.36) NS

Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
VACS Hobson 1993 RCT P	444	Asymptomatic carotid stenosis (50-99%) Male veterans Mean age 64.5	4.0y	Carotid endarterectomy + aspirine 650mg bd vs aspirin 650mg	- Jadad score: 4/5 - FU: 92% - ITT: yes 281 eligible patients refused randomization Patients in medical arm allowed to cross over to CEA after TIA
ACAS 1995 RCT P	1662	Asymptomatic carotid stenosis (>60%) Mean age 67 Exclusion pt older than 80	2.7y	Carotid endarterectomy + aspirin 325/d vs aspirin 325mg/d	- Jadad score: 5/5 - FU: 99% - ITT: yes 40% of surgeon applicants rejected. Patients in medical arm allowed to cross over to CEA after TIA
ACST 1994 RCT P	3120	Asymptomatic carotid stenosis (>60%) Excl: history of endarterectomy, coronary stenosis and cardiogenic embolism, >75y	3.4y	Immediate carotid endarterectomy + standard medical therapy incl antiplatelet drugs vs deferred carotid therapy + medical therapy incl antiplatelet drugs	- Jadad score: 5/5 - FU: 98% - ITT: yes -Patients in medical arm allowed to cross over to CEA after TIA Long term medical therapy did not differ significantly between groups. -Use of antihypertensive and lipid lowering drugs increased during the study.

Results ASCT after 10 years Halliday 2010	Primary outcome: Perioperative stroke or death or any subsequent stroke	ARR 4.6% (95%CI 1.2-7.9) **SS**	Remarks: -34% of patients initial deferred surgery underwent CEA within 10 years
	Risk CVA (non perioperative)	ARR 5.9% (95%CI 4.0-7.8) RR 0.54 (95%CI 0.43-0.68, p<0.0001) RRR 46% **SS**	

5.1.bis. Conclusion: Carotid endarterectomy + medical treatment vs. medical treatment alone in case of asymptomatic carotid stenosis

<table>
<tr><td colspan="6">Carotid endarterectomy plus medical therapy vs. medical therapy alone for asymptomatic carotid stenosis. (MA Chambers: ACAS '95, ACST '94, Hobson '93 (VACS))</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th colspan="3">Results</th></tr>
<tr><td rowspan="4">N=3,

n=5223</td><td rowspan="4">2.7-4y</td><td rowspan="4">-asymptomatic carotid artery stenosis
-2 trials > 60% stenosis, 1 trial 50-99%
-mostly male
-mean age 64.5-67y</td><td>Perioperative stroke or death or any subsequent stroke</td><td colspan="2">Reported in 3/3 trials
RR 0.69 (95%CI 0.57-0.83) SS in favour of surgery
VA-trial: 1% ARR over 4y
ACAS-trial: 3% ARR over 2.7y
ACST-trial: 3.1% ARR over 3.4y
ACST-trial: 4.6% ARR over 10y</td></tr>
<tr><td>Perioperative stroke or death or subsequent ipsilateral stroke over 3-4 years</td><td colspan="2">Reported in 3/3 trials
RR 0.71 (95%CI 0.55-0.90) SS in favour of surgery</td></tr>
<tr><td>Any stroke or death</td><td colspan="2">Reported in 3/3 trials
RR 0.92 (95%CI 0.83-1.02) NS</td></tr>
<tr><td>Perioperative stroke or death</td><td colspan="2">Reported in 2/3 trials
RR 6.49 (95%CI 2.53-16.61) SS in favour of medical treatment</td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><td>Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td colspan="2">→Moderate quality of evidence</td></tr>
<tr><td>OK</td><td>OK</td><td>-1 for no contemporary medical therapy</td><td>OK</td><td colspan="2"></td></tr>
</table>

Carotid endarterectomy + medical treatment is more effective than medical treatment alone in reducing the risk of stroke in patients with an asymptomatic carotid stenosis (60-99%): the risk of peri-operative stroke, mortality or recurrent stroke diminished with 31%. For the same endpoint, the results in 1 of the trials after 10 years follow-up showed an absolute risk reduction of 4.6%; this means NNT=22. For the composite endpoint of any stroke and mortality, no significant differences could be found.

The medical treatment was suboptimal in the first years of these trials (antihypertensives and statins); consequently these results are not fully applicable to the current treatment of carotid stenosis.

These results can only be interpreted in the context of a peri-operative risk of stroke or mortality <3%.

GRADE: moderate quality of evidence

5.2. Carotid endarterectomy + medical treatment vs. medical treatment alone in case of symptomatic carotid stenosis

Ref	N/n	Comparison	Outcomes	Results
Rerkasem* 2011 Design: meta-analysis Search date: 26/10/2010	N= 3 n= 6092	Surgery + best medical therapy vs best medical therapy In patients with symptomatic carotid artery stenosis	Any stroke or operative death	<30% stenosis**: RR 1.25 (95%CI 0.99 -1.56) (2/3 trials) 30-49% stenosis: RR 0.97 (95%CI 0.79-1.19) (2/3 trials) **50-69% stenosis: RR 0.77 (95%CI 0.63-0.94) (3/3 trials)** NNT at 5y to prevent 1 event: 13 **70-99% stenosis: RR 0.53 (95%CI 0.42-0.67) (3/3 trials)** Near-occlusion: RR 0.95 (95%CI 0.59-1.53) (2/3 trials)
			Ipsilateral ischaemic stroke and any operative stroke or operative death	<30% stenosis: RR 1.33 (95%CI 0.99 -1.79) (2/3 trials) 30-49% stenosis: RR 0.89 (95%CI 0.69-1.16) (2/3 trials) 50-69% stenosis: RR 0.82 (95%CI 0.64-1.05) (3/3 trials) NNT at 5y to prevent 1 event: 22 **70-99% stenosis: RR 0.40 (95%CI 0.30-0.54) (3/3 trials)** NNT at 5y to prevent 1 event: 6 Near-occlusion: RR 1.04 (95%CI 0.58-1.86) (2/3 trials)

Characteristics of included studies: see below

**: NASCET measured

Remarks:

-As trials differed in the methods of measurement of carotid stenosis and in the definition of stroke, the authors did a pooled analysis of individual patient data on 6092 patients after reassessment of the carotid angiograms and outcomes from all three trials using the primary electronic data files and redefined outcome events where necessary to achieve comparability.

-Complication rate of surgery less than 7% (risk of stroke or death)

-subgroup analysis showed most benefit in men, patients aged 75 years or over, and patient randomized within two weeks after their last ischaemic event.

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
ECST 1998 RCT	3024	-mean age 63 -78% TIA, 50% stroke -Ischaemic cerebrovascular event ipsilateral to carotid stenosis, within 6 months of randomization -67-99% stenosis (NASCET-measured)	2.7y	-Carotid endarterectomy as soon as possible vs avoid surgery if at all possible, for as long as possible. -Both groups medication (ASA ? dose)	- Jadad score: 3/5 - FU: 99% - ITT: yes
NASCET 1991 RCT	2926	-mean age 66y -68% TIA, 32% stroke -Ischaemic cerebrovascular event ipsilateral to carotid stenosis, within 4 months of randomization -0-99% stenosis (NASCET-measured) -life expectancy of minimal 5y	18mo	-Carotid endarterectomy as soon as possible vs no carotid endarterectomy for stenosis 70-99% -Carotid endarterectomy as soon as possible versus carotid endarerectomy in the event of progression to > 70% -Both groups medication (ASA 1300mg)	- Jadad score: 3/5 - FU: 100% - ITT: yes
VASCP Mayberg 1991 RCT	193	-mean age 65 -76% TIA, 24% stroke -only men - Ischaemic cerebrovascular event ipsilateral to carotid stenosis, within 4 months of randomization -50-99% stenosis (NASCET-measured)	1y	-Carotid endarterectomy as soon as possible vs no carotid endarterectomy for stenosis 70-99% -Both groups medication (ASA 325mg)	- Jadad score: 3/5 - FU: 99% - ITT: yes -trial stopped after results of NASCET and ECST

5.2.bis. Conclusion: Carotid endarterectomy + medical treatment vs. medical treatment alone in case of symptomatic carotid stenosis

Carotid endarterectomy plus medical therapy vs medical therapy alone for symptomatic carotid stenosis. (MA Rerkasem: Boiten '96 (ECST), Barnett '91 (NASCET), Mayberg '91 (VACSP))				
N/n	**Duration**	**Population**	**Results**	
N=3, n=6092	1-2.7y	-Symptomatic carotid artery stenosis -NASCET measured -mean age 63-65 - Non disabling Ischaemic cerebrovascular event ipsilateral to carotid stenosis, within 4 to 6 months of randomization -mostly male	Any stroke or operative death	<30% stenosis: RR 1.25 (95%CI 0.99 -1.56) (2/3 trials)
				30-49% stenosis: RR 0.97 (95%CI 0.79-1.19) (2/3 trials)
				50-69% stenosis: RR 0.77 (95%CI 0.63-0.94) (3/3 trials) NNT at 5y to prevent 1 event: 13
				70-99% stenosis: RR 0.53 (95%CI 0.42-0.67) (3/3 trials)
				Near-occlusion: RR 0.95 (95%CI 0.59-1.53) (2/3 trials)
			Ipsilateral ischaemic stroke and any operative stroke or operative death	<30% stenosis: RR 1.33 (95%CI 0.99 -1.79) (2/3 trials)
				30-49% stenosis: RR 0.89 (95%CI 0.69-1.16) (2/3 trials)
				50-69% stenosis: RR 0.82 (95%CI 0.64-1.05) (3/3 trials) NNT at 5y to prevent 1 event: 22
				70-99% stenosis: RR 0.40 (95%CI 0.30-0.54) (3/3 trials) NNT at 5y to prevent 1 event: 6
				Near-occlusion: RR 1.04 (95%CI 0.58-1.86) (2/3 trials)

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
-1 for not blinding	OK	OK	OK	

- These trials show a clear superiority of carotid endarterectomy + medical treatment compared to medical treatment alone in patients with carotid artery stenosis 70-99% (NASCET measurement). 6 patients should undergo surgery to prevent to prevent 1 ipsilateral ischaemic stroke / any stroke / operative death for a follow-up period of 5 years.
- Benefit from surgery was greatest in men, patients aged 75 y or over, and patients randomized within 2 weeks after their last ischaemic event.
- These results are generalisable only to centers with low complication rates (7% risk of stroke or death).
- The benefit of surgery was smaller in case of 50-69% stenosis (NNT= 22 / 5 years).
- There was no evidence of benefit in other degrees of stenosis.

GRADE: moderate quality of evidence

5.3. Intra-extracranial bypass+ medical treatment vs. medical treatment alone in case of symptomatic occlusion of the carotid artery

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Powers 2011 COSS Design: RCT P	n= 195 mean age 58 Incl -recent symptomatic atherosclerotic internal carotid artery occlusion. -ateriographically confirmed complete occlusion -hemispheric symptoms within 120 days -hemodynamic cerebral ischemia identified by PETscan -intracranial and extracranial arteries suitable for anastomosis	2y	Anastomosis of superficial temporal artery branch to a middle cerebral artery + medical therapy vs medical therapy alone	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 0/2 ATTRITION: 1/1 - FU: 99% - ITT: yes - Other important methodological remarks? -trial terminated early for futility: a clinically meaningful difference in favor of surgery would not be detectable without a increase in sample size -open label - Sponsor: National Institute of Neurological Disorders and Stroke (NINDS
				All stroke and death 30 days after surgery or randomization and ipsilateral ischemic stroke (PE) 2 years after randomization	ARR 1.7 (21% surg group vs 22.7% non surg) (95%CI -10.4 to 13.8), p=0.78 NS	
				All stroke	ARR 3.5 (23.4% surg group vs 26.9% non surg- (95%CI -9.2 to 16.1), p=0.59 NS	
				Death	ARR 4.0 (95%CI -1.2 to 9.7), p=0.13	

5.3.bis. Conclusion: . Intra-extracranial bypass+ medical treatment vs. medical treatment alone in case of symptomatic occlusion of the carotid artery

xtracranial-intracranial bypass plus medication versus medication alone. (Powers 2011, COSS)				
N/n	**Duration**	**Population**	**Results**	
N=1, n 195	2y	-mean age 58 -recent symptomatic atherosclerotic internal carotid artery occlusion. -ateriographically confirmed complete occlusion -hemispheric symptoms within 120 days -hemodynamic cerebral ischemia identified by PETscan -intracranial and extracranial arteries suitable for anastomosis	All stroke and death 30 days after surgery or randomization and ipsilateral ischemic stroke 2 years after randomization (PE)	ARR= 1.7 (21% surg group vs 22.7% non surg) (95%CI -10.4 to 13.8), p=0.78 NS
			All stroke	ARR= 3.5 (23.4% surg group vs 26.9% non surg- (95%CI -9.2 to 16.1), p=0.59 NS
			Death	ARR= 4.0 (95%CI -1.2 to 9.7), p=0.13

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
-1 for not blinding	NA	OK	OK	

Extra-intracranial bypass in addition to medical treatment is not superior to medical treatment alone in patients with a recent symptomatic occlusion of the internal carotid artery.

GRADE: Moderate quality of evidence

5.4. Endovascular + medical treatment vs. medical treatment alone in case of (a)symptomatic carotid stenosis

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Ederle 2009 CAVATAS -MED Design: RCT P	-n= 40 -mean stenosis of 79% in endovascular vs 82% In medical group -age: 67y endovascular 71.5 medical treatment <u>Incl:</u> -Patients with carotid stenosis not suitable for endarterectomy for surgical or medical contraindications <u>Excl:</u> -disabling stroke without useful recovery or function	10y	Endovascular treatment* vs medical treatment (according to local guidelines and protocols) Asymptomatic stenosis: 25% in endovascular group, 50% in medical group	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 0/2 ATTRITION: 1/1 - FU: 100% - ITT: yes - Other important methodological remarks? -underpowered - Important differences in baseline risk factors between treatment groups -patients assigned to endovascular treatment were younger than patients assigned to medical treatment (67 vs 71,5y) -twice as many patients in medical group had history of ischaemic heart disease. -More patients with elevated cholesterol in endovascular group (13 vs 3). -No data relating to antihypertensive or lipid-lowering medication. -no protocol with targets for blood pressure control of cholesterol levels - Sponsor: not industry funded
				Stroke or death (PE) 3y cumulative rate	36% vs 35.4%, HR: 1.02 (95%CI 0.41-2.57) NS	
				Any Stroke	20% vs 20% HR: 1.01 (95%CI 0.25-4.02) NS	
				Any stroke or TIA	35% vs 50%, HR: 0.66 (95%CI 0.09-2.33) NS	
				Death	35% vs 40% HR 0.88 (95%CI 0.32-2.43) NS	
				Harms		
				Risk of stroke, retinal infarction or death within 30 days of treatment	5% in endovascular group (95%CI 0.1-24.9)	

*: 9 patients balloon angioplasty without stenting, 7 patients received stentin (35%), 4 patients did not undergo assigned treatment. This trial started in ’92, stents available from ’94.

5.4.bis. Conclusion: Endovascular + medical treatment vs. medical treatment alone in case of (a)symptomatic carotid stenosis

Endovasculaire aanpak versus medicatie bij carotis stenose. (Ederle 2009, CAVATAS)				
N/n	**Duration**	**Population**	**Results**	
N=1, n=40	10y	-mean stenosis of 79% in endovascular vs 82% In medical group -mean age: 67y endovascular 71.5 medical treatment -Patients with carotid stenosis not suitable for endarterectomy for surgical or medical contraindications	Stroke or death (PE) 3y cumulative rate	36% vs 35.4%, HR: 1.02 (95%CI 0.41-2.57) NS
			Any Stroke	20% vs 20% HR: 1.01 (95%CI 0.25-4.02) NS
			Any stroke or TIA	35% vs 50%, HR: 0.66 (95%CI 0.09-2.33) NS
			Death	35% vs 40% HR 0.88 (95%CI 0.32-2.43) NS
			Risk of stroke, retinal infarction or death within 30 days of treatment	5% in endovascular group (95%CI 0.1-24.9)

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Very low quality of evidence**
-2 for not blinding and important differences between treatment groups	NA	OK	-1 for less than 40 patients in each treatment group	

This trial of low methodologial quality could not demonstrate any superiority of endovascular treatment (angioplasty with/without stent) compared to medical treatment alone in patients unsuitable for carotid endarterectomy.

GRADE: Very low quality of evidence

6. Summary of results: risk reduction in patients with AF and a history of stroke/TIA

6.0. Legend of the evidence tables

Ref	n / Population	Duration	Comparison	Efficacy outcomes (with indication of primary endpoint)		Harms	Methodological
Design: - RCT P / CO - MA - SR	n= -mean age - baseline data: • AF y/n • Previous stroke/TIA • CHADS score • TTR INR			Vascular events (composite endpoint, definition according to trial)		Other AE	- Jadad score RANDO: /2 BLINDING: /2 ATTRITION: /1 - FU: % - ITT: Yes/No - Other important methodological remarks? - Sponsor:
				Stroke			
				Ischemic stroke			
				Systemic embolism			
				Hemorrhagic stroke			
				Mortality			
				Vascular mortality			
				Myocardial infarction			
				Any bleeding			
				Major bleeding (definition according to trial)			
				Minor bleeding			
				Intracranial bleeding			

AE= adverse event
AF= atrial fibrillation
AR= absolute risk
ARR= absolute risk reduction
CI= Confidence Interval
CO= crossover RCT
FU= follow-up
HR= hazard ratio
ICH= intracerebral haemorrhage
IS= ischaemic stroke
ITT= intention-to-treat analysis
MA= meta-analysis
MI= myocardial infarction
N= number of patients
NR= not reported
NS= not statistically significant
NT= no statistical test
OAC= oral anticoagulants
OR= odds ratio
P= parallel RCT
PE= primary endpoint
RR= relative risk
RRR= relative risk reduction
RIND= reversible ischaemic neurological deficit
SA= subgroupanalysis
SAH= subarachnoid hemorrhage
SE= standard error
SS= statistically significant
SR= systematic review
TIA= transient ischaemic attack
TTR INR= percent time in therapeutic INR range

6.1. Oral anticoagulants in patients with AF and previous stroke/TIA

6.1.1. Adjusted-dose oral anticoagulants vs. placebo

Ref	N/n	Comparison	Outcomes	
*Cochrane review Saxena Design: meta-analysis Search date: 2003	N= 2 n= 485	Oral anticoagulants (OAC) vs. control / placebo For the prevention of recurrent vascular events in patients with - nonrheumatic AF - and a previous TIA or minor ischemic stroke Long-term treatment (>6 m)	All vascular events (N=2, n=485)	OAC= 20% pla= 33% OR= 0.55 (95% CI 0.37-0.82) **SS in favour of oral anticoagulants**
			Recurrent stroke (N=2, n=485)	OAC= 9% pla= 23% OR= 0.36 (95% CI 0.22-0.58) **SS in favour of oral anticoagulants** → 90 vascular events (mainly strokes) are prevented if 1000 patients are treated for 1 year
			Any intracranial bleeding (N=2, n=485)	OR= 0.13 (95% CI 0.00-6.49) NS
			Major intracranial bleeding (N=1, n=439)	OR= 4.32 (1.55-12.10) **SS more frequent with oral anticoagulants** → annual excess 21/1000 patients treated

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
EAFT (European Atrial Fibrillation Trial)1993 RCT	439	- nonrheumatic AF - TIA or minor stroke in previous 3 m - haemorrhage excluded by means of CT; other cardioembolic sources excluded - mean age 72 y	2.3 y	Oral anticoagulants (INR 2.-5-4.0) vs. control Primary outcome: composite events of vascular death, non-fatal stroke, non-fatal AMI or systemic embolism.	- Jadad score: 3/5 - FU: 99% - ITT: yes
VA-SPINAF Ezekowitz 1992	46	- nonrheumatic AF - previous stroke (interval between stroke and randomization unknown) - mean age 67 y	1.7 y	Warfarin (estimated INR 1.4-2.8) vs. placebo Primary outcome: clinically evident cerebral infarction	- Jadad score: 4/5 - FU: NR - ITT: yes

6.1.1.bis. Conclusion: Adjusted-dose oral anticoagulants vs. placebo

<table>
<tr><td colspan="6">Oral anticoagulants (OAC, INR 1.4-4.0) vs placebo/control (MA Saxena 2003:EAFT 1993, VA-Spinaf Ezekowitz 1992))</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="4">N=2, n= 485</td><td rowspan="4">1.7-2.3 y</td><td rowspan="4">- patients with non rheumatic AF
- previous TIA or minor stroke
- mean age 70 y</td><td>Recurrent stroke</td><td colspan="2">Reported in 2/2 trials
OAC=9% vs. pla=23%
OR= 0.36 (95% CI 0.22-0.58) SS
→ 90 vascular events (mainly strokes) are prevented if 1000 patients are treated for 1 year</td></tr>
<tr><td>All vascular events</td><td colspan="2">Reported in 2/2 trials
OAC= 20% vs. pla= 33%
OR= 0.55 (95% CI 0.37-0.82)</td></tr>
<tr><td>Any intracranial bleeding</td><td colspan="2">Reported in 2/2 trials
OR= 0.13 (95% CI 0.00-6.49)
NS</td></tr>
<tr><td>Major intracranial bleeding</td><td colspan="2">Reported in the largest trial
OR= 4.32 (1.55-12.10)
→ SS more frequent with oral anticoagulants
→ annual excess 21/1000 patients treated</td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><td colspan="2">Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td>→High quality of evidence</td></tr>
<tr><td colspan="2">OK</td><td>OK</td><td>OK</td><td>OK</td><td></td></tr>
</table>

- In patients with AF and a previous stroke or TIA, oral anticoagulants are more effective than placebo in reducing the risk of recurrent stroke and the total incidence of cardiovascular events. Treatment of 1.000 patients during 1 year can prevent 90 cardiovascular events, mostly strokes.

GRADE : high quality of evidence

- Patients treated with oral anticoagulants had a higher risk of major intracranial bleeding, compared to control. Treatment of 1.000 patients during 1 year leads to 21 major intracranial bleedings, compared to control.

6.1.2. Adjusted-dose warfarin vs. low-intensity or minidose warfarin

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Yamaguchi 2000 Design: RCT	n= 115 Japanese patients -non-valvular atrial fibrillation -previous ischemic stroke -mean age: 66 -mean CHADS score: NR -TTR INR: 67.3% (conventional-intensity group INR 2.2 – 3.5) and 91.7% (low-intensity group INR 1.5 - 2.1) <u>Inclusion criteria</u> -age < 80y -definite or possible cardioembolic stroke or TIA due to NVAF at 1 to 6 months before study entry <u>Exclusion criteria</u> - Intracardiac thrombus, left ventricular aneurysm, - severe congestive heart failure -acute myocardial infarction <1 month, CABG<12 months, PTCI<3months - dilated cardiomyopathy, , severe renal or liver diseases - past history of intracerebral hemorrhage - pregnancy - cancer.	Mean follow-up: 1.8y	Conventional – intensity (INR 2.2 – 3.5) vs low-intensity (INR 1.5 -2.1) warfarin therapy	**Efficacy**		- Jadad score 3/5 RANDO: 2/2 BLINDING:0 /2 (open-label) ATTRITION: 1/1 - FU: 83% - ITT: ? - Other important methodological remarks: Early termination of study due to increased rate of bleeding complications in the conventional-intensity group; insufficient power; incomplete reporting of results - Sponsor: Research funds from the Ministry of Health and Welfare of Japan
				Ischemic Stroke (brain infarction, systemic embolism, TIA, amaurosis fugax) (PE)	1.1%/y Conv.–intensity vs low-intensity 1.7%/y NS: p>0.99	
				Harms		
				Bleeding outcomes		
				Major hemorrhagic complication	**6.6%/y Conv.–intensity vs low-intensity 0%/y** **SS: p=0.0103**	
				Minor hemorrhagic complication	2.0%/y Conv.–intensity vs low-intensity 0%/y NS: p=0.23	
				AE's		

6.1.2.bis. Conclusion: Adjusted-dose warfarin vs. low-intensity or minidose warfarin

Conventional-intensity (INR 2.2-3.5) versus low-intensity or minidose (INR 1.5-2.1) warfarin (Yamaguchi 2000)				
N/n	**Duration**	**Population**	**Results**	
N=1, n=115	1.8 y	-Japanese patients -non-valvular atrial fibrillation -previous ischemic stroke -mean age: 66	Ischemic stroke (brain infarction, systemic embolism, TIA, amaurosis fugax) (PE)	conventional= 1.1%/y low-intensity= 1.7%/y → NS (p>0.99)
			Stroke	NR
			Mortality	NR
			Cardiovascular events	NR
			Major hemorrhagic complication	conventional= 6.6%/y low-intensity 0%/y → SS (p=0.0103)
			Minor hemorrhagic complication	conventional= 2.0%/y low-intensity= 0%/y → NS (p=0.23)
GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Low quality of evidence**
-2 for incomplete reporting of results and sparse data	NA	OK	OK	

- 1 small trial in patients with AF and previous ischaemic stroke found no significant difference between adjusted-dose and low-dose warfarin in ischaemic stroke rate. No other outcomes were reported.

GRADE: low quality of evidence

- In the group treated with adjusted-dose warfarin, significantly more major bleedings occurred. For this reason the trial was stopped prematurely.

6.1.3. Oral anticoagulants vs. antiplatelets

Ref	N/n	Comparison	Outcomes	
Cochrane 2011* Design: meta-analysis Search date: 26 July 2004	N= 2 n= 1371	Oral anticoagulants vs antiplatelet therapy For the prevention of recurrent vascular events in patients with - nonrheumatic AF - and a previous TIA or minor ischemic stroke Long-term treatment: ≥1y	All major vascular events (vascular death, recurrent stroke, MI or systemic embolism)	**OR= 0.67 (95%CI 0.50-0.91)** ⇨ **SS in favour of oral anticoagulants**
			Recurrent strokes	**OR= 0.49 (95% CI 0.33-0.72)** ⇨ **SS in favour of oral anticoagulants**
			Any intracranial bleed	OR= 1.99 (95% CI 0.40-9.88) ⇨ NS
			Major extracranial bleed	**OR= 5.16 (95% CI 2.08-12.83)** ⇨ **SS in favour of antiplatelet therapy**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
EAFT 1993	1007 (455)	- nonrheumatic AF - TIA or minor stroke in previous 3m - hemorrhage excluded by means of CT; other cardioembolic sources excluded	Mean 2.3y	oral anticoagulants (INR 2.5-4.0) vs aspirin 300mg/d OAC/ASA also compared to placebo	- Jadad score: 2/5 - FU: NR - ITT: yes
SIFA Morocutti 1997	916	- nonrheumatic AF - TIA or minor stroke in previous 15d - hemorrhage excluded by means of CT; other cardioembolic sources excluded	1y	oral anticoagulants (INR 2.0-3.5) vs indobufen 100 or 200mg twice daily	- Jadad score: 2/5 - FU: NR - ITT: yes

OAC=oral anticoagulants, ASA=acetylsalicylic acid

Remarks

- In the SIFA trial indobufen was administered at the recommended dose of 200mg twice daily, which was lowered to 100mg twice daily in patients with impaired renal function (creatinine clearance <80ml/min; 25% of participants in indobufen group)

6.1.3.bis. Conclusion: Oral anticoagulants vs. antiplatelets

<table>
<tr><td colspan="6">Oral anticoagulants (INR: 2.0-4.0) vs antiplatelet therapy (ASA 300mg, indobufen 100mg or 200mg BID) (EAFT 1993, Morocutti 1997)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th colspan="3">Results</th></tr>
<tr><td rowspan="4">N= 2
n= 1371</td><td rowspan="4">Mean: 1.6y</td><td rowspan="4">- nonrheumatic AF
- prior TIA or minor stroke
-hemorrhage excluded by means of CT; other cardioembolic sources excluded</td><td>All major vascular events (vascular death, recurrent stroke, MI or systemic embolism)</td><td colspan="2">OR= 0.67 (95%CI 0.50-0.91)
⇨ SS in favour of oral anticoagulants</td></tr>
<tr><td>Recurrent strokes</td><td colspan="2">OR= 0.49 (95% CI 0.33-0.72)
⇨ SS in favour of oral anticoagulants</td></tr>
<tr><td>Any intracranial bleed</td><td colspan="2">OR= 1.99 (95% CI 0.40-9.88)
⇨ NS</td></tr>
<tr><td>Major extracranial bleed</td><td colspan="2">OR= 5.16 (95% CI 2.08-12.83)
⇨ SS in favour of antiplatelet therapy</td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><th>Quality</th><th>Consistency</th><th>Directness</th><th>Imprecision</th><th colspan="2">→Moderate quality of evidence</th></tr>
<tr><td>-1
open label, missing data</td><td>OK</td><td>OK</td><td>OK</td><td colspan="2"></td></tr>
</table>

- Oral anticoagulants are significantly more effective than antiplatelet agents at reducing major vascular events, including vascular mortality, recurrence of stroke, myocardial infarction or systemic embolism in patients with AF and a history of stroke/TIA. The risk of recurrent stroke was significantly reduced with oral anticoagulants, compared to antiplatelet agents.

GRADE: moderate quality of evidence

- Treatment with antiplatelets was associated with a lower risk of major extracranial bleedings, compared to oral anticoagulants. The incidence of intracranial bleedings was not significantly different between both treatment groups.

6.2. Antiplatelet drugs in patients with AF and previous stroke/TIA

No trials could be found in this specific study population.

7. Summary of results: risk reduction in patients with AF without previous stroke/TIA

7.0. Legend of the evidence tables

Ref	n / Population	Duration	Comparison	Efficacy outcomes (with indication of primary endpoint)		Harms	Methodological
Design: - RCT P / CO - MA - SR	n= -mean age - baseline data: • AF y/n • Previous stroke/TIA • CHADS score • TTR INR			Vascular events (composite endpoint, definition according to trial)		Other AE	- Jadad score RANDO: /2 BLINDING: /2 ATTRITION: /1 - FU: % - ITT: Yes/No - Other important methodological remarks? - Sponsor:
				Stroke			
				Ischemic stroke			
				Systemic embolism			
				Hemorrhagic stroke			
				Mortality			
				Vascular mortality			
				Myocardial infarction			
				Any bleeding			
				Major bleeding (definition according to trial)			
				Minor bleeding			
				Intracranial bleeding			

AE= adverse event
AF= atrial fibrillation
AR= absolute risk
ARR= absolute risk reduction
CI= Confidence Interval
CO= crossover RCT
FU= follow-up
HR= hazard ratio
ICH= intracerebral haemorrhage
IS= ischaemic stroke
ITT= intention-to-treat analysis
MA= meta-analysis
MI= myocardial infarction
N= number of patients
NR= not reported
NS= not statistically significant
NT= no statistical test
OAC= oral anticoagulants
OR= odds ratio
P= parallel RCT
PE= primary endpoint
RR= relative risk
RRR= relative risk reduction
RIND= reversible ischaemic neurological deficit
SA= subgroupanalysis
SAH= subarachnoid hemorrhage
SE= standard error
SS= statistically significant
SR= systematic review
TIA= transient ischaemic attack
TTR INR= percent time in therapeutic INR range

7.1. Risk reduction in patients with AF and high thrombo-embolic risk

7.1.1. Oral anticoagulants in patients with AF and high thrombo-embolic risk

7.1.1.1. Adjusted-dose warfarin vs. low-dose warfarin+ASA

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
SPAF III 1996 Design : RCT	n= 1.044 -non-valvular atrial fibrillation -increased risk of stroke -mean age : 72 -38% previous thromboembolism (96% stroke or TIA) -mean CHADS score: NR -TTR INR:61 % (adjusted warfarin group) <u>Inclusion</u> Documented constant or recurrent AF ≤6 months + One or more high-risk features: -Impaired left ventricular function -Systolic blood pressure >160 mm Hg -previous thromboembolism > 30 days prior to entry <u>Exclusion</u> -Mitral stenosis/prosthetic cardiac valves -CI to aspirin 325 mg/day -CI to warfarin (previous intracranial haemorrhage, recent [6 months] gastrointestinal bleeding, previous severe haemorrhage during warfarin with therapeutic INR, severe alcohol habituation,regular use of nonsteroidal anti-inflammatory drugs)	Mean follow-up: 1.1y	Adjusted-dose warfarin (INR 2·0–3·0) vs low intensity, fixed dose warfarin (INR : 1·2–1·5 for initial dose adjustment) + aspirin (325 mg/day)	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING:0 /2 (open-label) ATTRITION: 1/1 - FU: 81% - ITT: yes - Early termination of the study after the second interim analysis due to the superiority of adjusted-dose warfarin relative to combination therapy. - Sponsor: Grant from National Institute of Neurological disorders and stroke (USA).
				Ischaemic stroke or systemic embolism (PE)	**1.9% /y Adjusted warfarin vs fixed warfarin+ASA 7.9%/y SS: ARI: 6.00% (95% CI: 3.4%-8.6%) p<0.0001**	
				Disabling ischaemic stroke	**1.2% /y Adjusted warfarin vs fixed warfarin+ASA 4.8%/y SS (graphic representation)**	
				Fatal Ischaemic stroke	0.2% /y Adjusted warfarin vs fixed warfarin+ASA 0.9%/y NT	
				All disabling/fatal strokes	**1.7% /y Adjusted warfarin vs fixed warfarin+ASA 5.6%/y SS: ARI: 3.9% (95% CI: 1.6%-6.1%) p=0.0007**	
				TIA	2.7% /y Adjusted warfarin vs fixed warfarin+ASA 4.5%/y NT	
				Mortality	5.9% /y Adjusted warfarin vs fixed warfarin+ASA 7.2%/y NT	
				Myocardial infarction	0.9% /y Adjusted warfarin vs fixed warfarin+ASA 1.8%/y NT	
				Primary event or vascular death	**6.4% /y Adjusted warfarin vs fixed warfarin+ASA 11.8%/y SS: ARI: 5.4% (95% CI: 1.9%-8.9%) p=0.002**	
				Harms		
				Bleeding outcomes		
				Intracranial bleeding	0.5% /y Adjusted warfarin vs fixed warfarin+ASA 0.9%/y NT	
				Major bleeding	2.1% /y Adjusted warfarin vs fixed warfarin+ASA 2.4%/y NS (graphic representation)	
				Minor bleeding	0.7% /y Adjusted warfarin vs fixed warfarin+ASA 1.2%/y NT	
				AE's	NR	

- The mean INR during follow-up of patients taking combination therapy (n=521) was 1·3, compared with 2·4 for those taking adjusted-dose warfarin (n=523).
- Major haemorrhage was assessed by the criteria of Landefeld, et al.(20)

7.1.1.1.bis Conclusion: Adjusted-dose warfarin vs. low-dose warfarin+ASA

Adjusted doses warfarin (INR 2-3) vs low-intensity, fixed dose warfarin (INR 1.2-1.5) + acetylsalicylic acid 325 mg/d (SPAF III 1996)				
N/n	**Duration**	**Population**	Results	
N=1, n= 1044	1.1 y	-non-valvular atrial fibrillation -increased risk of stroke -mean age 72 y -38% previous thromboembolism (96% stroke or TIA)	Ischaemic stroke or systemic embolism (PE)	Adjusted warfarin 1.9% /y fixed warfarin+ASA 7.9%/y SS: ARI: 6.00% (95% CI: 3.4%-8.6%) p<0.0001
			Disabling ischaemic stroke	Adjusted warfarin 1.2% /y fixed warfarin+ASA 4.8%/y SS
			Fatal ischaemic stroke	NT
			TIA	NT
			Mortality	NT
			Myocardial infarction	NT
			Primary event or vascular death	Adjusted warfarin 6.4% /y fixed warfarin+ASA 11.8%/y SS: ARI: 5.4% (95% CI: 1.9%-8.9%) p=0.002
			Intracranial bleeding	NT
			Major bleeding	NS
			Minor bleeding	NT

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Low quality of evidence**
-2 for incomplete reporting of results and no separate analysis for patients with/without previous stroke	NA	OK	OK	

- Adjusted-dose warfarin (INR 2-3) was compared to low-dose warfarin (INR 1.5-2)+ ASA 325 mg/d in patients with AF and elevated risk of stroke. Adjusted-dose warfarin was more effective than the association for the prevention of ischemic stroke and systemic embolism. Data on mortality and fatal stroke were not statistically tested.

GRADE: low quality of evidence

- No significant differences were found between warfarine INR 2-3 and the association in the incidence of major bleedings. Other safety outcomes were not statistically tested.

7.1.1.2. Adjusted-dose warfarin vs. low- or minidose warfarin

7.1.1.2.1. Adjusted-dose warfarin vs. low- or minidose warfarin

Ref	N/n	Comparison	Outcomes	With or without aspirin	Without aspirin
Perret-Guillaume 2004* Design: meta-analysis Search date: August 2002	N= 4 n= 2753	Adjusted-dose warfarin (2.0-3.0) vs Minidose or low-dose warfarin (INR ≤1.6)	Ischemic stroke	RR=0.46 (95% CI: 0.20-1.07)	RR=0.67 (95% CI: 0.33-1.36)
			All thrombotic events (CVA, MI, systemic embolism)	**RR=0.50 (95% CI: 0.25-0.97)** **=> SS in favour of adjusted-dose warfarin**	RR=0.63 (95% CI: 0.38-1.04)
			Major haemorrhage	RR=1.23 (95% CI: 0.67-2.27)	RR=1.62 (95% CI: 0.58-4.54)
		In patients with AF with or without prior stroke or TIA Mean age: 73.7y			

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
SPAF3 1996	1044	- AF constant or recurrent + ≥1 high risks: °impaired left ventricular function °SBP>160mmHg °prior CVA, TIA or systemic embolism >30d prior to entry (±40% of all participants) °female and >75y -adults	Mean follow-up: 1.1y	Fixed low-dose warfarin (0.5-3mg/d) + aspirin 325mg/d Vs Adjusted-dose warfarin (INR 2-3)	- Jadad score: 2/5 - FU: 100% - ITT: yes Stopped before completion when the rate of primary events in patients given combination therapy was significantly higher than those given adjusted-dose warfarin.
AFASAK2 Gullov 1998	677	-nonvalvular chronic AF -≥18y -60% male	2.5y	Fixed minidose warfarin 1.25mg/d Vs Fixed minidose warfarin 1.25mg/d + aspirin 300mg/d Vs Aspirin 300mg/d Vs Adjusted-dose warfarin (INR 2-3)	- Jadad score: 2/5 - FU: 100% - ITT: yes Stopped before completion when results of SPAF3 were disclosed.
MWNAF Pengo 1998	303	-chronic AF ->60y -68.5% male	2.5y	Fixed minidose warfarin 1.25mg/d Vs Adjusted-dose warfarin (INR 2-3)	- Jadad score: 2/5 - FU: NR - ITT: yes Stopped before completion when results of SPAF3 were disclosed.
PATAF 1999 Hellemons	729	-confirmed chronic or intermittent AF -≥60y -65% male	Mean follow-up: 2.7y	Adjusted-dose warfarin (INR 2.5-3.5) Vs Low-dose warfarin (INR 1.1-1.6) Vs (Aspirin 150mg/d)	- Jadad score: 3/5 - FU: 100% - ITT: yes

Remarks

- The analysed studies were open-label and clinically heterogeneous. Minidose or low-dose warfarin is combined or not with aspirin, and studies are not totally comparable regarding the dosage of warfarin.
- Another limit is the premature stop of two trials (AFASAK2 and MWNAF) considering the results of SPAF3, thus these trials are underpowered.

7.1.1.2.1.bis. Conclusion: Adjusted-dose warfarin vs. low- or minidose warfarin

<table>
<tr><td colspan="6">Adjusted-dose warfarin (INR:2-3) vs ow-dose warfarin (1.25mg/d) (SPAF3 1996, Gullov 1998, Pengo 1998, Hellemons 1999)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="4">N=4
n= 2753</td><td rowspan="4">Mean: 1.9y</td><td rowspan="4">Nonvalvular chronic AF

Mean age: 73.7y</td><td>Outcomes</td><td>With or without aspirin</td><td>Without aspirin</td></tr>
<tr><td>Ischemic stroke</td><td>RR=0.46 (95% CI: 0.20-1.07)</td><td>RR=0.67 (95% CI: 0.33-1.36)</td></tr>
<tr><td>All thrombotic events (CVA, MI, systemic embolism)</td><td>RR=0.50 (95% CI: 0.25-0.97) => SS in favour of adjusted-dose warfarin</td><td>RR=0.63 (95% CI: 0.38-1.04)</td></tr>
<tr><td>Major haemorrhage</td><td>RR=1.23 (95% CI: 0.67-2.27)</td><td>RR=1.62 (95% CI: 0.58-4.54)</td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><td colspan="2">Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td>→Low quality of evidence</td></tr>
<tr><td colspan="2">-1
Incomplete reporting of results</td><td>OK</td><td>-1
Heterogeneous population</td><td>OK</td><td></td></tr>
</table>

- Low-dose warfarin (1.25 mg/d) is associated with an elevated incidence of thrombo-embolism (stroke, MI and systemic embolism) compared to adjusted-dose warfarin INR 2-3. INR 2-3 is advised in patients with non-valvular AF.
- No significant differences were found for the incidence of stroke.

GRADE: low quality of evidence

- Low-dose warfarin did not reduce the bleeding risk, compared to adjusted-dose.
- The trials pooled in this meta-analysis are clinically heterogeneous and also open-label. A few included trials lacked statistical power. In some cases patients were additionally treated with ASA; therefore it is difficult to draw conclusions for the effect of each treatment separately.

7.1.1.2.2. Adjusted dose warfarin: Lower target INR (1.5-2.0) vs standard target INR (2.0-3.0) in the elderly (30% high risk and 70% moderate)

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Pengo '10 Design: RCT P	n= 267 - mean age 80 y - $CHADS_2$ score: 1-2 (moderate risk)= 70% 3-4 (high risk)= 30% - TTR INR: lower target group: TTR(1.5-2) 50% TTR(2-3) 35% standard target group: TTR(1.5-2) 22% TTR (2-3) 65% <u>Incl</u> - non-valvular atrial fibrillation - >75y <u>Excl</u> - <u>Previous cerebral ischaemia (stroke or TIA)</u> - Major bleeding < 6 m - Uncontrolled BP (>180/110mmHg) - Chronic renal failure (serum creatinine >3mg/dl) - Chronic hepatic failure (baseline INR >1.5) - Chronic alcoholism and psychiatric disorders - Congestive heart failure (NYHA class III-IV)	Mean 5.1-5.3y	Lower target INR 1.8 (range 1.5-2.0) vs standard target INR 2.5 (range 2.0-3.0)	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING:1/2 ATTRITION: 1/1 - FU: 94% - ITT: yes - Other important methodological remarks? - Underpowered (power calculations based on higher event rates) - No AE's reported - Sponsor: NR
				Tromboembolism (= ischaemic stroke and visceral systemic embolism) and major bleeding (PE)	Lower target INR: 3.5/100 patient years Higher target INR: 5.0/100 patient years NS: HR=0.7 (95%CI 0.4-1.1), p=0.1	
				Tromboembolism (ischemic stroke and visceral systemic embolism)	Lower target INR: 1.6/100 patient years Standard target INR: 2.0/100 patient years NS: HR=0.8 (95%CI 0.4-1.8), p=0.6	
				All cause mortality	Lower target INR:11,2/100 patient years Standard target INR: 10/100 patient years NS: HR=1.1 (95%CI 0.79-1.52), p=0.5	
				Cardiovascular mortality	Lower target INR:7.5/100 patient years Standard target INR: 6.7/100 patient-years NS: HR=1.1 (95%CI 0.73-1.63), p=0.7	
				Myocardial infarction	Lower target INR: 1.2/100 patient years Standard target INR: 1.3/100 patient years NS: HR=0.9 (95%CI 0.3-2.2), p=0.7	
				Median INR	Lower target INR: 1.86 (IQR 1.58-2.23) Standard target INR: 2.24 (IQR 1.88-2.67) **SS: p<0.001**	
				Harms		
				Bleeding outcomes		
				Major bleeding (Intracranial, ocular, retroperitoneal, major joint, transfusion need ≥2 blood units, decrease in Hb ≥ 2g/dl)	Lower target INR:1.9/100 patient years Standard target INR: 3.0/100 patient years NS: HR=0.6 (95%CI 0.3-1.2), p=0.1	
				Intracranial bleeding	Lower target INR:0.7/100 patient years Standard target INR: 1.1/100 patient years NR	
				AE's		
				NR		

	- Life expectancy <12m - Programmed pharmacological or electrical cardioversion - acute myocardial infarction <1m - history of vavular heart disease or dilated cardiomyopathy - antiplatelet therapy - other indications for oral anticoagulation				

7.1.1.2.2.bis. Conclusion: Adjusted dose warfarin: Lower target INR (1.5-2.0) vs standard target INR (2.0-3.0) in the elderly (30% high risk and 70% moderate)

<table>
<tr><td colspan="6">Lower target INR (1.5-2.0) vs standard target INR (2.0-3.0) in eldery patients with non-valvular Atrial fibrillation (Pengo 2010)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="8">N=1,
n=267</td><td rowspan="8">Mean
5.2y</td><td rowspan="8">- non-valvular atrial fibrillation
- mean age 80y
- TTR INR:
lower target group:
TTR(1.5-2) 50%
TTR(2-3) 35%
standard target group:
TTR(1.5-2) 22%
TTR (2-3) 65%

<u>Exclusion</u>
- <u>Previous cerebral ischaemia (stroke or TIA)</u>
- Uncontrolled BP
- Chronic renal failure
- Chronic hepatic failure
- CHF (III-IV)
- AMI <1m
- Major bleeding <6 months</td><td colspan="3">Efficacy</td></tr>
<tr><td>Tromboembolism and major bleeding</td><td colspan="2">3.5/100 patient years
vs 5.0/100 patient years
NS: HR=0.7 (95%CI 0.4-1.1)</td></tr>
<tr><td>Tromboembolism</td><td colspan="2">1.6/100 patient years
vs 2.0/100 patient years
NS: HR=0.8 (95%CI 0.4-1.8)</td></tr>
<tr><td>Major bleeding</td><td colspan="2">1.9/100 patient years
vs 3.0/100 patient years
NS: HR=0.6 (95%CI 0.3-1.2)</td></tr>
<tr><td>Median INR</td><td colspan="2">1.86 (IQR 1.58-2.23) vs 2.24 (IQR 1.88-2.67)
SS: p<0.001</td></tr>
<tr><td colspan="3">AE’s</td></tr>
<tr><td colspan="3">NR</td></tr>
<tr><td colspan="6"></td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><td>Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td colspan="2">→ Moderate quality of evidence</td></tr>
<tr><td>OK</td><td>NA</td><td>OK</td><td>-1 for inadequate power</td><td colspan="2"></td></tr>
</table>

- The results of this trial suggest that a lower target INR (1.5-2.0) is as effective as standard target INR (2.0-3.0) for the composite endpoint ‘thromboembolism and major bleeding’ in patients with advanced age.
This trial was insufficiently powered, therefore no conclusions can be made on base of this study.

GRADE: moderate quality of evidence

- The rate of major bleeding was lower in the group with lower-target INR, but this difference was not statistically significant. The concept of a lower target INR seems an interesting line of thought in this frail population, so further evidence is needed.

7.1.1.3. Adjusted-dose warfarin vs. antiplatelets/associations

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
ACTIVE-W 2006 Design: RCT	n= 6.706 -non-valvular atrial fibrillation -increased risk of stroke -15% with previous stroke/TIA -69% permanent AF -mean age : 70 -mean CHADS score: 2 -TTR INR: 64% -77% receiving oral anticoagulant as baseline medication before randomisation <u>Inclusion</u> -AF (electrocardiographic evidence) – at least 1 following risk factor: age ≥75 ; treatment for systemic hypertension; previous stroke, TIA, or non-CNS systemic embolus; left ventricular dysfunction (left ventricular ejection fraction < 45%); peripheral arterial disease -If 54<age <75 and no risk factor(as described above) then either diabetes mellitus	Median follow-up duration: 1.28y	Oral anticoagulation (INR 2-3) vs clopidogrel (75mg) plus aspirin (75-100mg)	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING:0 /2 (open treatment) ATTRITION: 1/1 - FU: 90% - ITT: yes - Other important methodological remarks: • Started as a non-inferiority trial; • Blinded adjudication of outcomes; • Early termination of the trial (due to superiority of oral anticoagulation vs clopidogrel and aspirin) • Selection bias in favour of oral anticoagulation therapy • For patients new to both treatments, the benefits of oral anticoagulation therapy relative to clopidogrel plus aspirin are not well defined by this study. - Sponsor:
				First event - Stroke (ischemic or hemorrhagic) or non-CNS systemic embolism, myocardial infarction or vascular death (PE)	**Clopidogrel plus ASA 5.60%/y vs Oral anticoagulation 3.93%/y RR =1.44 (95% CI 1.18 – 1.76) p=0.0003**	
				Stroke	**Clopidogrel plus ASA 2.39%/y vs Oral anticoagulation 1.40%/y RR =1.72 (95% CI 1.24 – 2.37) p=0.001**	
				Ischemic stroke	**Clopidogrel plus ASA 2.15%/y vs Oral anticoagulation 1.00%/y RR =2.17 (95% CI 1.51 – 3.13) p<0.0001**	
				Hemorrhagic stroke	**Clopidogrel plus ASA 0.12%/y vs Oral anticoagulation 0.36%/y RR =0.34 (95% CI 0.12 – 0.93) p=0.036**	
				Mortality	Clopidogrel plus ASA 3.80%/y vs Oral anticoagulation 3.76%/y RR =1.01 (95% CI 0.81 – 1.26) p=0.91	
				Vascular death	Clopidogrel plus ASA 2.87%/y vs Oral anticoagulation 2.52%/y RR =1.14 (95% CI 0.88 – 1.48) p=0.34	
				Non-vascular death	Clopidogrel plus ASA 0.93%/y vs Oral anticoagulation 1.24%/y RR =0.76 (95% CI 0.50 – 1.15) p=0.20	
				Myocardial infarction	Clopidogrel plus ASA 0.86%/y vs Oral anticoagulation 0.55%/y RR =1.58 (95% CI 0.94 – 2.67) p=0.09	
				Non-CNS systemic embolism	**Clopidogrel plus ASA 0.43%/y vs Oral anticoagulation 0.10%/y RR =4.66 (95% CI 1.58 – 13.8) p=0.005**	
				Net benefit : PE +major	**Clopidogrel plus ASA 7.56%/y vs**	

	previous coronary artery disease. Exclusion -CI for clopidogrel or for oral anticoagulant (such as prosthetic mechanical heart valve); - peptic ulcer disease < 6 months; -previous intracerebral haemorrhage; -significant thrombocytopenia - mitral stenosis			bleed	**Oral anticoagulation 5.45%/y** **RR =1.41 (95% CI 1.19– 1.67) p<0.0001**	Sanofi-Aventis and Bristol-Myers Squibb
				Net benefit : PE +major bleed + death	**Clopidogrel plus ASA 8.32%/y vs** **Oral anticoagulation 6.45%/y** **RR =1.31 (95% CI 1.12 – 41.54) p=0.0008**	
				Non-disabling stroke	**Clopidogrel plus ASA 1.00%/y vs** **Oral anticoagulation 0.4%/y** **RR =2.49 (95% CI 1.42 – 4.37) p=0.0002**	
				Disabling stroke	Clopidogrel plus ASA 1.39%/y vs Oral anticoagulation 0.95%/y RR =1.47 (95% CI 0.98– 2.20) p=0.06	
				Fatal stroke	Clopidogrel plus ASA 0.33%/y vs Oral anticoagulation 0.36%/y RR =0.93(95% CI 0.45– 1.94) p=0.85	
				Harms		
				Bleeding outcomes		
				Major bleeding	Clopidogrel plus ASA 2.42%/y Oral anticoagulation 2.21%/y RR =1.10 (95% CI 0.83 – 1.45) p=0.53	
				Any bleeding	**Clopidogrel plus ASA 15.40%/y** **Oral anticoagulation 13.21%/y** **RR =1.21 (95% CI 1.08 – 1.35) p=0.001**	
				Severe bleeding	Clopidogrel plus ASA 1.70%/y Oral anticoagulation 1.57%/y NS:RR =1.09 (95% CI 0.78 – 1.52) p=0.62	
				Fatal bleeding	Clopidogrel plus ASA 0.17%/y Oral anticoagulation 0.26%/y NS:RR =0.64 (95% CI 0.25 – 1.66) p=0.36	
				Minor bleeding	**Clopidogrel plus ASA 13.58%/y** **Oral anticoagulation 11.45%/y** **SS:RR =1.23 (95% CI 1.09 – 1.39) p=0.0009**	
				Intracranial bleeding	Clopidogrel plus ASA 0.49%/y Oral anticoagulation 0.26%/y NS: p=0.08	
				AE's		

7.1.1.3.bis Conclusion: Adjusted-dose warfarin vs. antiplatelets/associations

Oral anticoagulants (INR 2-3) vs clopidogrel 75 mg/d + acetylsalicylic acid 75-100 mg/d (ACTIVE-W 2006)				
N/n	**Duration**	**Population**	**Results**	
N=1, n= 6706	1.3 y	- patients with non-valvular atrial fibrillation -increased risk of stroke -15% with previous stroke/TIA -69% permanent AF -mean age 70 y -mean CHADS score: 2 -TTR INR: 64% -77% receiving oral anticoagulant as baseline medication before randomisation	First event - Stroke (ischemic or hemorrhagic) or non-CNS systemic embolism, myocardial infarction or vascular death (PE)	Oral anticoagulation 3.93%/y Clopidogrel plus ASA 5.60%/y RR =1.44 (95% CI 1.18 -1.76) p=0.0003
			Stroke	Oral anticoagulation 1.40%/y Clopidogrel plus ASA 2.39%/y RR =1.72 (95% CI 1.24-2.37) p=0.001
			Ischemic stroke	Oral anticoagulation 1.00%/y Clopidogrel plus ASA 2.15%/y RR =2.17 (95% CI 1.51- 3.13) p<0.0001
			Hemorrhagic stroke	Oral anticoagulation 0.36%/y Clopidogrel plus ASA 0.12%/y RR =0.34(95% CI 0.12 – 0.93) p=0.036
			Non-disabling stroke	Oral anticoagulation 0.4%/y Clopidogrel plus ASA 1.00%/y RR =2.49 (95% CI 1.42- 4.37) p=0.0002
			Disabling stroke	NS
			Mortality	NS
			Vascular mortality	NS
			Myocardial infarction	NS
			Major bleeding	NS
			Any bleeding	Clopidogrel plus ASA 15.40%/y Oral anticoagulation 13.21%/y RR =1.21 (95% CI 1.08 – 1.35) p=0.001
			Severe bleeding	NS
			Fatal bleeding	NS
			Minor bleeding	Clopidogrel plus ASA 13.58%/y Oral anticoagulation 11.45%/y SS:RR =1.23 (95% CI 1.09 – 1.39) p=0.0009
			Intracranial bleeding	NS

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
OK	NA	-1 (most enrolled patients already taking oral anti-coagulants)	OK	

- This trial assessed whether clopidogrel 75 mg/ + ASA 75-100 mg/d was non-inferior to adjusted-dose oral anticoagulants (target INR 2-3) in patients with AF and elevated thrombo-embolic risk (mean CHADS score 2). Oral anticoagulants were found to be superior to antiplatelet agents in the prevention of cardiovascular events, including ischaemic and hemorrhagic stroke. Mortality and the incidence of myocardial infarction did not differ significantly.

GRADE: moderate quality of evidence

- Total bleeding rates were higher in patients treated with the combination of antiplatelets. No differences were found in rates of severe or fatal haemorrhages.

7.1.1.4. Apixaban vs. ASA

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Connolly 2011 (AVERROES) Design: RCT, P	n= 5.599 -mean age 70 -mean CHADS score 2 (36% 0-1, 35% 2) -TTR INR: not appicable <u>Inclusion</u> - documented atrial fibrillation - ≥ 50 y -increased risk of stroke (prior stroke/TIA, ≥75 y, hypertension, diabetes, heart failure, peripheral arterial disease) -not suitable (demonstrated of expected) for vitamin K antagonist therapy <u>Exclusion</u> - valvular disease requiring surgery - high risk of bleeding - serious bleeding <6mo - life expectancy <1y - severe renal failure - liver failure	1.1y	Apixaban 2x5mg/d vs aspirin 81-324mg (65%of patients 81 mg) Apixaban 2x2,5mg for patients >80y, <60kg, or creat >1.5mg/dl	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: 0/1 - FU: NR - ITT: yes - Other important methodological remarks? -522 centers in 36 countries - heterogenous population -Early termination of study for clear benefit in favor of apixaban - Sponsor: Bristol Myers Squibb and Pfizer
				Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Apixaban: 1.6%/y Aspirin: 3.7%/y **Apixaban SS better: HR= 0.45 (95%CI 0.32-0.62), p<0.001**	
				Ischemic stroke	Apixaban: 1.1%/y Aspirin: 3.0%/y **Apixaban SS better: HR= 0.37 (95%CI 0.25-0.55), p<0.001**	
				Stroke, systemic embolism, myocardial infarction, death from vascular c ause, or major bleeding event	Apixaban: 5.3% Aspirin: 7.2% **Apixaban SS better: HR 0.74 (95%CI 0.60-0.90), p = 0.003**	
				Hemorrhagic stroke	Apixaban: 0.2%/y Aspirin: 0.3%/y NS : HR= 0.67 (95%CI 0.24-1.88), p=0.45	
				Disabling or fatal stroke	Apixaban: 1.0%/y Aspirin: 2.3%/y **Apixaban SS better: HR= 0.43 (95%CI 0.28-0.65), p<0.001**	
				Mortality	Apixaban: 3.5%/y Aspirin: 4.4%/y NS: HR= 0.79 (95%CI 0.62-1.02), p=0.07	
				Myocardial infarction	Apixaban: 0.8%/y Aspirin: 0.9%/y NS: HR= 0.86 (95%CI 0.50-1.48), p=0.59	
				Harms		
				Bleeding outcomes		
				Intracranial	NS: 0.4%/y vs 0.4%/y HR = 0.85 (95%CI 0.38-1.90) p=0.69	
				Any bleeding	NR	
				Major bleeding	NS 1.4%/y vs 1.2%/y HR = 1.13 (95%CI 0.74-1.75) p=0.57	
				Fatal bleeding	NS: 0.1%/y vs 0.2%/y HR = 0.67 (95%CI 0.38-1.90) p=0.53	
				Nonmajor clinically relevant bleeding	NS: 3.1%/y vs 2.7%/y HR = 1.15 (95%CI 0.86-1.54) p=0.35	

				GI-bleeding	NS: 0.4%/y vs 0.4%/y HR = 0.86 (95%CI 0.40-1.86) p=0.71	
				AE's		
				Change in liver function	NS	

Results predefined subgroup analysis

In patients with previous stroke or TIA, 2.39% strokes or systemic embolisms per year occurred in the apixaban group compared with 9.16% per year in the aspirin group (hazard ratio is 0.29 with 95% confidence interval between 0.15 and 0.60). In those without previous stroke or TIA, 1.68% events per year occurred in the apixaban group compared with 3.06% per year in the aspirin group (hazard ratio is 0.51 with 95% confidence interval between 0.35 and 0.74). Major bleeding was more frequent in patients with history of stroke or TIA than in patients without (hazard ratio is 2.88 with 95% confidence interval between 1.77 and 4.55) but risk of this event did not differ between treatment groups.

In patients with atrial fibrillation, apixaban is similarly effective whether or not patients have had a previous stroke or TIA. Given that those with previous stroke or TIA have a higher risk of stroke, the absolute benefits might be greater in these patients.

7.1.1.4.bis. Conclusion: Apixaban vs. ASA

Apixaban 2x5mg/d vs acetylsalicylic acid (81-324 mg/d) (Connolly 2011, AVERROES)				
N/n	**Duration**	**Population**	**Results**	
N=1, n=5.599	1.1y	-mean age 70 -mean CHADS score 2 (36% 0-1, 35% 2) -not suitable (demonstrated of expected) for vitamin K antagonist therapy <u>Exclusion</u> - valvular disease requiring surgery - high risk of bleeding - serious bleeding <6mo - life expectancy <1y - severe renal failure - liver failure	**Efficacy**	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Apixaban: 1.6%/y Aspirin: 3.7%/y **Apixaban SS better: HR= 0.45 (95%CI 0.32-0.62), p<0.001**
			Ischemic stroke	Apixaban: 1.1%/y Aspirin: 3.0%/y **Apixaban SS better: HR= 0.37 (95%CI 0.25-0.55), p<0.001**
			Disabling or fatal stroke	Apixaban: 1.0%/y Aspirin: 2.3%/y **Apixaban SS better: HR= 0.43 (95%CI 0.28-0.65), p<0.001**
			Hemorrhagic stroke	Apixaban: 0.2%/y Aspirin: 0.3%/y NS : HR= 0.67 (95%CI 0.24-1.88), p=0.45
			Mortality	Apixaban: 3.5%/y Aspirin: 4.4%/y NS: HR= 0.79 (95%CI 0.62-1.02), p=0.07
			Myocardal infarction	Apixaban: 0.8%/y Aspirin: 0.9%/y NS: HR= 0.86 (95%CI 0.50-1.48), p=0.59
			Harms	
			Intracranial bleeding	NS: 0.4%/y vs 0.4%/y HR = 0.85 (95%CI 0.38-1.90) p=0.69
			Major bleeding	NS 1.4%/y vs 1.2%/y HR = 1.13 (95%CI 0.74-1.75) p=0.57
			Fatal bleeding	NS: 0.1%/y vs 0.2%/y HR = 0.67 (95%CI 0.38-1.90) p=0.53
			GI-bleeding	NS: 0.4%/y vs 0.4%/y HR = 0.86 (95%CI 0.40-1.86) p=0.71

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Low quality of evidence**
-1 for early termination of study (clear benefit of apixaban)	NA	-1 for 36% CHADS 0-1	OK	

- In patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable, apixaban was more effective than ASA. Apixaban was superior tot ASA for the composite endpoint of stroke and systemic embolism (HR 0.45), for ischaemic stroke (HR 0.37) and for disabling or fatal stroke (HR 0.43). Mortality and incidence of haemorrhagic stroke did not differ significantly. Safety outcomes (bleeding) were not significantly different between treatment groups.

GRADE: low quality of evidence

- Adverse events: no statistical test.

7.1.1.5. Apixaban vs. warfarin

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Granger 2011 ARISTOTLE Design: RCT, P	n= 18.201 -19% prior stroke, TIA or systemic embolism -mean age 70 y -mean CHADS score 2.1 -34% CHADS score 1 -TTR INR: 62.2% <u>Inclusion</u> - atrial fibrillation or flutter - increased risk of stroke = at least 1 additional risk factor: ≥75y, previous stroke or TIA, heart failure, diabetes, hypertension <u>Exclusion</u> - Mitral stenosis - Prosthetic heart valve - Stroke < 7d - Creat clearance <25ml/min	1.8y	apixaban 2x5mg/d vs warfarin (INR 2.0-3.0) (2*2.5mg for >80y or creat >1.5mg/dl)	**Efficacy**		- Jadad score RANDO:2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 99% - ITT: yes - Other important methodological remarks? -non-inferiority design combined with superiority design, with intention to treat analysis (no per protocol analysis) -34% low risk and anticoagulants possibly not first choice - heterogeneous population - Sponsor: Bristol-Myers Squibb and Pfizer
				Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Apixaban 1.27%/y vs 1.60%/y warfarin **Superior: HR= 0.79 (95%CI 0.66-0.95)** **p<0.001 for noninferiority** **p = 0.01 for superiority**	
				Ischemic stroke	Apixaban 1.19%/y vs 1.51%/y warfarin **Superior: HR 0.79 (95%CI 0.65-0.95), p = 0.01**	
				Hemorrhagic stroke	Apixaban 0.24%/y vs 0.47%/y warfarin **Superior: HR 0.51 (95%CI 0.35-0.75), p<0.001**	
				Mortality	Apixaban 3.52%/y vs 3.94%/y warfarin **Superior: HR 0.89 (95%CI 0.80-0.998), p=0.047**	
				Myocardial infarction	Apixaban 0.53%/y vs 0.61%/y warfarin NS: HR 0.37 (95%CI 0.66-1.17), p=0.37	
				Harms		
				Bleeding outcomes		
				Intracranial	Apixaban 0.33%/y vs 0.80%/y warfarin **SS less intracranial bleedings with apixaban: HR 0.42 (95%CI 0.30-0.58), p<0.001**	
				Any bleeding	Apixaban 18.1%/y vs warfarin 25.8%/y **SS less any bleedings with apixaban, p<0.001**	
				ISTH major bleeding	Apixaban 2.13%/y vs warfarin 3.09%/y **SS less ISTH major bleedings with apixaban, p <0.001**	
				Fatal bleeding	NR	
				GI-bleeding	Apixaban 0.76%/y vs warfarin 0.86%/y NS, p = 0.37	
				AE's		
				No statistical analysis		

*<u>ISTH</u> bleeding definition:
Major bleeding: fall in hemoglobin of ≥2 g/dl or with transfusion of ≥2 units of PRBC or whole blood or that occurs in a critical location i.e. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial or that causes death.
Minor bleeding: does not meet criteria for major bleeding and requires medical or surgical intervention to treat the bleeding

7.1.1.5.bis. Conclusion: Apixaban vs. warfarin

Apixaban 2x5mg/x vs warfarin (INR 2-3) (Granger 2011, ARISTOTLE)				
N/n	**Duration**	**Population**	**Results**	
N=1, n=18.201	1.8y	- atrial fibrillation or flutter - increased risk of stroke: at least 1 additional risk factor: ≥75y, previous stroke or TIA, heart failure, diabetes, hypertension -19% prior stroke, TIA or systemic embolism -mean age 70 y -mean CHADS score 2.1 -34% CHADS2 score 1 -TTR INR: 62.2% <u>Exclusion</u> - Mitral stenosis - Prosthetic heart valve - Stroke < 7d - Creat clearance <25ml/min	**Efficacy**	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Apixaban 1.27%/y vs 1.60%/y warfarin **Superior: HR= 0.79 (95%CI 0.66-0.95)** **p<0.001 for noninferiority** **p = 0.01 for superiority**
			Ischemic stroke	Apixaban 1.19%/y vs 1.51%/y warfarin **Superior: HR 0.79 (95%CI 0.65-0.95), p = 0.01**
			Hemorrhagic stroke	Apixaban 0.24%/y vs 0.47%/y warfarin **Superior: HR 0.51 (95%CI 0.35-0.75), p<0.001**
			Mortality	Apixaban 3.52%/y vs 3.94%/y warfarin **Superior: HR 0.89 (95%CI 0.80-0.998), p=0.047**
			Myocardial infarction	Apixaban 0.53%/y vs 0.61%/y warfarin NS: HR 0.37 (95%CI 0.66-1.17), p=0.37
			Harms	
			Intracranial bleeding	Apixaban 0.33%/y vs 0.80%/y warfarin **SS less intracranial bleedings with apixaban: HR 0.42 (95%CI 0.30-0.58), p<0.001**
			Any bleeding	Apixaban 18.1%/y vs warfarin 25.8%/y **SS less any bleedings with apixaban, p<0.001**
			ISTH major bleeding	Apixaban 2.13%/y vs warfarin 3.09%/y **SS less ISTH major bleedings with apixaban, p <0.001**
			Fatal bleeding	NR
			GI-bleeding	Apixaban 0.76%/y vs warfarin 0.86%/y NS, p = 0.37
			AE's	No statistical analysis

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
OK	NA	-1 for 34% patients with CHADS2 = 1	OK	

- In this trial apixaban 2x 5 mg/d was superior to warfarin (INR 2-3) for efficacy and safety outcomes. Apixaban was superior for the primary composite endpoint stroke (ischaemic and haemorrhagic) and systemic embolism (HR 0.79). Rates of ischaemic stroke, haemorrhagic stroke and mortality were also significantly lower with apixaban. The risk of myocardial infarction did not differ significantly.
Apixaban was associated with a lower risk of bleeding, including intracranial and major haemorrhages. The risk of gastro-intestinal bleeding was not significantly different.
34% of the study population had a CHADS2-score of 1. Oral anticoagulants are mainly indicated in CHADS2-score 2 or higher.

GRADE: moderate quality of evidence

- Adverse events: no statistical test.

7.1.1.6. Dabigatran vs. warfarin

7.1.1.6.1. Dabigatran 2x110mg/d vs warfarin

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Connolly 2009 RE-LY + subgroup analyses Design: RCT P	n= 18.113 -mean age 71y -mean CHADS score 2.1 -30% CHADS score 0 or 1 -20% previous CVA/TIA -TTR INR: 64% <u>Inclusion</u> - atrial fibrillation - increased risk of stroke: previous stroke/TIA, heart failure, ≥75y, or 65-74Y+diabetes, hypertension, coronary artery disease <u>Exclusion</u> - stroke <14d or severe stroke <6m - severe heart valve disorder -Increased risk of hemorrhage - creatinine clearance < 30ml/min - liver failure	2y	Dabigatran 2x110mg/d vs warfarin INR 2.0-3.0	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING:0/2 ATTRITION: 1/1 - FU: 99% - ITT: yes - Other important methodological remarks? - warfarin therapy not blinded (open label) - non-inferiority design combined with superiority design, with intention to treat analysis (no per protocol analysis) - Sponsor: Boehringer Ingelheim
				Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Dabigatran 110mg: 1.53%/y Warfarine: 1.69%/y **Non-inferior**: **RR 0.91 (95%CI 0.74-1.11), p<0.001 for noninferiority,** Not superior (p=0.34)	
				Ischemic or unspecified stroke	Dabigatran 110mg: 1.34%/y Warfarine: 1.20%/y NS: RR 1.11 (95%cI 0.8 9-1.40) (p=0.35)	
				Hemorrhagic stroke	Dabigatran 110mg: 0.12%/y Warfarine: 0.38%/y **Superior: RR 0.31 (95%CI 0.17-0.56), p<0.001**	
				Mortality	Dabigatran 110mg: 3.75%/y Warfarine: 4.13%/y NS: RR 0.91 (95%CI 0.80-1.03) (p=0.13)	
				Myocardial infarction	Dabigatran 110mg: 0.72%/y Warfarine: 0.53%/y NS: RR 1.35 (95%CI 0.98-1.87) (p=0.07)	
				Harms		
				Bleeding outcomes		
				Intracranial	Dabigatran 110mg 0.23%/y vs warfarine 0.74%/y **SS less intracranial bleedings with dabigatran 110mg: RR 0.31 (95%CI 0.20-0.47), p<0.001**	
				Major life threatening bleeding	1.22%/y vs 1.80%/y **SS less major life threatening bleedings with dabigatran 110mg: RR 0.68 (95%CI 0.55-0.83), p<0.001**	
				Major or minor bleeding	14.62%/y vs 18.15%/y **SS less major or minor bleedings with dabigatran 110mg: RR = 0.78 (95%CI 0.74-0.83) P<0.001**	

				Minor bleeding	13.16%/y vs 16.37%/y **SS less minor bleedings with dabigatran 110mg** **RR = 0.79 (95%CI 0.74-0.84), p<0.001**	
				Major non life threatening bleeding	1.66%/y vs 1.76%/y NS: RR 0.94 (95%CI 0.78-1.15), p=0.56	
				GI-bleeding	1.12%/y vs 1.02/y NS: RR1.10 (95%CI 0.86-1.41), p=0.43	
				AE's		
				SS more dyspepsia with dabigatran11.8% vs 5.8% (p<0.001)		

7.1.1.6.1.bis Conclusion: Dabigatran 2x110mg/d vs warfarin

Dabigatran 2x110mg/d vs warfarin (INR 2-3) (Conolly 2009)				
N/n	**Duration**	**Population**	**Results**	
N=1 N = 18113	2y	-Atrial fibrillation -mean CHADS score 2.1 -mean age 71 -excl: Clearance <30ml/min, Severe valve disease, Stroke <14d or severe stroke <6mo, high risk of bleeding, liver disease, pregnancy	**Efficacy**	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Dabigatran 110mg: 1.53%/y Warfarine: 1.69%/y **Non-inferior**: **RR 0.91 (95%CI 0.74-1.11), p<0.001 for noninferiority,** Not superior (p=0.34)
			Ischemic or unspecified stroke	Dabigatran 110mg: 1.34%/y Warfarine: 1.20%/y NS: RR 1.11 (95%cI 0.8 9-1.40) (p=0.35)
			Hemorrhagic stroke	Dabigatran 110mg: 0.12%/y Warfarine: 0.38%/y **Superior: RR 0.31 (95%CI 0.17-0.56), p<0.001**
			Mortality	Dabigatran 110mg: 3.75%/y Warfarine: 4.13%/y NS: RR 0.91 (95%CI 0.80-1.03) (p=0.13)
			Myocardial infarction	Dabigatran 110mg: 0.72%/y Warfarine: 0.53%/y NS: RR 1.35 (95%CI 0.98-1.87) (p=0.07)
			Harms	
			Intracranial bleeding	Dabigatran 110mg 0.23%/y vs warfarine 0.74%/y **SS less intracranial bleedings with dabigatran 110mg: RR 0.31 (95%CI 0.20-0.47), p<0.001**
			Major life threatening bleeding	1.22%/y vs 1.80%/y **SS less major life threatening bleedings with dabigatran 110mg: RR 0.68 (95%CI 0.55-0.83), p<0.001**
			Major or minor bleeding	14.62%/y vs 18.15%/y **SS less major or minor bleedings with dabigatran 110mg: RR = 0.78 (95%CI 0.74-0.83), p<0.001**
			Minor bleeding	13.16%/y vs 16.37%/y **SS less minor bleedings with dabigatran 110mg RR = 0.79 (95%CI 0.74-0.84), p<0.001**
			GI-bleeding	1.66%/y vs 1.76%/y NS: RR 0.94 (95%CI 0.78-1.15), p=0.56
			Dyspepsia	**SS more dyspepsia 11.8% vs 5.8% (p<0.001)**
GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
-1 for not blinding	NA	OK	OK	

- This trial found that dabigatran 2x110 mg/d was non-inferior to warfarin for the composite endpoint stroke (ischaemic and haemorrhagic) and systemic embolism. Dabigatran was superior to warfarin in decreasing the risk of hemorraghic stroke (RR 0.31). Dabigatran was non-inferior to warfarin for the risk of ischemic stroke and for mortality. Dabigatran was not associated with an increase in myocardial infarction.

- Dabigatran 2x110mg was associated with significantly lower rates of intracranial (RR 0.31) and life threatening bleedings (RR 0.68). The incidence of major/minor bleeding (RR 0.78) and of minor bleeding (RR 0.79) was also significantly lower with dabigatran. No significant differences were found as to gastro-intestinal bleeding.
GRADE: Moderate quality of evidence

- Dabigatran 2x110mg was associated with a higher incidence of dyspepsia.

7.1.1.6.2. Dabigatran 2x150mg/d vs warfarin

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Connolly 2009 RE-LY + subgroup analyses Design: RCT P	n= 18.113 -mean age 71y -mean CHADS score 2.1 -30% CHADS score 0 or 1 -20% previous CVA/TIA -TTR INR: 64% <u>Inclusion</u> - atrial fibrillation -increased risk of stroke: previous stroke/TIA, heart failure, ≥75y, or 65-74Y+diabetes, hypertension, coronary artery disease <u>Exclusion</u> - stroke <14d or severe stroke <6m - severe heart valve disorder - ncreased risk of hemorrhage - creatinine clearance < 30ml/min - liver failure	2y	Dabigatran 2x150mg/d vs warfarin INR 2.0-3.0	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 0/2 ATTRITION: 1/1 - FU: 99% - ITT: yes - Other important methodological remarks? - warfarin therapy not blinded (open label) - non-inferiority design combined with superiority design, with intention to treat analysis (no per protocol analysis) - Sponsor: Boehringer Ingelheim
				Stroke (ischemic or hemorrhagic) or systemisch embolism (PE)	Dabigatran 150mg: 1.11%/y Warfarin: 1.69%/y **Superior: RR 0.66 (95%CI 0.53-0.82), p<0.001** **NNT= 172**	
				Ischemic or unspecified stroke	Dabigatran 150mg: 0.92%/y Warfarin: 1.20%/y **Superior : RR 0.76 (95%CI 0.60-0.98), p=0.03**	
				Hemorrhagic stroke	Dabigatran 150mg: 0.10%/y Warfarin: 0.38%/y **Superior: RR 0.26 (95%CI 0.14-0.49), p<0.001**	
				Mortality	Dabigatran 150mg: 3.64%/y Warfarin: 4.13%/y NS: RR 0.88 (95%CI 0.77-1.00) (p=0.051)	
				Myocardial infarction	Dabigatran 150mg: 0.74%/y Warfarin: 0.53%/y **SS more MI in dabigatran group: RR 1.38 (95%CI 1.00-1.91) p = 0.048**	
				Harms		
				Bleeding outcomes		
				Intracranial	Dabigatran 150mg 0.30%/y vs warfarin 0.74%/y **SS less intracranial bleedings with dabigatran: RR 0.40 (95%CI 0.27-0.60), p<0.001**	
				Major life threatening bleeding	1.45%/y vs 1.80%/y **SS less major life threatening bleedings with dabigatran: RR 0.81 (95%CI 0.66-0.99), p = 0.04**	
				Major non life threatening bleeding	1.88%/y vs 1.76%/y NS: RR 1.07 (95%CI 0.89-1.29), p=0.47	
				Myocardial infarction	Dabigatran 150mg: 0.74%/y Warfarin: 0.53%/y **SS more MI in dabigatran group: RR 1.38 (95%CI 1.00-1.91),**	
				GI-bleeding	1.51%/y vs 1.02%/y **SS more GI-bleedings with dabigatran: RR 1.50 (95%CI 1.19-1.89), p<0.001**	
				AE's		
				SS more dyspepsia 11.3% vs 5.8% (p<0.001)		

Results predefined subgroup analyses:

- *Eikelboom 2011*
  In patients with atrial fibrillation at risk for stroke, both doses of dabigatran compared with warfarin have lower risks of both intracranial and extracranial bleeding in patients <75 years. In those aged ≥75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.
- *Ezekowitz 2010*

Previous vitamin K antagonist exposure does not influence the benefits of dabigatran at either dose compared with warfarin.

- *Wallentin 2010*
  The benefits of 150mg dabigatran at reducing stroke, 110mg dabigatran at reducing bleeding, and both doses at reducing intracranial bleeding versus warfarin were consistent irrespective of quality of INR control.
- *Diener 2010*
  The effects of dabigatran 110mg and 150mg twice daily in patients with previous stroke or transient ischemic attack are consistent with those of other patients in the RE-LY trial, for whom, compared with warfarin, dabigatran 150mg reduced stroke or systemic embolism and dabigatran 110mg was non-inferior.

7.1.1.6.2. bis Conclusion: Dabigatran 2x150mg/d vs warfarin

Dabigatran 2x150 mg/d vs warfarin (INR 2-3) (Conolly 2009)				
N/n	**Duration**	**Population**	**Results**	
N=1 **N = 18113**	2y	-Atrial fibrillation -mean CHADS score 2.1 -mean age 71 -excl: Clearance <30ml/min, Severe valve disease, Stroke <14d or severe stroke <6mo, high risk of bleeding, liverdisease, pregnancy	**Efficacy**	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Dabigatran 150mg: 1.11%/y Warfarin: 1.69%/y **Superior: RR 0.66 (95%CI 0.53-0.82), p<0.001**
			Ischemic or unspecified stroke	Dabigatran 150mg: 0.92%/y Warfarin: 1.20%/y **Superior: RR 0.76 (95%CI 0.60-0.98), p=0.03**
			Hemorrhagic stroke	Dabigatran 150mg: 0.10%/y Warfarin: 0.38%/y **Superior: RR 0.26 (95%CI 0.14-0.49), p<0.001**
			Mortality	Dabigatran 150mg: 3.64%/y Warfarin: 4.13%/y NS: RR 0.88 (95%CI 0.77-1.00) (p=0.051)
			Myocardial infarction	Dabigatran 150mg: 0.74%/y Warfarin: 0.53%/y **SS more MI in dabigatran group: RR 1.38 (95%CI 1.00-1.91) p = 0.048**
			Harms	
			Intracranial bleeding	Dabigatran 150mg 0.30%/y vs warfarin 0.74%/y **SS less intracranial bleedings with dabigatran: RR 0.40 (95%CI 0.27-0.60), p<0.001**
			Major life threatening bleeding	1.45%/y vs 1.80%/y **SS less major life threatening bleedings with dabigatran: RR 0.81 (95%CI 0.66-0.99), p = 0.04**
			Major non life threatening bleeding	1.88%/y vs 1.76%/y NS: RR 1.07 (95%CI 0.89-1.29), p=0.47
			GI-bleeding	1.51%/y vs 1.02%/y **SS more GI-bleeding in dabigatran group: RR 1.50 (95%CI 1.19-1.89), p<0.001**
			Dyspepsia	SS more in dabigatran group **11.3% vs 5.8% (p<0.001)**

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
-1 for not blinding	NA	OK	OK	

- This trial found that dabigatran 2x150 mg/d is superior to warfarin for the composite endpoint of stroke (ischaemic and haemorrhagic) and systemic embolism (NNT= 172/2 years). These results were mainly due to a decrease in the risk of haemorrhagic stroke (RR 0.26). For the outcome 'ischemic or unspecified stroke' dabigatran was also superior to warfarin (borderline significance; RR 0.76).
- The incidence of life threatening bleeding was lower with dabigatran 2x150 mg (RR 0.81), but the rate of gastro-intestinal bleeding was higher with dabigatran, compared to warfarin (RR 1.50). The risk of myocardial infarction was also higher with dabigatran 2x150 mg (RR 1.38).

GRADE: moderate quality of evidence

- Dabigatran 2x150mg was associated with a higher incidence of dyspepsia.

7.1.1.7. Rivaroxaban vs. warfarin

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
23 Patel 2011 (ROCKET AF trial) Design: RCT, P + subgroup analysis 18 Fox 2011	n= 14.264 -mean age 73 -mean CHADS score 3.5 (100% CHADS≥2) -55% previous stroke, systemic embolism or transient ischemic attack -TTR INR: 55% <u>Inclusion</u> - non-valvular atrial fibrillation - moderate to high risk of stroke (prior stroke/TIA, or at least 2 risk factors: heart failure, hypertension, ≥75 y, diabetes) <u>Exclusion</u> - high bleeding risk - severe renal insufficiency or liver failure	707 days follow up	Rivaroxaban 15- 20mg/d vs Warfarin INR 2-3 <u>Renal insufficiency:</u> CrCl<30ml/min -> excluded CrCl 30-49ml/min -> 15mg rivaroxaban CrCl≥50ml/min -> 20mg rivaroxaban	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 2/2 ATTRITION: 1/1 - FU: 99% - ITT: per protocol and ITT analysis - Other important methodological remarks? - non-inferiority design combined with superiority design, with intention to treat analysis (no per protocol analysis) -low TTR in warfarin-arm: 55% vs 63-73% in other trials - Sponsor: Johnson and Johnson, Bayer Healthcare
				Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Per protocol Rivaroxaban: 1.7%/y vs warfarin:2.2%/y **SS: HR 0.79 (95%CI 0.66 – 0.96) p<0.001 for noninferiority** ITT: Rivaroxaban: 2.1%/y vs warfarin: 2.4%/y **SS : HR 0.88 (95%CI 0.74 – 1.03) p<0.001 for noninferiority,** p = 0.12 for superiority
				Ischemic stroke	Rivaroxaban 1.34% vs warfarin 1.42% NS: HR 0.94; 95%CI 0.75-1.17, p=0.581
				Hemorrhagic stroke	**Rivaroxaban 0.26% vs warfarin 0.44%** **HR 0.59 (95%CI 0.37-0.93) p=0.024**
				Mortality	Rivaroxaban 1.87% vs 2.21% warfarin NS: HR 0.85 (95%CI 0.70 – 1.02) p=0.073
				Myocardal infarction	Rivaroxaban 0.91% vs 1.12% warfarin NS: HR 0.81 (95%CI 0.63 – 1.06) p=0.121
				Harms	
				Bleeding outcomes	
				Intracranial	Rivaroxaban 0.5% vs 0.7% warfarin (p=0.02)
				Major bleeding*	3.6% vs 3.4% (NS: p=0.58)
				Decrease in Hb ≥ 2g/dl	2.8% vs 2.3% (NS: p=0.02)
				Fatal bleeding	**0.2% vs 0.5% (SS: p=0.003)**
				Nonmajor clinically relevant bleeding**	11.8% vs 11.4% (NS: p=0.35)
				GI-bleeding	**3.2% vs 2.2% (SS: p<0.001)**
				AE's	
				Epistaxis (10.14% vs 8.55%, SS: p<0.05) and hematuria (4.16% vs 3.420%, SS: p<0.05) SS more frequent in rivaroxaban group	

* Major bleeding was defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration >2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability.

** Non-major clinically relevant bleeding was defined as overt bleeding not meeting criteria for major bleeding but requiring medical intervention, unscheduled contact (visit or telephone) with a physician, temporary interruption of study drug (i.e., delayed dosing), pain, or impairment of daily activities.

Predefined subgroup analysis Fox 2011

Patients with AF and moderate renal insufficiency have higher rates of stroke and bleeding than those with normal renal function.
A pre-specified secondary analysis assessed the risks and benefits of the lower dose of rivaroxaban compared with warfarin in the high-risk cohort of patients with moderate renal insufficiency (2.950 patients, mean age 79y). This subanalysis was unable to demonstrate non-inferiority or superiority for the comparison of rivaroxaban versus warfarin in patients with moderate renal insufficiency (CrCl 30-49ml/min).

7.1.1.7.bis. Conclusion: Rivaroxaban vs. warfarin

Rivaroxaban 15-20 mg/d vs warfarin (INR 2-3) (Patel 2011, ROCKET AF)				
N/n	**Duration**	**Population**	**Results**	
N=1, n=14.264	707d follow up	-non-valvular atrial fibrillation -mean age 73 -mean CHADS2 score 3.5 (100% CHADS≥2) -55% previous stroke, systemic embolism or transient ischemic attack -TTR INR: 55% <u>Exclusion</u> - high bleeding risk - severe renal insufficiency or liver failure CrCl 30-49ml/min -> 15mg rivaroxaban CrCl≥50ml/min -> 20mg rivaroxaban	**Efficacy**	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Rivaroxaban: 2.1%/y vs warfarin: 2.4%/y **Not inferior: HR 0.88 (95%CI 0.74 – 1.03) p<0.001 for noninferiority, p = 0.12 for superiority (IIT)**
			Ischemic stroke	Rivaroxaban 1.34% vs warfarin 1.42% NS: HR 0.94; 95%CI 0.75-1.17, p=0.581
			Hemorrhagic stroke	**Rivaroxaban 0.26% vs warfarin 0.44% Superior: HR 0.59 (95%CI 0.37-0.93) p=0.024**
			Mortality	Rivaroxaban 1.87% vs 2.21% warfarin NS: HR 0.85 (95%CI 0.70 – 1.02) p=0.073
			Myocardal infarction	Rivaroxaban 0.91% vs 1.12% warfarin NS: HR 0.81 (95%CI 0.63 – 1.06) p=0.121
			Harms	
			Intracranial bleeding	**Rivaroxaban 0.5% vs 0.7% warfarin SS less intracranial bleeding with rivaroxaban: HR 0.67 (95% CI 0.47-0.93) (p=0.02)**
			Major bleeding	3.6% vs 3.4% (NS: p=0.58)
			Decrease in Hb ≥ 2g/dl	**2.8% vs 2.3% SS more decrease in Hb ≥ 2g/dl with rivaroxaban: HR 1.22 (95%CI 1.03-1.44) (p=0.02)**
			Fatal bleeding	**0.2% vs 0.5% SS less fatal bleeding with rivaroxaban: HR 0.50 (95%CI 0.31-0.79), p=0.003**
			Transfusion	**1.6% vs 1.3% SS more need of transfusion with rivaroxaban : HR 1.25 (95%CI 1.01-1.55), p = 0.04**
			GI-bleeding	**3.2% vs 2.2% SS more GI-bleeding with rivaroxaban (p<0.001)**
			AE	
			Epistaxis (10.14% vs 8.55%, SS: p<0.05) and hematuria (4.16% vs 3.420%, SS: p<0.05) SS more frequent in rivaroxaban group	
GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
OK	NA	-1 for low TTR warfarin group	OK	

- This trial found that rivaroxaban is non-inferior to warfarin in the prevention of stroke or systemic embolism in patients with AF and CHADS2-score ≥2. Rivaroxaban does not diminish the risk of ischaemic stroke, but leads to a decrease in the rate of haemorrhagic stroke (HR 0.59). Mortality and the incidence of myocardial infarction did not differ significantly between treatment groups.
- Rivaroxaban was associated with lower rates of intracranial (0.5% vs 0.7%, NNT 246) and fatal (0.2% vs 0.5%, NNT 254) bleedings. On the other hand, an increased risk of gastro-intestinal bleeding was found in patients treated with rivaroxaban (3.2% vs 2.2%, NNH 101).
Cases of decrease in Hb ≥ 2g/dl (2.8% vs 2.3%, NNH 138) and situations requiring transfusion (2.8% vs 2.3%, NNH 138) were also significantly more frequent in patients treated with rivaroxaban

GRADE: moderate quality of evidence

- Rivaroxaban is associated with higher rates of epistaxis and hematuria, compared to warfarin.

7.1.1.8. Dose comparison

7.1.1.8.1 Dabigatran 2x150mg/d vs dabigatran 2x110mg/d

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Connolly '09 Re-Ly Design: RCT P	n= 18.113 -mean age 71y -mean CHADS score 2.1 -30% CHADS score 0 or 1 -20% previous CVA/TIA -TTR INR: 64% <u>Inclusion</u> - atrial fibrillation - increased risk of stroke: previous stroke/TIA, heart failure, ≥75y, or 65-74Y+diabetes, hypertension, coronary artery disease <u>Exclusion</u> - stroke <14d or severe stroke <6m - severe heart valve disorder -Increased risk of hemorrhage - creatinine clearance < 30ml/min - liver failure	2y	Dabigatran 2*150mg vs Dabigatran 2*110mg	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING:2/2 ATTRITION: 1/1 - FU: 99% - ITT: yes - Other important methodological remarks? -non-inferiority trial - Sponsor: Boehringer Ingelheim
				Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Dabigatran 150mg:1.11%/y Dabigatran 110mg: 1.53%/y **Superior: RR 0.73 (95%CI 0.58-0.91), p = 0.005**	
				Ischemic or unspecified stroke	Dabigatran 150mg:0.92%/y Dabigatran 110mg: 1.34%/y **Superior: RR 0.69 (95%CI 0.54-0.88), p=0.002**	
				Hemorrhagic stroke	Dabigatran 150mg: 0.10%/y Dabigatran 110mg: 0.12%/y NS: RR 0.85 (95%CI 0.39-1.83), p=0.67	
				Mortality	Dabigatran 150mg: 3.64%/y Dabigatran 110mg: 3.75%/y NS: RR 0.97 (95%CI 0.85-1.11), p=0.66	
				Myocardial infarction	Dabigatran 150mg: 0.74%/y Dabigatran 110mg:0.72%/y NS: RR1.02 (95%CI 0.76-1.38), p=0.88	
				Harms		
				Bleeding outcomes		
				Intracranial	Dabigatran 150mg 0.30%/y vs 0.23%/y 110mg NS: RR 1.32 (95%CI 0.80-2.17), p=0.28	
				Major life threatening bleeding	1.45%/y vs 1.22%/y NS: RR 1.19 (95%CI 0.96-1.49), p=0.11	
				Major non life threatening bleeding	1.88%/y vs 1.66%/y NS: RR 1.14 (95%CI 0.95-1.39), p=0.17	
				Minor Bleeding	Dabigatran 150mg 14.84%/y vs 14.84%/y 110mg **SS more minor bleeding with 150 mg: RR 1.16 (95%CI 1.08-1.24), p<0.001**	
				Major or minor bleeding	Dabigatran 150mg 16.42%/y vs 14.62%/y 110mg **SS more major or minor bleeding with 150 mg: RR 1.16 (95%CI 1.09-1.23), p<0.001**	
				GI-bleeding	1.51%/y vs 1.12%/y **SS more GI-bleeding with 150mg: RR 1.36 (95%CI 1.09-1.70), p=0.007**	
				AE's		
				No statistical analysis		

7.1.1.8.1.bis. Conclusion: Dabigatran 2x150mg/d vs dabigatran 2x150mg/d

Dabigatran 2x150 mg/d vs dabigatran 2x110 mg/d (Conolly 2009)				
N/n	**Duration**	**Population**	**Results**	
N=1 **N = 18113**	2y	-Atrial fibrillation -mean CHADS score 2.1 -mean age 71 -excl: Clearance <30ml/min, Severe valve disease, Stroke <14d or severe stroke <6mo, high risk of bleeding, liverdisease, pregnancy	**Efficacy**	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Dabigatran 150mg:1.11%/y Dabigatran 110mg: 1.53%/y **SS: RR 0.73 (95%CI 0.58-0.91), p = 0.005**
			Ischemic or unspecified stroke	Dabigatran 150mg:0.92%/y Dabigatran 110mg: 1.34%/y **SS: RR 0.69 (95%CI 0.54-0.88), p=0.002**
			Hemorrhagic stroke	Dabigatran 150mg: 0.10%/y Dabigatran 110mg: 0.12%/y NS: RR 0.85 (95%CI 0.39-1.83), p=0.67
			Mortality	Dabigatran 150mg: 3.64%/y Dabigatran 110mg: 3.75%/y NS: RR 0.97 (95%CI 0.85-1.11), p=0.66
			Myocardial infarction	Dabigatran 150mg: 0.74%/y Dabigatran 110mg:0.72%/y NS: RR1.02 (95%CI 0.76-1.38), p=0.88
			Harms	
			Intracranial bleeding	Dabigatran 150mg 0.30%/y vs 0.23%/y 110mg NS: RR 1.32 (95%CI 0.80-2.17), p=0.28
			Major life threatening bleeding	1.45%/y vs 1.22%/y NS: RR 1.19 (95%CI 0.96-1.49), p=0.11
			Major non life threatening bleeding	1.88%/y vs 1.66%/y NS: RR 1.14 (95%CI 0.95-1.39), p=0.17
			Minor Bleeding	Dabigatran 150mg 14.84%/y vs 14.84%/y 110mg **SS more minor bleeding with 150 mg: RR 1.16 (95%CI 1.08-1.24), p<0.001**
			Major or minor bleeding	Dabigatran 150mg 16.42%/y vs 14.62%/y 110mg **SS more major or minor bleeding with 150 mg: RR 1.16 (95%CI 1.09-1.23), p<0.001**
			GI-bleeding	1.51%/y vs 1.12%/y **SS more GI-bleeding with 150mg: RR 1.36 (95%CI 1.09-1.70), p=0.007**

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→High quality of evidence**
OK	NA	OK	OK	

- Dabigatran 2x150 mg/d is more effective than dabigatran 2x110 mg/d for the primary composite endpoint of stroke (ischaemic and haemorrhagic) en systemic embolism (RR 0.73). This difference was mainly due to a decrease in the rate of ischaemic stroke (RR 0.69). Mortality, haemorrhagic stroke and myocardial infarction did not differ significantly. This superior efficacy is at the expense of a higher risk of gastro-intestinal (RR 1.36), minor (RR 1.16), and major or minor bleedings (RR 1.16).

GRADE: high quality of evidence

- Adverse events: no statistical test.

7.1.2 Antiplatelets in patients with AF and high thrombo-embolic risk

7.1.2.1. ASA + clopidogrel vs. ASA

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
ACTIVE A 2009 Design: RCT	n= 7754 -atrial fibrillation (64% permanent AF) - patients unsuitable for vitamin K-antagonists - high risk of stroke -85% hypertension -13% previous stroke or TIA -mean age : 71 -mean CHADS score : 2 - 72% patients with CHADS score ≤2 -TTR INR: % NA Inclusion -atrial fibrillation (at enrollment or ≥ 2 episodes of intermittent atrial fibrillation ≤ 6 months) -one of the following risk factors for stroke: an age of 75 years or more; systemic hypertension during treatment; previous stroke, TIA, or non–CNS systemic embolism; a left ventricular ejection fraction <45%; peripheral vascular disease; or an age of 55 to 74 years and	Median follow-up: 3.6y	clopidogrel 75mg/d plus acetylsalicylic acid 75-100mg/d vs placebo plus acetylsalicylic acid 75-100mg/d	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING:2 /2 ATTRITION:1 /1 - FU: 62% - ITT: yes - Other important methodological remarks? - If need of cardioversion, open-label treatment with vit K antagonists 4 weeks before and after - Although reported as a trial in high risk patients, about 1/3 of patients had CHADS score 0 or 1 - Sponsor: Sanofi-Aventis and Bristol-Myers Squibb
				Stroke (ischemic or hemorrhagic), myocardial infarction, non-CNS systemic embolism, death from vascular causes (PE)	**6.8%/y Clopidogrel + ASA vs ASA 7.6%/y SS:RR =0.89 (95% CI 0.81 – 0.98) p=0.01**	
				Stroke	**2.4%/y Clopidogrel + ASA vs ASA 3.3%/y SS:RR =0.72 (95% CI 0.62 – 0.83) p<0.001**	
				Ischemic stroke	**1.9%/y Clopidogrel + ASA vs ASA 2.8%/y SS:RR =0.68 (95% CI 0.57 – 0.80)**	
				Hemorrhagic stroke	0.17%/y Clopidogrel + ASA vs ASA 0.23%/y NS:RR =1.37 (95% CI 0.79 – 2.37)	
				Stroke of uncertain type	0.3%/y Clopidogrel + ASA vs ASA 0.4%/y NS:RR =0.81 (95% CI 0.54 – 1.22)	
				Fatal stroke	0.5%/y Clopidogrel + ASA vs ASA 0.7%/y NS:RR =0.75 (95% CI 0.55 – 1.03)	
				Nondisabling stroke	**0.9%/y Clopidogrel + ASA vs ASA 1.2%/y SS:RR =0.70 (95% CI 0.54 – 0.89) p=0.004**	
				Disabling or fatal stroke	**1.6%/y Clopidogrel + ASA vs ASA 2.1%/y SS:RR =0.74 (95% CI 0.62 – 0.89) p=0.001**	
				Mortality	6.4%/y Clopidogrel + ASA vs ASA 6.6%/y NS:RR =0.98 (95% CI 0.89 – 1.08) p=0.69	
				Death from vascular causes	4.7%/y Clopidogrel + ASA vs ASA 4.7%/y NS:RR =1.00 (95% CI 0.89 – 1.12) p=0.97	
				Non-CNS systemic embolism	0.4%/y Clopidogrel + ASA vs ASA 0.4%/y NS:RR =0.96 (95% CI 0.66 – 1.40) p=0.84	
				Myocardial infarction	0.7%/y Clopidogrel + ASA vs ASA 0.9%/y NS:RR =0.78 (95% CI 0.59 – 1.03) p=0.08	
				Harms		
				Bleeding outcomes		
				Major bleeding	**2.0%/y Clopidogrel + ASA vs ASA 1.3%/y SS:RR =1.57 (95% CI 1.29 – 1.92) p<0.001**	
				Severe bleeding	**1.5%/y Clopidogrel + ASA vs ASA 1.0%/y**	

	diabetes mellitus or coronary artery disease. Exclusion -required a vitamin K antagonist or clopidogrel -any of the following risk factors for hemorrhage: documented peptic ulcer disease ≤ 6 months; a history of intracerebral hemorrhage; significant thrombocytopenia <50×10^9 per liter); ongoing alcohol abuse.				**SS:RR =1.57 (95% CI 1.25 – 1.98) p<0.001**	
				Fatal bleeding	0.3%/y Clopidogrel + ASA vs ASA 0.2%/y NS:RR =1.56 (95% CI 1.29 – 1.92) p=0.07	
				Minor bleeding	**3.5%/y Clopidogrel + ASA vs ASA 1.4%/y** **SS:RR =2.42 (95% CI 2.03 – 2.89) p<0.001**	
				Any bleeding	**9.7%/y Clopidogrel + ASA vs ASA 5.7%/y** **SS:RR =1.68 (95% CI 1.52 – 1.85) p<0.001**	
				Intracranial	**0.4%/y Clopidogrel + ASA vs ASA 0.2%/y** **SS:RR =1.87 (95% CI 1.19– 2.94) p=0.006**	
				Extracranial	**1.6%/y Clopidogrel + ASA vs ASA 1.1%/y** **SS:RR =1.51 (95% CI 1.21– 1.88) p<0.001**	
				GI bleeding	**1.1%/y Clopidogrel + ASA vs ASA 0.5%/y** **SS:RR =1.96 (95% CI 1.46– 2.63) p<0.001**	
				GI bleeding with transfusion	**0.9%/y Clopidogrel + ASA vs ASA 0.5%/y** **SS:RR =1.93 (95% CI 1.42– 2.63) p<0.001**	
				AE's		

Major hemorrhage was defined as any overt bleeding requiring transfusion of at least two units of blood or any overt bleeding meeting the criteria for severe hemorrhage, which included any of the following: fatal hemorrhage, a drop in the hemoglobin level of 5.0 g per deciliter or more, hypotension requiring inotropic agents, intraocular bleeding leading to substantial loss of vision, requirement for surgical intervention, symptomatic intracranial hemorrhage, or requirement for transfusion of four units or more of blood.
Minor bleeding was defined as any nonmajor bleeding associated with modification of the study-drug regimen.

7.1.2.1.bis Conclusion: ASA + clopidogrel vs. ASA

Clopidogrel 75 mg/d plus acetylsalicylic acid 75-100 mg/d vs acetylsalicylic acid 75-100 mg/d (Active A 2009)				
N/n	**Duration**	**Population**	**Results**	
N=1, n= 7754	3.6 y	- patients with atrial fibrillation - patients unsuitable for vitamin K-antagonists - high risk of stroke -85% hypertension -13% previous stroke or TIA -mean age 71 y -mean CHADS score : 2 - 72% patients with CHADS score ≤2	Stroke (ischemic or hemorrhagic), myocardial infarction, non-CNS systemic embolism, death from vascular causes (PE)	6.8%/y Clopidogrel + ASA vs ASA 7.6%/y SS: RR =0.89 (95% CI 0.81 – 0.98) p=0.01
			Stroke	2.4%/y Clopidogrel + ASA vs ASA 3.3%/y SS: RR =0.72 (95% CI 0.62 – 0.83) p<0.001
			Ischemic stroke	1.9%/y Clopidogrel + ASA vs ASA 2.8%/y SS: RR =0.68 (95% CI 0.57 – 0.80)
			Hemorrhagic stroke	NS
			Fatal stroke	NS
			Nondisabling stroke	0.9%/y Clopidogrel + ASA vs ASA 1.2%/y SS: RR =0.70 (95% CI 0.54 – 0.89) p=0.004
			Disabling or fatal stroke	1.6%/y Clopidogrel + ASA vs ASA 2.1%/y SS: RR =0.74 (95% CI 0.62 – 0.89) p=0.001
			Mortality	NS
			Vascular mortality	NS
			Myocardial infarction	NS
			Major bleeding	2.0%/y Clopidogrel + ASA vs ASA 1.3%/y SS: RR =1.57 (95% CI 1.29 – 1.92) p<0.001
			Any bleeding	9.7%/y Clopidogrel + ASA vs ASA 5.7%/y SS: RR =1.68 (95% CI 1.52 – 1.85) p<0.001
			Intracranial	0.4%/y Clopidogrel + ASA vs ASA 0.2%/y SS: RR =1.87 (95% CI 1.19– 2.94) p=0.006
			Extracranial	1.6%/y Clopidogrel + ASA vs ASA 1.1%/y SS: RR =1.51 (95% CI 1.21– 1.88) p<0.001
			GI bleeding	1.1%/y Clopidogrel + ASA vs ASA 0.5%/y SS: RR =1.96 (95% CI 1.46– 2.63) p<0.001

GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
OK	NA	-1for heterogeneous study population	OK	

- The association of clopidogrel and ASA was compared to ASA alone in patients for whom vitamin K antagonist therapy was unsuitable. About 2/3 of the population had an elevated risk of stroke. The combination therapy was superior to ASA alone for the prevention of major vascular events, predomininantly stroke. Mortality and risk of myocardial infarction were not significantly different between treatment groups. NNT= 125 for the primary composite endpoint.

GRADE: moderate quality of evidence

- The combination treatment was associated with an elevated risk of major bleedings (NNH=143).

7.2. Risk reduction in patients with AF and low to moderate thrombo-embolic risk

7.2.1. Oral anticoagulants in patients with AF and low to moderate thrombo-embolic risk

7.2.1.1. Oral anticoagulants vs. placebo

Ref	N/n	Comparison	Outcomes	
Aguilar, Cochrane Stroke Group* Design: meta-analysis Search date: 2009	N= 5 n= 2.313	Oral anticoagulants vs control In patients with chronic non-valvular AF Without history of stroke/TIA Low to moderate risk of stroke/TIA Mean achieved INR: 2.0-2.6	All strokes (ischemic and hemorrhagic)	**OR=0.39 (95% CI 0.26-0.59)** in favour of treatment with OACs ⇨ 25 strokes would be prevented yearly per 1000 participants given OACs
			Ischemic strokes	**OR=0.34 (95% CI 0.23-0.52)** in favour of treatment with OACs ⇨ 25 strokes would be prevented yearly per 1000 participants given OACs
			Disabling or fatal strokes	**OR=0.47 (95% CI 0.28-0.80)** in favour of treatment with OACs ⇨ 12 strokes would be prevented yearly per 1000 participants given OACs
			Myocardial infarction	OR=0.87 (95% CI 0.32-2.42)
			Systemic arterial emboli	OR=0.45 (95% CI 0.13-1.57)
			Intracranial hemorrhage	OR=2.38 (95% CI 0.54-10.5)
			Major extracranial bleeding	OR=1.07 (95% CI 0.53-2.12)
			Vascular death	OR=0.84 (95% CI 0.56-1.30)
			Stroke, MI or vascular death	**OR=0.57 (95% CI 0.42-0.76)** in favour of treatment with OACs ⇨ 25 events would be prevented yearly per 1000 participants given OACs
			All cause mortality	**OR=0.69 (95% CI 0.50-0.94)** in favour of treatment with OACs ⇨ 17 deaths would be prevented yearly per 1000 participants given OACs

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
AFASAK I Petersen 1989 RCT	1007 (630)	- chronic non-rheumatic AF (intermittent AF excl) - no stroke or TIA 1m before trial - no anticoagulation during 6m prior - median age: 74.2y - 54% male	mean 1.2y	adjusted-dose warfarin vs placebo (vs aspirin 75mg) INR target range: 2.8-4.2	- Jadad score: 3/5 - FU: NR - ITT: yes Remarks: °6% of participants had prior stroke and/or TIA °38% withdrawn from OAC and 15% from placebo °trial was stopped early at an interim analysis
BAATAF 1990 RCT	420	- chronic sustained or intermittent non-valvular AF - no stroke within previous 6m - no TIA for which patient is being treated - no mitral stenosis, no prosthetic heart valves, no intracardiac thrombus, no LV aneurysm,… - no neurological condition predisposing to intracranial hemorrhage - mean age: 68y - 75% male	2.2y	warfarin vs placebo estimated equivalent INR: 1.5-2.7	- Jadad score: 3/5 - FU: 100% - ITT: yes Remarks: °3% of participants had prior stroke and/or TIA °10% withdrawn from OAC °trial was stopped early at an interim analysis
CAFA Connolly 1991 RCT	378	- chronic non-valvular AF ≥1m or paroxysmal AF ≥3x during previous 3m - no stroke or TIA in previous year - no MI within 1m - no mitral stenosis or prosthetic heart valve - no uncontrolled hypertension - no hyperthyroidism	mean 1.3y	warfarin vs placebo target INR range: 2-3	- Jadad score: 4/5 - FU: NR - ITT: yes Remarks: °4% of participants had prior stroke and/or TIA °26% withdrawn from OAC and 23% from placebo
SPAF I 1991 RCT	1330 (421)	- non-valvular chronic AF within 1y (constant or intermittent) - no stroke or TIA in previous 2y - no risk factor for cardiogenic embolism - mean age: 67y	1.3y	warfarin vs placebo (vs aspirin) approximate INR equivalent: 2-4.5	- Jadad score: 2/5 - FU: 100% - ITT: yes Remarks: °8% of participants had prior

		- 71% male			stroke and/or TIA °11% withdrawn from OAC °trial was stopped early at an interim analysis
SPINAF 1992	571 (525 without prior stroke) men only	- Primary prevention: chronic non-valvular AF (excl intermittent AF) - Secondary prevention: stroke ≥1m before trial - no rheumatic heart disease, mitral stenosis, prosthetic heart valve, coronary artery bypass surgery - no MI within 1m prior to trial - no TIA within 5y	mean 1.7y	warfarin vs placebo estimated INR equivalent: 1.4-2.8	- Jadad score: 4/5 - FU: 97% - ITT: yes Remarks: °30% withdrawn from warfarin °trial was stopped early at an interim analysis

7.2.1.1.bis. Conclusion: Oral anticoagulants vs. placebo

Oral anticoagulants vs placebo (Petersen 1989, BAATAF 1990, Connolly 1991, SPAF I 1991, SPINAF 1992)				
N/n	**Duration**	**Population**	**Results**	
N= 5 n= 2313	Mean 1.5y	-chronic AF -no history stroke/TIA -low to moderate risk of stroke/TIA -mean age: 69y -74% men -mean achieved INR: 2.0-2.6	All strokes	Reported in 5/5 trials **OR=0.39 (95% CI 0.26-0.59)** in favour of treatment with OACs
			Ischemic strokes	Reported in 5/5 trials **OR=0.34 (95% CI 0.23-0.52)** in favour of treatment with OACs
			Disabling or fatal strokes	Reported in 5/5 trials **OR=0.47 (95% CI 0.28-0.80)** in favour of treatment with OACs
			Myocardial infarction	Reported in 3/5 trials OR=0.87 (95% CI 0.32-2.42)
			Systemic arterial emboli	Reported in 5/5 trials OR=0.45 (95% CI 0.13-1.57)
			Intracranial hemorrhage	Reported in 5/5 trials OR=2.38 (95% CI 0.54-10.5)
			Major extracranial bleeding	Reported in 5/5 trials OR=1.07 (95% CI 0.53-2.12)
			Vascular death	Reported in 5/5 trials OR=0.84 (95% CI 0.56-1.30)
			Stroke, MI or vascular death	Reported in 5/5 trials **OR=0.57 (95% CI 0.42-0.76)** in favour of treatment with OACs
			All cause mortality	Reported in 5/5 trials **OR=0.69 (95% CI 0.50-0.94)** in favour of treatment with OACs
GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
-1 for methodological weakness	OK	OK	OK	

- Oral anticoagulants were examined in patients with AF without previous stroke or TIA and with a low to moderate risk for thrombo-embolic events. In this population, treatment with oral anticoagulants significantly reduced the incidence of stroke (OR=0.39, 95% BI 0.26-0.59). The oral antociagulants were adjusted to an INR 2-3. Total mortality was also significantly reduced in the groups treated with oral anticoagulants.

GRADE: moderate quality of evidence

- No statistically significant differences were found between oral anticoagulants and placebo as to the incidence of intracranial or major bleeding.

7.2.1.2. Adjusted-dose warfarin vs. ASA

Ref	N/n	Comparison	Outcomes	
Owen 2010* Design: meta-analysis Search date: ?	N= 7 n= 4059 In patients with chronic non-valvular AF Without history of stroke/TIA Low to moderate risk of stroke/TIA	Warfarin Vs ASA (<300mg/d) Reported in 4/7 studies, 2620 patients in total	Stroke	**OR=0.51 (95% CI: 0.35-0.75)** **SS in favour of warfarin**
			Mortality	OR=0.71 (95% CI: 0.43-1.18) NS
		Warfarin Vs ASA (>300mg/d) Reported in 3/7 studies, 1439 patients in total	Stroke	OR=0.96 (95% CI: 0.62-1.47) NS
			Mortality	OR=0.98 (95% CI: 0.70-1.37) NS

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Warfarin vs ASA <300mg/d					
AFASAK1 Petersen 1989	1007	- adults with chronic AF - no cerebrovascular events in past month - median age: 74.2 y - target INR: 2.8-4.2	Mean: 1.2y	Warfarin vs ASA 75mg/d vs placebo	- Jadad score: 3/5 - FU: NR - ITT: yes
ATAFS 2006	704	- nonvalvular AF - 19% of participants had previous stroke or TIA	?	Warfarin vs ASA 150mg/d	Study in Chinese
BAFTA Mant 2007	973	- non-rheumatic chronic AF - age ≥75y - target INR:2-3	1.8y	Warfarin vs ASA 75mg/d	- Jadad score: 3/5 - FU: 97% - ITT: yes
PATAF Hellemons 1999	272	- confirmed chronic or intermittent AF - ≥60y - target INR: 2.5-3.5	2.7y	Warfarin vs ASA 150mg/d	- Jadad score: 3/5 - FU: 100% - ITT: yes
Warfarin vs ASA >300mg/d					
AFASAK2 Gullov 1998	339	- nonvalvular chronic AF - ≥18y - target INR: 1.8-3.2	2.5y	Warfarin vs ASA 325mg/d	- Jadad score: 2/5 - FU: 100% - ITT: yes
SPAF2 (<75y) 1994	715	- non-rheumatic AF - <75y - mean INR: 2.7	Mean: 3.1y	Warfarin vs ASA 325mg/d	- Jadad score: 3/5 - FU: 99% - ITT: no
SPAF2 (≥75y) 1994	385	- non-rheumatic AF - ≥75y - mean INR: 2.6	Mean: 2y	Warfarin vs ASA 325mg/d	- Jadad score: 3/5 - FU: 99% - ITT: no

Remarks

Information on mean achieved INR in warfarin treatment groups is not given in all studies.

In the SPAF2 trial randomization was stratified according to age over or under 75 years. The results were presented for the two groups separately

7.2.1.2.bis Conclusion: Adjusted-dose warfarin vs. ASA

<table>
<tr><td colspan="6">Acetylsalicylic acid vs oral anticoagulants (MA Owen 2010: Petersen 1989, ATAFS 2006, Mant 2007, Hellemons 1999, Gullov 1998, SPAF2 1994)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="7">N= 7
n= 4059</td><td rowspan="7">Mean: 2.2y</td><td rowspan="7">- patients with chronic non-valvular AF
- without history of stroke/TIA</td><td colspan="3">Warfarin vs ASA (<300mg/d)
Reported in 4/7 trials</td></tr>
<tr><td>Stroke</td><td colspan="2">OR=0.51 (95% CI: 0.35-0.75)
SS in favour of warfarin</td></tr>
<tr><td>Mortality</td><td colspan="2">OR=0.71 (95% CI: 0.43-1.18) NS</td></tr>
<tr><td colspan="3">Warfarin vs ASA (>300mg/d)
Reported in 3/7 trials</td></tr>
<tr><td>Stroke</td><td colspan="2">OR=0.96 (95% CI: 0.62-1.47) NS</td></tr>
<tr><td>Mortality</td><td colspan="2">OR=0.98 (95% CI: 0.70-1.37) NS</td></tr>
<tr><td colspan="6">GRADE assessment</td></tr>
<tr><td>Quality</td><td>Consistency</td><td>Directness</td><td>Imprecision</td><td colspan="2" rowspan="2">→ Low quality of evidence</td></tr>
<tr><td>-1
missing information in one (Chinese) study</td><td>-1
conflicting study results</td><td>OK</td><td>OK</td></tr>
</table>

- Warfarin is more effective than ASA (<300 mg/d) at reducing the risk of stroke in patients with AF without previous stroke/TIA. The difference is no longer significant with ASA in doses of >300 mg/d. No significant differences were found for mortality.

GRADE: low quality of evidence

- This meta-analysis reports no data on adverse events.

7.2.1.3. Low-dose warfarin + ASA vs. control

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Edvardsson 2003 Design: RCT	n= 668 -mean age : 73 -low to medium risk (≤4%/y) of stroke -sotalol treatment ➔ at rest 60-100bpm and Qtc <0.52sec -mean CHADS score :NR -TTR INR: %?(9% >1,3 in the treatment group, NA in the no anticoagulation group) <u>Inclusion</u> -non-valvular atrial fibrillation - without previous stroke or TIA <u>Exclusion</u> -Patients with ischaemic heart disease receiving aspirin -severe heart failure (NYHA III/IV) -bradycardia<60bpm -severe hypertension SBP>190; DBP>110 -known bleeding disorder	Mean follow up period: 33 months	Warfarin 1,25mg/d (fixed dose) + aspirin 75mg/d vs no anticoagulation	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 0/2 (open label) ATTRITION: 1/1 - FU: 76% - ITT: yes - Other important methodological remarks? Underpowered trial - Sponsor: Bristol Myers Squibb
				Stroke (ischemic or hemorrhagic) (PE)	W/A 9.6% vs 12.3% no anticoagulation NS: HR = 0.78 (95% CI 0.49-1.23), p=0.28	
				Mortality (all cause)	W/A 9.3% vs 10.8% no anticoagulation NS: HR = 0.86 (95% CI 0.53-1.40), p=0.55	
				Myocardial infarction	W/A 4.2% vs 5.4% no anticoagulation NS: HR = 0.77 (95% CI 0.38-1.55), p=0.46	
				TIA	W/A 3.3% vs 4.5% no anticoagulation NS: HR = 0.73 (95% CI 0.33-1.58), p=0.42	
				Cardiovascular morbidity	W/A 17.7% vs 22.2% no anticoagulation NS: HR = 0.76 (95% CI 0.52-1.10), p=0.14	
				Peripheral embolism	W/A 1.5% vs 1.5% no anticoagulation NS: HR = 0.99 (95% CI 0.29-3.42), p=0.99	
				Stroke + TIA	W/A 11.7% vs 16.5% no anticoagulation NS: HR = 0.70 (95% CI 0.46-1.05), p=0.09	
				Harms		
				Bleeding outcomes		
				Intracranial	NR	
				Any bleeding	W/A= 5.7% no anticoagulation= 1.2% p=0.003	
				Fatal bleeding	NR	
				Nonmajor clinically relevant bleeding	NR	
				GI-bleeding	NR	
				AE's		
				No statistical analysis		

7.2.1.3.bis Conclusion: Low-dose warfarin + ASA vs. control

Warfarin fixed low dose (1.25 mg/d) + acetylsalicylic acid 75 mg/d vs no anticoagulation (Edvardsson 2003)				
N/n	**Duration**	**Population**	**Results**	
N= 1, n= 668	33 m	- non valvular atrial fibrillation - low to medium (≤4%/y) risk of stroke	Stroke (ischemic or hemorrhagic) (PE)	W/A 9.6% vs 12.3% no anticoagulation NS
			Mortality (all cause)	W/A 9.3% vs 10.8% no anticoagulation NS
			Myocardial infarction	W/A 4.2% vs 5.4% no anticoagulation NS
			TIA	W/A 3.3% vs 4.5% no anticoagulation NS
			Cardiovascular morbidity	W/A 17.7% vs 22.2% no anticoagulation NS
			Any bleeding	W/A 5.7% vs no anticoagulation 1.2% p=0.003
			Fatal bleeding	NR
			Minor bleeding	NR
GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→Moderate quality of evidence**
-1 for limited safety outcomes and lack of power	NA	OK	OK	

- The association of low-dose warfarin + ASA 75 mg/d was compared to no anticoagulation in 1 trial with patients with AF and low to moderate thrombo-embolic risk (≤4%/year). No significant differences were found between both treatment groups as to the incidence of stroke or TIA. Mortality was not significantly different neither.

GRADE: moderate quality of evidence

- In pateints treated with the association of warfarin + ASA, more bleedings occurred. The authors of this study state that the combination treatment can prevent 18 strokes, but at the expense of 15 bleedings requiring treatment.

7.2.2. Antiplatelet agents in patients with AF and low to moderate thrombo-embolic risk

7.2.2.1. Antiplatelets vs. control

Ref	N/n	Comparison	Outcomes	
Aguilar 2011 Cochrane* Design: meta-analysis Search date: 9 June 2005	N= 3 n= 1.965	Aspirin (75mg-325mg) vs placebo or control In patients with non-valvular AF No previous history of stroke/TIA Low to moderate risk of stroke/TIA Mean age: 70y 38% women Average duration: 1.3y per patient	All strokes (ischemic and hemorrhagic)	OR=0.70 (95% CI 0.47-1.07) ⇨ NS
			Ischemic strokes (fatal and non-fatal)	OR=0.70 (95% CI 0.46-1.07) ⇨ NS
			Disabling or fatal strokes or intracranial hemorrhage	OR=0.86 (95% CI 0.50-1.49) ⇨ NS
			Myocardial infarction	OR=0.47 (95% CI 0.19-1.14) ⇨ NS
			Systemic arterial emboli	OR=0.67 (95% CI 0.19-2.33) ⇨ NS
			Intracranial hemorrhage	OR=1.32 (95% CI 0.22-7.80) ⇨ NS
			Major extracranial bleeding	OR=1.14 (95% CI 0.44-2.98) ⇨ NS
			Vascular death	OR=0.82 (95% CI 0.54-1.25) ⇨ NS
			Stroke, MI or vascular death	**OR=0.71 (95% CI 0.51-0.97)** in favour of aspirin
			All cause mortality	OR=0.75 (95% CI 0.54-1.04) ⇨ NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
AFASAK I Petersen 1989 RCT	1007 (672)	- Chronic non-rheumatic AF - No cerebrovascular events within past month - No prior anticoagulation therapy during last 6m - Median age: 74.2y - 54% male	Mean 1.2y	Aspirin 75mg vs placebo (vs warfarin)	- Jadad score: 4/5 - FU: NR - ITT: yes Remarks: ° 14% of participants were withdrawn from assigned therapy
LASAF Posada 1999	285	- Primary AF - No history of angina, MI or TIA - Mean age: 62y	1.5y	Aspirin 125mg daily Vs Aspirin 125mg on alternate days Vs Placebo	- Jadad score: 3/5 - FU: NR - ITT: yes Remarks: ° Method of allocation NR ° Unpublished data obtained from author ° Non-blinded ° Withdrawal from assigned therapy: 28%
SPAF I 1991	1330 (1120)	- Non-rheumatic chronic AF in preceding 12m - No history of stroke or TIA during previous 2y - Mean age: 67y - 71% male	1.3y	Aspirin 325mg Vs Placebo (vs warfarin)	- Jadad score: 3/5 - FU: 100% - ITT: yes Remarks: ° Method of allocation NR ° Off therapy: 5% aspirin, 6.6% placebo

Remarks

- Aspirin was associated with consistent but modest reductions in stroke and other ischemic events that were of marginal statistical significance
- No significant increases in hemorrhagic events were seen in treatment with aspirin in these trials

Ref	n / Population	Duration	Comparison	Outcomes		Methodological
Sato 2006 Design: RCT	n= 871 japanese patients -mean age :65 -45% of high risk patients (defined as patients with hypertension, previous cerebrovascular disease or heart failure) -2.5% previous cerebrovascular disease -mean CHADS score :NR -TTR INR: % NA -<u>Inclusion:</u> -non-valvular atrial fibrillation - low risk of stroke -<u>Exclusion:</u> -uncontrolled hypertension -severe heart failure (NYHA class IV) -symptomatic thromboembolic disease<1year -intracranial bleeding, gastrointestinal hemorrhage <6 months -patients with other indications for anticoagulant therapy	768±403 d	Aspirin 150-200mg vs no treatment	**Efficacy**		- Jadad score RANDO: 2/2 BLINDING: 0/2 (open label) ATTRITION: 1/1 - FU: 79% - ITT: yes - Early termination of the trial (due to no superiority of aspirin) - Although the study population is presented as having low risk of stroke, 45% of patients are at high risk. - Sponsor: Research funds from the Ministry of Health and Education
				Cardiovascular death Ischemic stroke or TIA (PE)	Aspirin 3,1% per year vs 2,4% per year no treatment NS p=0,175	
				Ischemic Stroke	Aspirin 3.99% vs 4,04% no treatment NS p=0,967	
				TIA	Aspirin 1.64% vs 4.49% no treatment NS p=0,101	
				Hemorrhagic stroke		
				Mortality	Aspirin 2.35% vs 2.02% no treatment NS p=0,101	
				Myocardial infarction		
				Harms		
				Bleeding outcomes		
				Intracranial	Aspirin 0,94% vs 0,45% no treatment NT	
				Any bleeding	NR	
				Decrease in Hb ≥ 2g/dl	NR	
				Fatal bleeding	NR	
				Nonmajor clinically relevant bleeding	NR	
				GI-bleeding	NR	
				Major bleeding	Aspirin 1,6% vs 0,4% no treatment NS p=0,101	
				AE's		
				Gastrointestinal side effects Aspirin 2.35% vs 0% no treatment NS p=0.001		

Major bleeding was defined as fatal bleeding , bleeding needed for hospital admission for treatment, blood transfusion, or a decrease of hemoglobin concentration >4g/dL

7.2.2.1.bis.Conclusion: Antiplatelets vs. control

Acetylsalicylic acid (75mg-325mg) vs placebo (Petersen 1989, Posada 1999, SPAF I, Sato 2006)				
N/n	**Duration**	**Population**	**Results**	
N= 4 n= 2836	Mean 1.5y per patient	-non-valvular AF -no previous cerebrovascular events -mean age: 69.2y -67.6% men	All strokes (ischemic and hemorrhagic)	Reported in 3/4 trials OR=0.70 (95% CI 0.47-1.07) => NS
			Ischemic stroke	Reported in 3/4 trials OR=0.70 (95% CI 0.46-1.07) => NS Reported in 1/4 trials Aspirin 3.99% vs 4.04% placebo (p=0.967) => NS
			Myocardial infarction	Reported in 3/4 trials OR=0.47 (95% CI 0.19-1.14) => NS
			Intracranial bleeding	Reported in 3/4 trials OR=1.32 (95% CI 0.22-7.80) => NS Reported in 1/4 trials Aspirin 0.94% vs 0.45% placebo => NT
			Major bleeding	Reported in 3/4 trials OR=2.57 => NS Reported in 1/4 trials Aspirin 1.6% vs 0.4% placebo (p=0.101) => NS
			Stroke, MI or vascular death	Reported in 3/4 trials **OR=0.71 (95% CI 0.51-0.97) => SS** in favour of aspirin treatment
			Mortality	Reported in 3/4 trials OR=0.96 => NS Reported in 1/4 trials Aspirin 2.35% vs 2.02% placebo (p=0.101) => NS
			GI side effects	Reported in 1/4 trials
GRADE assessment				
Quality	**Consistency**	**Directness**	**Imprecision**	**→High quality of evidence**
OK	OK	OK	OK	

- Acetylsalicylic acid was compared to control in 4 trials with patients with chronic AF without previous stroke/TIA and with low to moderate thrombo-embolic risk. ASA was examined in doses of 75-325 mg/d. ASA was not effective at reducing the risk of stroke or myocardial infarction

GRADE: high quality of evidence

- No significant differences were found as to adverse events

- Remark: in the study from 2006, 45% high-risk patients were included.

8. Adverse events (French)

8.1. Principaux effets indésirables des antagonists de la vitamine K

- L'hémorragie constitue le principal effet indésirable des antagonistes de la vitamine K. L'incidence annuelle des hémorragies sévères dans l'étude AFFIRM (4060 patients sur 3,5 ans) a été de 2% par an. Il existe un lien étroit entre l'intensité du traitement anticoagulant et le risque hémorragique. Des études randomisées ont montré que le meilleur rapport coût/bénéfice se situe à un INR entre 2 et 3.
- Les réactions allergiques sont très rares. Le traitement avec des antagonistes de la vitamine K entraîne toutefois une réaction diminuée aux tests cutanés.
- Des cas d'uricosurie ont été rapportés sous dicoumarol.
- Dans des cas exceptionnels, une nécrose cutanée induite par la prise d'antagonistes de la vitamine K peut être observée. C'est le cas chez 0,01 à 0,1% des patients. Le cas échéant, la morbidité de cette complication est cependant importante: malgré un traitement adéquat, la moitié des patients concernés doivent subir une intervention nécessitant ou pas des greffes de peau. La prévention de la nécrose cutanée induite par la coumarine peut consister à augmenter progressivement la dose, et ceci plus particulièrement chez les patients âgés.
- Les antagonistes de la vitamine K ont un effet vasodilateur sur les coronaires, les veines périphériques et les capillaires, ce qui provoque le syndrome des orteils pourpres. La vasodilatation périphérique peut aussi être responsable d'une sensation de froid ressentie par certains patients.
- Quelques cas seulement de dommage hépatique ont été rapportés. Il s'agit habituellement d'une pathologie de type cholestatique survenant dix jours environ après le début du traitement avec des antagonistes de la vitamine K.
- L'instauration d'un traitement antithrombotique pendant la grossesse est liée à un risque élevé connu, aussi bien pour la mère que pour l'enfant à naître. Les femmes enceintes courent un risque accru de fausse couche et d'hémorragie périnatale. Les antagonistes de la vitamine K sont tératogènes. Ils passent aussi dans le lait maternel, mais cela n'aurait pas d'effet sur le nourrisson. Certains experts recommandent néanmoins de régulièrement déterminer le temps de prothrombine des bébés allaités dont la mère prend des antagonistes de la vitamine K et d'éventuellement leur administrer 1mg de vitamine K par voie orale par semaine.

Source

Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), *2006*, *Pages 983-1000*

8.2. Effets indésirables de l'apixaban

Remarque: non disponible en Belgique, mais approuvé au niveau européen depuis le 18 mai 2011

- Comme tous les anticoagulants, l'apixaban augmente le risque d'hémorragie et ce médicament ne peut être administré que lorsque l'hémostase est atteinte. Les hémorragies, l'anémie et les ecchymoses représentent 1-10% de l'ensemble des effets indésirables connus. Les hémorragies gastro-intestinales sont moins fréquentes (1-0.1%) Dans l'étude ARISTOTLE, chez les patients souffrant de fibrillation auriculaire traités avec apixaban, le pourcentage total des hémorragies a été de 18 % par an.
- La prudence est de rigueur en cas d'utilisation combinée d'apixaban et d'aspirine en raison d'une éventuelle augmentation du risque d'hémorragie.
- Apixaban est déconseillé chez les patients souffrant d'insuffisance rénale sévère chez lesquels la clairance créatinique <15ml/min et chez les patients en dialyse.
- On ne dispose que d'une expérience clinique limitée avec apixaban chez les patients âgés, mais selon son fabricant, ce médicament peut être administré à des patients de plus de 65 ans. L'administration de ce médicament est néanmoins limitée en cas de poids corporel inférieur à 50kg ou supérieur à 120kg.
- Apixaban est contre-indiqué chez les patients atteints de troubles hépatiques liés à des troubles de la coagulation et à un risque d'hémorragie d'importance clinique. Aucun ajustement de la dose n'est nécessaire chez les patients souffrant de troubles de la fonction hépatique légers à modérés.
- En ce qui concerne l'utilisation pédiatrique d'apixaban, on ne dispose d'aucune donnée et il est donc déconseillé d'administrer apixaban à des patients <18 ans.
- Apixaban n'est pas conseillé pendant la grossesse et l'allaitement étant donné que son effet dans ces conditions est encore inconnu.

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8.3. Effets indésirables du dabigatran

- L'effet indésirable le plus fréquent de dabigatran est l'hémorragie. Des hémorragies sont survenues chez environ 14% des patients au total. La fréquence des hémorragies sévères (y compris les saignements des plaies) a été de moins de 2%. L'épistaxis et les hémorragies gastro-intestinales sont fréquentes et observées chez 1 à 10 patients sur 100 patients traités. Ces hémorragies peuvent mener à une anémie et à une diminution de la quantité d'hémoglobine.
- Des douleurs abdominales, une diarrhée et des nausées sont également fréquemment rapportées. Il ressort de l'étude RE-LY que la dyspepsie est significativement plus fréquente sous traitement par dabigatran que sous traitement par warfarine. On n'a pas noté d'augmentation significative des enzymes hépatiques mais il convient de rester vigilant. L'agence américaine des médicaments (FDA) a estimé que dans un cas de dommage hépatique un lien de causalité avec le dabigatran était probable.
- L'agence européenne des médicaments (EMA) recommande d'évaluer la fonction rénale avant de commencer un traitement par dabigatran et de la surveiller ensuite régulièrement pendant le traitement. En cas d'insuffisance rénale sévère (clairance créatinique <30ml/min), dabigatran est contre-indiqué.
- Dans une récente méta-analyse d' Uchino et Hernandez (Arch Int Med 2012; doi:10.1001) comparativement à celle d'autres antithrombotiques, l'utilisation de dabigatran a été corrélée à un risque accru d'infarctus du myocarde et du syndrome coronarien aigu.
- Dans l'étude RE-LY, des cas d'hypersensibilité, d'angioedème et de réactions anaphylactiques ont été observés chez moins de 0,1% des patients traités.
- L'utilisation de dabigatran chez les enfants de moins de 18 ans n'est pas recommandée en raison de l'absence de données d'innocuité et d'efficacité.
- On ne dispose pas de suffisamment de données sur l'utilisation de dabigatran chez les femmes enceintes et on ne dispose pas de données cliniques sur l'effet de dabigatran sur les nourrissons allaités.
- Il n'existe pas d'antidote, ce qui constitue un désavantage en cas d'hémorragie sévère. De plus, jusqu'ici, aucun test de laboratoire n'existe pour suivre l'effet anticoagulant du dabigatran.

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8.4. Effets indésirables du rivaroxaban

- L'effet indésirable le plus fréquent de rivaroxaban est l'hémorragie, éventuellement postopératoire, qui peut parfois entraîner une anémie et une thrombocytopénie. Ces hémorragies se présentent sous la forme d'une épistaxis, d'hémorragies gastro-intestinales et urologiques ainsi que d'hématomes. Des hémorragies d'importance clinique ont été observées chez environ 15% des patients traités par an dans l'étude ROCKET.
- Les patients sous traitement de rivaroxaban doivent effectuer régulièrement des tests hépatiques afin de surveiller toute éventuelle augmentation des cGT et des transaminases, ainsi que de la LDH et de la phosphatase alcaline. On note aussi parfois une augmentation de la bilirubinémie; de rares cas d'augmentation de la bilirubine conjuguée ont également été rapportés.
- Nausées, fièvre et œdème périphérique sont observés chez 1-10% des patients qui prennent du rivaroxaban.
- On note parmi les effets indésirables moins fréquents du rivaroxaban, les étourdissements, les maux de tête, la tachycardie, l'hypotension, la constipation, la diarrhée, les douleurs abdominales, la dyspepsie, les vomissements, la sécheresse de la bouche, une baisse générale de force et d'énergie, des douleurs dans les membres, une augmentation de l'amylase/lipase et une augmentation de la sécrétion d'exsudats.
- Dans certains cas exceptionnels, le rivaroxaban peut provoquer une syncope. Une dermatite et une urticaire sont également rares.
- Le rivaroxaban ne peut pas être administré aux femmes enceintes ou qui allaitent.
- Selon l'Agence européenne des médicaments (EMA), les autres contre-indications à l'administration du rivaroxaban sont les hémorragies actives ou les pathologies hépatiques liées à un risque hémorragique accru. Le rivaroxaban doit de préférence être évité en cas d'insuffisance rénale sévère (clairance créatinique <30ml/min); si la clairance créatinique <50ml/min, un ajustement de dose est conseillé.
- Il n'existe pas d'antidote, ce qui constitue un désavantage en cas d'hémorragie sévère.

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Appendix 1 Clinical evidence

ClinicalEvidence

Stroke: secondary prevention

Search date February 2009

Gregory YH Lip and Lalit Kalra

ABSTRACT

INTRODUCTION: People with a history of stroke or transient ischaemic attack (TIA) are at high risk of all vascular events, such as myocardial infarction (MI), but are at particular risk of subsequent stroke (about 10% in the first year and about 5% each year thereafter). METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of preventive non-surgical interventions in people with previous stroke or transient ischaemic attack? What are the effects of preventive surgical interventions in people with previous stroke or transient ischaemic attack? What are the effects of preventive anticoagulant and antiplatelet treatments in people with atrial fibrillation and previous stroke or transient ischaemic attack? What are the effects of preventive anticoagulant and antiplatelet treatments in people with atrial fibrillation and without previous stroke or transient ischaemic attack? What are the effects of preventive anticoagulant and antiplatelet treatments in people with atrial fibrillation and without previous stroke or transient ischaemic attack and with low to moderate risk of stroke or transient ischaemic attack? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2009 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 130 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: alternative antiplatelet regimens to aspirin, anticoagulation (oral dosing, or in those with sinus rhythm), aspirin (high or low dose), blood pressure reduction, carotid and vertebral percutaneous transluminal angioplasty (PTA), carotid endarterectomy (in people with: asymptomatic but severe carotid artery stenosis, less than 0% symptomatic carotid artery stenosis, moderate [30%–49%] symptomatic carotid artery stenosis, moderately severe [50%–69%] symptomatic carotid artery stenosis, severe [greater than 70%] symptomatic carotid artery stenosis, or symptomatic near occlusion of the carotid artery), cholesterol reduction, vitamin B supplements (including folate), and different regimens to lower blood pressure.

QUESTIONS

INTERVENTIONS

IN PEOPLE WITH PREVIOUS STROKE OR TIA: NON-SURGICAL PREVENTION

Beneficial

Unknown effectiveness

Unlikely to be beneficial

Likely to be ineffective or harmful

IN PEOPLE WITH PREVIOUS STROKE OR TIA: SURGICAL PREVENTION

Beneficial

Likely to be beneficial

Unknown effectiveness

Key points

- Prevention in this context is the long-term management of people with previous stroke or TIA, and of people at high risk of stroke for other reasons, such as atrial fibrillation.

  Risk factors for stroke include: previous stroke or TIA; increasing age; hypertension; diabetes; cigarette smoking; and emboli associated with atrial fibrillation, artificial heart valves, or MI.

- Antiplatelet treatment effectively reduces the risk of stroke in people with previous stroke or TIA.

  High-dose aspirin (500–1500 mg/day) seems as equally effective as low-dose aspirin (75–150 mg/day), although it may increase GI adverse effects.

  Adding dipyridamole to aspirin is beneficial in reducing composite vascular end points and stroke compared with aspirin alone. Risk reduction appears greater with extended-release compared with immediate-release dipyridamole.

  The net risk of recurrent stroke or major haemorrhagic event is similar with clopidogrel and aspirin plus dipyridamole.

- Treatments to reduce blood pressure are effective for reducing the risk of serious vascular events in people with previous stroke or TIA.

  Blood pressure reduction seems beneficial irrespective of the type of qualifying cerebrovascular event (ischaemic or haemorrhagic), or even whether people are hypertensive.

  Aggressive blood pressure lowering should not be considered in people with acute stenosis of the carotid or vertebral arteries, because of the risk of precipitating a stroke.

- Carotid endarterectomy effectively reduces the risk of stroke in people with greater than 50% carotid stenosis, is not effective in people with 30% to 49% carotid stenosis, and increases the risk of stroke in people with less than 30% stenosis. However, it does not seem beneficial in people with near occlusion.

- Cholesterol reduction using statins seems to reduce the risk of stroke irrespective of baseline cholesterol or coronary artery disease (CAD).

  Non-statin cholesterol reduction does not seem to reduce the risk of stroke.

- We found insufficient evidence to judge the efficacy of carotid percutaneous transluminal angioplasty, carotid percutaneous transluminal angioplasty plus stenting, or vertebral percutaneous transluminal angioplasty in people with recent carotid or vertebral TIA or stenosis.

- Vitamin B supplements (including folate) do not seem beneficial in reducing mortality or the risk of stroke.

- Anticoagulation does not seem beneficial in reducing stroke in people with previous ischaemic stroke and normal sinus rhythm, but does increase the risk of intra- and extracranial haemorrhage. This is especially true for patients with TIAs or minor ischaemic stroke as the qualifying event.

- In people with atrial fibrillation, oral anticoagulants reduce the risk of stroke in people with previous stroke or TIA, and in people with no previous stroke or TIA who are at high risk of stroke or TIA, but we don't know whether they are effective in people with no previous stroke or TIA who are at low risk of stroke or TIA.

In people with atrial fibrillation, we don't know whether aspirin reduces the risk of stroke in people with previous stroke or TIA, or in people without previous stroke or TIA who are at low risk of stroke or TIA, but they may be unlikely to be effective in people without previous stroke or TIA who are at high risk of stroke or TIA.

DEFINITION

Prevention in this context is the long-term management of people with previous stroke or transient ischaemic attack (TIA), and of people at high risk of stroke for other reasons such as atrial fibrillation. **Stroke:** Stroke is characterised by rapidly developing clinical symptoms and signs of focal, and at times global, loss of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. Ischaemic stroke is stroke caused by vascular insufficiency (such as cerebrovascular thromboembolism) rather than by haemorrhage.**TIA:** This is similar to a mild ischaemic stroke, except that symptoms last for less than 24 hours. [1] For management of stroke in the acute phase, see review on stroke management.

INCIDENCE/ PREVALENCE

See incidence/prevalence under review on stroke management.

AETIOLOGY/ RISK FACTORS

See aetiology under review on stroke management. Risk factors for stroke include: previous stroke or TIA; increasing age; hypertension; diabetes; cigarette smoking; and emboli associated with atrial fibrillation, artificial heart valves, or MI. The relationship with cholesterol is less clear. Overviews of prospective studies of healthy middle-aged people found no association between total cholesterol and overall stroke risk. [2] [3] [4] However, two of the overviews found that higher cholesterol increased the risk of ischaemic stroke, but reduced the risk of haemorrhagic stroke. [3] [4]

PROGNOSIS

People with a history of stroke or TIA are at high risk of all vascular events, such as MI, but are at particular risk of subsequent stroke (about 10% in the first year and about 5% each year thereafter [see figure 1, p 40 , and figure 1 in secondary prevention of ischaemic cardiac events]). [5] [6] [7] This risk of stroke after a TIA is greatest in the first 2 weeks, especially in people who are older, have diabetes or hypertension, and have unilateral weakness that lasts for more than 1 hour. [8] [9] People with intermittent atrial fibrillation treated with aspirin should be considered at similar risk of stroke compared with people with sustained atrial fibrillation treated with aspirin (rate of ischaemic stroke/year: 3.2% with intermittent *v* 3.3% with sustained). [10]

AIMS OF INTERVENTION

To prevent death or disabling stroke, as well as other serious non-fatal outcomes, especially MI, in people with previous stroke or TIA, with minimal adverse effects from treatment.

OUTCOMES

Stroke, MI, mortality, disability, dependency, and adverse effects.

METHODS

Clinical Evidence search and appraisal February 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2009, Embase 1980 to February 2009, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials, Issue 1, 2009 (1966 to date of issue). An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. For questions in people with atrial fibrillation, this was supplemented by one author's own search in January 2006. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. Where we did not find systematic reviews or RCTs solely in people with previous stroke or TIA, or with subgroup analyses in this population, we included systematic reviews and RCTs in mixed populations; those with previous stroke or TIA, or other risk factors, with appropriate comments on their generalisability. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome

of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 41).

QUESTION **What are the effects of preventive non-surgical interventions in people with previous stroke or TIA?**

OPTION **ANTIPLATELET TREATMENT VERSUS NO ANTIPLATELET TREATMENT**

Contributed by Lalit Kalra

Cardiovascular events

Antiplatelet treatment compared with placebo/no antiplatelet treatment Antiplatelet treatment is more effective at reducing serious cardiovascular events (stroke, MI) in people with a previous stroke or TIA (high-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits:

Antiplatelet treatment versus placebo or no treatment:

We found two systematic reviews, each identifying different RCTs. [7] [11] The first systematic review (search date 1997; 195 RCTs; 135,640 people at high risk of vascular disease: previous stroke or TIA, acute stroke, ischaemic heart disease, heart failure, cardiac valve disease, atrial fibrillation, peripheral arterial disease, diabetes, and haemodialysis) compared antiplatelet treatment (mostly aspirin) versus placebo or no antiplatelet treatment. [7] It found that, in people with previous stroke or TIA (21 RCTs; 18,270 people), antiplatelet treatment significantly reduced serious vascular events (stroke, MI, or vascular death) after 3 years compared with placebo or no antiplatelet treatment (18% with antiplatelet treatment *v* 21% with placebo or no antiplatelet treatment; OR 0.78, 95% CI 0.73 to 0.85). Antiplatelet treatment also reduced the separate outcomes of stroke, MI, vascular death, and death (see figure 1, p 40). For every 1000 people with previous stroke or TIA treated for about 3 years, antiplatelet treatment prevented 25 non-fatal strokes (P less than 0.0001), six non-fatal MIs (P = 0.0009), and 15 deaths (P = 0.002). [7] The second review (search date 2007; 12 RCTs; 43,041 people with definite or presumed ischaemic stroke) evaluated the efficacy of antiplatelet therapy for acute ischaemic stroke. [11] The primary outcome was death or dependency in the acute phase, but the review also included recurrent ischaemic stroke as a secondary outcome. It found that antiplatelet treatment significantly reduced the incidence of recurrent ischaemic stroke compared with control (551/21321 [2.6%] with antiplatelets *v* 708/21279 [3.3%] with control; OR 0.77, 95% CI 0.68 to 0.86; P less than 0.00001). The range of follow-up in the included RCTs ranged from 21 days to 6 months. [11]

Harms:

Antiplatelet treatment versus placebo or no treatment:

The first systematic review found that, in people with previous stroke or TIA, antiplatelet treatment was associated with higher rates of major extracranial haemorrhage (haemorrhages requiring hospital admission or blood transfusion) and intracranial haemorrhage compared with no antiplatelet treatment (major extracranial haemorrhage: AR: 0.97% with antiplatelet treatment *v* 0.47% with no antiplatelet treatment; OR 2.0, CI not reported; intracranial haemorrhage: AR: 0.64% with antiplatelet treatment *v* 0.56% with no antiplatelet treatment; OR 1.2, CI not reported). [7] The estimated excess risk of bleeding was about one to two additional major extracranial bleeds per 1000 people a year. [7] The second review reported that during the treatment period, antiplatelet therapy was associated with a small but significant increase in symptomatic intracranial haemorrhages compared with placebo (235/21321 [1.1%] with antiplatelets *v* 176/21279 [0.8%] with control; OR 1.33, 95% CI 1.10 to 1.62; P = 0.004). [11]

We found two further systematic reviews on harms associated with antiplatelet treatment. The first review (search date 1997; 16 RCTs; 55,462 people) found that aspirin increased intracranial haemorrhage by about one event per 1000 people treated for 3 years. [12] The second review (search date 1999; 24 RCTs) assessed the effects of aspirin on GI bleeding. [13] It found that aspirin significantly increased GI bleeding compared with placebo or no aspirin (OR 1.68, 95% CI 1.51 to 1.88).

Comment:

Clinical guide:

The review found a large and highly significant reduction in non-fatal stroke, along with a smaller, but still significant, reduction in non-fatal MI. [7] The review reported that, although the reduction in vascular mortality (7 fewer deaths per 1000 people treated; P = 0.04) was only marginally significant, the reduction in all-cause mortality (15 fewer deaths per 1000 people treated; P = 0.002) strongly reinforced the conclusion that prolonged antiplatelet treatment reduces the risk of death. The strength of the evidence is such that comparing antiplatelet treatment versus placebo or no

treatment is no longer an area of uncertainty. The large absolute reductions in serious vascular events produced by antiplatelet treatment far outweighed any absolute hazards in people at high risk of vascular disease, including those with prior ischaemic stroke or TIA.

OPTION BLOOD PRESSURE REDUCTION VERSUS PLACEBO OR NO TREATMENT

Cardiovascular events

Any treatment to reduce blood pressure compared with placebo/no treatment Treatments to reduce blood pressure (beta-blockers, diuretics, ACE inhibitors) are more effective at 3 years at reducing stroke, MI, and total vascular events in people with a prior stroke or TIA (high-quality evidence).

ACE inhibitors compared with placebo ACE inhibitors are more effective at reducing MI in people with a prior stroke or TIA, but no more effective at reducing stroke or vascular events (moderate-quality evidence).

Diuretics compared with placebo/no treatment Diuretics are more effective at reducing stroke and vascular events in people with a prior stroke or TIA, but no more effective at reducing MI (moderate-quality evidence).

Diuretic plus ACE inhibitor compared with placebo/no treatment A diuretic plus an ACE inhibitor is more effective at reducing stroke, MI, and vascular events in people with a prior stroke or TIA (moderate-quality evidence).

Beta-blockers compared with placebo/no treatment Beta-blockers are no more effective at reducing stroke, MI, or vascular events in people with a prior stroke or TIA (moderate-quality evidence).

Angiotensin receptor blockers compared with placebo Angiotensin receptor blockers seem no more effective at reducing stroke or vascular events in people with a prior stroke or TIA (moderate-quality evidence).

Mortality

Any treatment to reduce blood pressure compared with placebo/no treatment Treatments to reduce blood pressure (beta-blockers, diuretics, ACE inhibitors) are no more effective at reducing vascular death or all-cause mortality in people with a prior stroke or TIA (moderate-quality evidence).

Angiotensin receptor blockers compared with placebo Angiotensin receptor blockers seem no more effective at reducing all-cause mortality in people with a prior stroke or TIA (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41

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Benefits:

We found two systematic reviews and one subsequent RCT comparing treatments to reduce blood pressure (beta-blockers, diuretics, ACE inhibitors, calcium channel blockers, or angiotensin receptor blockers) versus placebo or no treatment. [14] [15] [16]

Treatments to reduce blood pressure versus placebo or no treatment:

The first review (search date not reported; 7 RCTs; 15,527 people with a prior stroke or TIA followed up for 2–5 years) [14] found that antihypertensive treatment (beta-receptor antagonists, diuretics, ACE inhibitors) reduced blood pressure by a mean of 8 mm Hg systolic/4 mm Hg diastolic, and significantly reduced stroke, MI, and total vascular events after a mean of 3 years of treatment compared with placebo or no treatment (stroke: 689/7779 [9%] with treatment *v* 888/7748 [11%] with control; OR 0.76, 95% CI 0.63 to 0.92; MI: 244/7729 [3%] with treatment *v* 311/7699 [4%] with control; OR 0.79, 95% CI 0.63 to 0.98; total vascular events [stroke, MI, or vascular death]: 993/7729 [13%] with treatment *v* 1232/7699 [16%] with control; OR 0.79, 95% CI 0.66 to 0.95). However, blood pressure reduction did not significantly reduce vascular death or all-cause mortality compared with placebo or no treatment (vascular death: OR 0.86, 95% CI 0.70 to 1.06; all-cause mortality: OR 0.91, 95% CI 0.79 to 1.05). [14] The second systematic review (search date 2003) examined the effects of blood pressure reduction generally in all population groups, not just in those with previous stroke or TIA (absolute numbers of those people with previous stroke or TIA not reported). [15] In subgroup analysis, it found that, in those people with stroke or previous TIA, treatments to reduce blood pressure significantly reduced the risk of stroke compared with placebo (RCTs in whom "most" or "all" had a history of stroke or TIA: RRR 22%, 95% CI 12% to 31%; RCTs and absolute numbers in analysis not reported; results presented graphically). [15]

ACE inhibitors versus placebo:

The first review found that, compared with placebo, ACE inhibitors significantly reduced MI, but did not significantly reduce stroke or vascular events (2 RCTs; 3574 people; MI: OR 0.74, 95% CI 0.56 to 0.98; stroke: OR 0.92, 95% CI 0.75 to 1.13; vascular events: OR 0.83, 95% CI 0.61 to 1.12). [14]

Diuretics versus placebo or no treatment:
The first review found that, compared with placebo or no treatment, diuretics significantly reduced stroke and vascular events, but did not significantly reduce MI (3 RCTs; 6216 people; stroke: OR 0.68, 95% CI 0.50 to 0.92; vascular events: OR 0.75, 95% CI 0.63 to 0.90; MI: OR 1.06, 95% CI 0.63 to 1.78). [14]

Diuretic plus ACE inhibitor versus placebo or no treatment:
The first review found that a diuretic plus an ACE inhibitor significantly reduced stroke, MI, and vascular events compared with placebo or no treatment (1 RCT; 3544 people; stroke: OR 0.55, 95% CI 0.45 to 0.68; MI: OR 0.55, 95% CI 0.38 to 0.79; vascular events: OR 0.58, 95% CI 0.48 to 0.69). [14]

Beta-blockers versus placebo or no treatment:
The first review found that beta-blockers did not significantly reduce stroke, MI, or vascular events compared with placebo (2 RCTs; 2193 people; stroke: OR 0.93, 95% CI 0.72 to 1.20; MI: OR 0.94, 95% CI 0.60 to 1.45; all vascular events: OR 1.01, 95% CI 0.81 to 1.27). [14]

Angiotensin receptor blockers versus placebo:
We found one RCT (20,332 people with previous ischaemic stroke; mean follow-up 2.5 years) comparing telmisartan 80 mg once daily versus placebo. [16] It found no significant difference between telmisartan and placebo in recurrent stroke, all-cause mortality, or major cardiovascular events (a composite outcome of cardiovascular mortality, recurrent stroke, or MI) (recurrent stroke: 880/10,146 [9%] with telmisartan *v* 934/10,186 [9%] with placebo; HR 0.95, 95% CI 0.86 to 1.04; all-cause mortality: 755/10,146 [7%] with telmisartan *v* 740/10,186 [7%] with placebo; HR 1.03, 95% CI 0.93 to 1.14; major cardiovascular events: 1289/10,146 [13%] with telmisartan *v* 1377/10,186 [14%] with placebo; HR 0.94, 95% CI 0.87 to 1.02). [16]

Harms:

The systematic reviews gave no information on adverse effects. [14] [15] Two RCTs identified by the first systematic review found that atenolol increased the risk of adverse effects leading to discontinuation of treatment (most commonly fatigue, cold extremities, bradycardia, dizziness, or subjective discomfort) compared with placebo (first RCT: 108/732 [15%] with atenolol *v* 56/741 [8%] with placebo; significance data not reported; second RCT: 63/372 [17%] with atenolol *v* 35/348 [10%] with placebo; significance data not reported). [17] [18] The largest RCT identified by the first review found that perindopril with or without added indapamide slightly but significantly increased the risk of people discontinuing treatment compared with placebo (714/3051 [23%] with treatment *v* 636/3054 [21%] with placebo; P = 0.02). [19] Another RCT identified by the first review found that ramipril slightly increased the risk of people discontinuing treatment compared with placebo (1343/4645 [29%] with ramipril *v* 1268/4652 [27%] with placebo; significance data not reported). These adverse-event data were based on analyses of people with and without prior cerebrovascular events. [20] The subsequent RCT found that drug discontinuation owing to adverse effects was significantly more common with telmisartan compared with placebo (1450/10,146 [14%] with telmisartan *v* 1127/10,186 [11%] with placebo; P less than 0.001). [16] Adverse effects that were significantly more common with telmisartan compared with placebo included hypotensive symptoms, syncope, and nausea (hypotensive symptoms: 393/10,146 [4%] with telmisartan *v* 186/10,186 [2%] with placebo; P less than 0.001; syncope: 21/10,146 [0.2%] with telmisartan *v* 6/10,186 [0.1%] with placebo; P = 0.004; nausea: 104/10,146 [1%] with telmisartan *v* 72/10,186 [0.7%] with placebo; P = 0.01). There was no significant difference in headache between the two groups (231/10,146 [2%] with telmisartan *v* 203/10,186 [2%] with placebo; P = 0.16). [16]

Comment:

The first systematic review found that a larger reduction in blood pressure was associated with a greater relative reduction in stroke and in vascular events. [14] The review also found that the effects of treatments to reduce blood pressure on stroke and on all vascular events varied according to the antihypertensive regimen used; those drug regimens that reduced blood pressure the most also achieved the greatest reduction in stroke or vascular events. [14] The second review, which included RCTs in all population groups (not just people with previous stroke or TIA), performed a meta-regression analysis to assess the relationship between net reduction in systolic blood pressure and the risk of stroke. [15] The review found that a dose–response relationship existed between blood pressure and stroke risk, and that a 10 mm Hg reduction in systolic blood pressure was associated with a relative reduction in the risk of stroke of 31% (further details not reported). [15] The first review found that, across all control groups, the average risk of stroke 11.5%, and the average risk of vascular events 16% (ARR for stroke and for vascular events with treatment compared with control: 3%, about 1% a year). [14] The largest RCT included in the review compared 4 years of the ACE inhibitor perindopril plus the diuretic indapamide (added at the discretion of the treating physician) versus placebo. The relative risk reduction of stroke and vascular events remained similar, regardless of baseline blood pressure and the type of qualifying cerebrovascular event (ischaemic or haemorrhagic). [19] It found that, compared with placebo, perindopril plus the diuretic

indapamide reduced blood pressure by 9/4 mm Hg, and reduced stroke and major vascular events (stroke: RR 0.72, 95% CI 0.62 to 0.83; major vascular events: RR 0.74, 95% CI 0.66 to 0.84). [19]

Clinical guide:
Overviews of observational studies in healthy middle-aged and older people, as well as in those with a history of cerebrovascular events, found no evidence of a threshold below which treatment was ineffective for reducing stroke, at least down as far as about 115/75 mm Hg. [3] [21] [22] [23] However, it seems appropriate to be particularly cautious about lowering blood pressure in people with known severe stenosis of the carotid or vertebral arteries, because of the possibility of precipitating a stroke. [24] Observational studies in people with severe bilateral stenosis found that lower blood pressure was associated with an increased risk of stroke, suggesting that aggressive blood pressure reduction may not be advisable in this group. [25]

OPTION CHOLESTEROL REDUCTION

Contributed by Lalit Kalra

Cardiovascular events
Statins compared with placebo Statins are more effective at reducing strokes at 4.3 to 5 years (moderate-quality evidence).

Non-statins compared with placebo Non-statin cholesterol-lowering treatments are no more effective at reducing the risk of stroke in people with a prior stroke or TIA (moderate-quality evidence).

Mortality
Statins compared with placebo Statins are more effective at reducing mortality at 1 to 6 years. In people who have had a stroke or TIA within the past 6 months, atorvastatin is more effective at reducing a fatal stroke, but is no more effective at reducing overall mortality (moderate-quality evidence).

Non-statins compared with placebo Clofibrate is no more effective at 3.5 years at reducing the risk of mortality in people with a previous stroke or TIA (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits:

Statins versus placebo:
We found two systematic reviews (search dates 2003 and 2006) which together identified 47 RCTs, [26] [27] and we found one subsequent RCT. [28] The first review (search date 2003; 26 RCTs in 97,981 people with CHD, raised and normal cholesterol levels, diabetes, prior ischaemic stroke or TIA, and older people) did not present results separately for people with a previous ischaemic stroke or TIA. [26] The review found that statins significantly reduced stroke after a mean of 4.3 years compared with placebo or no treatment (1285/47,090 [3%] with statins *v* 1605/47,038 [3%] with control; OR 0.79, 95% CI 0.73 to 0.85). [26]

The second review (search date 2006; 42 RCTs in 121,285 people; follow-up 1–6 years) assessed statin therapy used as primary or secondary intervention for stroke prevention. [27] It found that, compared with placebo or no treatment, statins significantly reduced mortality, all-cause stroke, and ischaemic stroke (mortality: RR 0.88, 95% CI 0.83 to 0.93; all-cause stroke: RR 0.84, 95% CI 0.79 to 0.91; ischaemic stroke: RR 0.81, 95% CI 0.69 to 0.94; absolute numbers not reported). [27] The review did not perform a subgroup analysis of people with previous stroke or TIA. One RCT identified by the second review investigated secondary prevention of stroke, comparing statins (atorvastatin 80 mg/day) versus placebo in people with a stroke or TIA within the last 6 months. [29] The RCT (4731 people; LDL cholesterol 2.6–4.9 mmol/L, with no known CHD) found that atorvastatin significantly reduced non-fatal or fatal stroke at a median follow-up of 4.9 years compared with placebo (non-fatal or fatal stroke: 265/2365 [11%] with atorvastatin *v* 311/2366 [13%] with placebo; pre-specified adjusted HR for variables such as time since event, entry event [stroke or TIA], age, and sex: 0.84, 95% CI 0.71 to 0.99; P = 0.03; ARR at 5 years: 2.2%, 95% CI 0.2% to 4.2%). The mean LDL cholesterol level was significantly lower in the statin group than in the placebo group (1.9 mmol/L with atorvastatin *v* 3.3 mmol/L with placebo; P less than 0.001). The RCT found no significant difference between groups in overall mortality (216/2365 [9.1%] deaths with atorvastatin *v* 211/2366 [8.9%] deaths with placebo; P = 0.98).

The subsequent RCT was a secondary analysis of the data in the subgroup of people with carotid atherosclerosis (1007 people with previous stroke or TIA in the last 6 months and carotid stenosis not requiring revascularisation). [28] It found that atorvastatin significantly reduced the risk of any stroke compared with placebo (stroke: 55/491 [11%] with atorvastatin *v* 83/516 [16%] with placebo; HR 0.67, 95% CI 0.47 to 0.94; P = 0.02). There was also a significant reduction in the risk of major

coronary events (cardiac death, non-fatal MI, or resuscitated cardiac arrest) with atorvastatin compared with placebo (major coronary event: 19/491 [4%] with atorvastatin *v* 33/516 [6%] with placebo; HR 0.57, 95% CI 0.32 to 1.00; P = 0.05). [28]

Non-statin cholesterol-lowering treatments versus placebo:
We found no systematic reviews that reported results separately for people with previous stroke or TIA. We found one systematic review (search date not reported) comparing the effects of both statin and non-statin drug treatments versus placebo on stroke in people with and without prior stroke or TIA. [4] The review found no significant difference in the risk of stroke between non-statin drug treatments and placebo (12 relevant RCTs; 169/12,143 [1%] with non-statins *v* 270/15,376 [2%] with placebo; OR 1.04, 95% CI 0.85 to 1.28). [4] We found one additional RCT [30] and two subsequent RCTs [31] [32] assessing the outcome of stroke.

The additional RCT (532 men who had had a previous stroke or TIA) found no significant difference in mortality after 3.5 years between clofibrate and placebo (AR: 13% with clofibrate *v* 16% with placebo; P value not reported). [30] The first subsequent RCT (2531 men with CHD) found no significant difference in the risk of stroke between gemfibrozil and placebo (AR: 5% with gemfibrozil *v* 6% with placebo; RRR +25%, 95% CI –6% to +47%). [31] The second subsequent RCT (3090 people with previous MI or stable angina, including 58 people with previous stroke or TIA) found no significant difference in the risk of stroke after follow-up for about 6 years between bezafibrate 400 mg and placebo (AR: 4.6% with bezafibrate *v* 5.0% with placebo; P = 0.66). [32]

Harms:

Statins versus placebo:
The first systematic review found no significant difference between statins and placebo in haemorrhagic stroke (0.32% with statins *v* 0.36% with placebo; OR 0.90, 95% CI 0.65 to 1.22). [26] The second systematic review also found no significant difference between statins and placebo in haemorrhagic stroke (RR 0.94, 95% CI 0.68 to 1.30; absolute numbers not reported). [27] One RCT reported by the second systematic review looked specifically at treatment with statins for secondary prevention of stroke. [29] In contrast to the findings of the first two systematic reviews, it found that atorvastatin was associated with a significantly increased risk of haemorrhagic stroke compared with placebo (haemorrhagic stroke: 55/2365 [2%] with atorvastatin *v* 33/2366 [1%] with placebo; HR 1.66, 95% CI 1.08 to 2.55). It found no significant difference in rates of serious adverse events (any serious adverse event: 988/2365 [42%] with statin *v* 975/2366 [41%] with placebo; rhabdomyolysis: 2/2365 [0.09%] with statins *v* 3/2366 [0.13%] with placebo; P values not reported; reported as not significant). It found that elevated liver enzyme values were significantly more common with atorvastatin compared with placebo (alanine or aspartate aminotransferase over 3 times upper limit of normal on 2 consecutive readings: 51/2365 [2%] with atorvastatin *v* 11/2366 [1%] with placebo; P less than 0.001) but no liver failure was reported (no further data reported). [29]

The subsequent RCT of secondary prevention of stroke in people with carotid atherosclerosis found similar rates of myalgia, myopathy, and liver enzyme elevation with atorvastatin and placebo (myalgia: 27/491 [5%] with atorvastatin *v* 19/516 [4%] with placebo; myopathy: 2/491[0.4%] with atorvastatin *v* 1/516 [0.2%] with placebo; proportion of patients with enzyme elevation 3 times the upper limit of normal on 2 consecutive measurements: 3/491 [0.6%] with atorvastatin *v* 1/516 [0.2%] with placebo; significance assessments not reported). [28]

We found two additional systematic reviews specifically addressing harms associated with statins. The first additional systematic review (35,000 people and 158,000 person-years of observation) found no significant difference in overall adverse effects between statins and placebo (48 RCTs; 1063/14,197 [8%] with statins *v* 923/10,568 [9%] with placebo; ARR +1%, 95% CI –1% to +3%). [33] It also found that eight people treated with statins and five people given placebo had rhabdomyolysis (no further data reported). None of the RCTs reported any cases of liver failure. Fifty-five people (0.17%) given statins and 43 (0.13%) people given placebo had raised serum creatine kinase levels (at least 10 times the upper limit of normal), with 13 people reporting muscle symptoms with statins and four people with placebo (no further data reported for either outcome). A total of 449 people (1.3%) given statins and 383 people (1.1%) given placebo had raised alanine aminotransferase levels (at least 3 times upper limit of normal) (no further data reported). [33]

In contrast, the second additional systematic review (search date not reported; 18 RCTs, 71,108 people; 301,374 person-years of follow-up) of adverse events associated with statins in all populations (not limited to those with previous stroke or TIA) found that statin treatment significantly increased the risk of any adverse event by 39% compared with placebo (OR 1.40, 95% CI 1.09 to 1.80; P = 0.008; NNH 197, CI not reported). [34] Serious adverse events such as creatine phosphokinase over 10 times the upper limit of normal were infrequent (NNH 3400, CI not reported), and rhabdomyolysis was rare (NNH 7428, CI not reported). It reported that atorvastatin was associated with the greatest risk of adverse events, and fluvastatin with the least risk, and that simvastatin, pravastatin, and lovastatin had similar risks of adverse events. [34] Less-severe adverse events,

such as myalgia and liver enzyme elevations, were responsible for about two-thirds of adverse events reported in trials. [34]

Non-statin cholesterol-lowering treatments versus placebo:
We found no systematic reviews that reported results separately for people with previous stroke or TIA. One systematic review found no significant difference between cholesterol reduction (using statins or non-statin treatments) and placebo or no treatment in deaths due to circulatory diseases other than ischaemic heart disease and stroke (675 deaths; OR for treatment *v* no treatment per 1.0 mmol/L decrease in serum cholesterol 0.87, 95% CI 0.73 to 1.03); cancer (2293 deaths; OR for treatment *v* no treatment per 1.0 mmol/L decrease in serum cholesterol 1.06, 95% CI 0.96 to 1.16); injuries and suicide (324 deaths; OR for treatment *v* no treatment per 1.0 mmol/L decrease in serum cholesterol 0.94, 95% CI 0.72 to 1.23); adverse effects other than circulatory diseases or cancer (1363 deaths; OR for treatment *v* no treatment per 1.0 mmol/L decrease in serum cholesterol 0.88, 95% CI 0.78 to 1.01). [33] The RCT comparing clofibrate versus placebo found similar rates of adverse effects (mainly nausea and vomiting) between groups (23/268 [9%] with clofibrate *v* 28/264 [11%] with placebo; P value not reported). [30] The RCT comparing gemfibrozil with placebo found no significant difference between treatments in the rate of cancer or of death from any specific cause, and no significant difference between treatments in any symptom apart from dyspepsia (40% with gemfibrozil *v* 34% with placebo; P = 0.002). [31] The RCT comparing bezafibrate with placebo found similar adverse effect rates for treatments (no further data reported). [32]

Drug safety alert:
The UK Medicines and Healthcare products Regulatory Agency (MHRA) has issued a drug safety alert on the increased risk of haemorrhagic stroke associated with high doses of atorvastatin in people with recent stroke: see harms of statins section above (www.mhra.gov.uk).

Comment:

Clinical guide:
The relative risk reduction of stroke and of ischaemic heart disease events seems proportional to the size of the reduction in LDL cholesterol, with one review reporting that the effects of statins on stroke were closely associated with LDL cholesterol, such that each unit increase in LDL increased mortality risk by 0.3% (RR 1.003, 95% CI 1.0005 to 1.006, P = 0.02). [27] The relative reduction in major vascular events was similar among those people with different pretreatment concentrations of cholesterol and triglycerides, in all age groups included, and irrespective of a prior history of CAD, ischaemic stroke or TIA, ischaemic heart disease, peripheral arterial disease, or diabetes. [35] One RCT, specifically designed to investigate the effects of high-dose atorvastatin on preventing recurrent stroke in people with recent TIA or stroke, found that statins reduced non-fatal or fatal stroke; but post-hoc analysis suggested that it was associated with a small increase in the proportion of haemorrhagic strokes compared with placebo. [29] Cholesterol lowering with statins is associated with a low adverse-event profile. [3] [36] [33] [37]

OPTION ALTERNATIVE ANTIPLATELET REGIMENS TO ASPIRIN

Contributed by Lalit Kalra

Cardiovascular events
Thienopyridines compared with aspirin We don't know whether thienopyridines (ticlopidine or clopidogrel) are more effective at reducing the risk of serious vascular events (stroke, MI, or vascular death) in people with a previous stroke or TIA (low-quality evidence).

Clopidogrel plus aspirin compared with aspirin alone Clopidogrel plus aspirin increases the rate of severe bleeding, and is no more effective at reducing the risk of a primary composite end point of MI, stroke, or cardiovascular death at 28 months in people with ischaemic stroke, TIA, clinically evident CVD, or multiple risk factors including previous stroke or TIA (moderate-quality evidence).

Clopidogrel plus aspirin compared with clopidogrel alone Clopidogrel plus aspirin increases the rate of severe bleeding, and is no more effective at reducing a primary composite end point of ischaemic stroke, MI, vascular death, or readmission to hospital for acute ischaemia at 18 months in people with a recent ischaemic stroke or TIA (high-quality evidence).

Dipyridamole plus aspirin compared with aspirin alone Dipyridamole plus aspirin is more effective at reducing serious vascular events (stroke, MI, vascular death) in people with a previous ischaemic stroke or TIA (moderate-quality evidence).

Dipyridamole plus aspirin compared with clopidogrel Dipyridamole plus aspirin and clopidogrel seem equally effective at reducing serious vascular events (stroke, MI, vascular death) in people with a previous stroke or TIA (moderate-quality evidence).

Trifusal compared with aspirin Triflusal seems equally effective at reducing a primary outcome of ischaemic stroke, MI, or vascular death in people with a prior ischaemic stroke or TIA (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, **see table, p 41 .**

Benefits:

Thienopyridines (clopidogrel and ticlopidine) versus aspirin:
We found two systematic reviews (search dates 1997 [7] and 1999) [38] and one subsequent RCT [39] comparing thienopyridines versus aspirin. The first systematic review (4 RCTs; 3791 people at high risk of vascular events, mean treatment duration: 3 years) found no significant difference between ticlopidine and aspirin in serious vascular events at the end of treatment (stroke, MI, or vascular death: 21% with ticlopidine *v* 23% with aspirin; OR 0.88, 95% CI 0.75 to 1.03). [7] It also found that the risk of serious vascular events was similar with clopidogrel and aspirin (1 RCT; 19,185 people: 10% with clopidogrel *v* 11% with aspirin; OR 0.90, 95% CI 0.82 to 0.99). The second systematic review (4 RCTs) found that ticlopidine or clopidogrel marginally reduced vascular events after about 2 years compared with aspirin (OR 0.91, 95% CI 0.84 to 0.98; ARR 1.1%, 95% CI 0.2% to 1.9%). [38] The subsequent RCT (1809 African-American people with a recent non-cardioembolic ischaemic stroke) compared ticlopidine (500 mg/day) versus aspirin (650 mg/day) over 2 years, and found no significant difference between treatments in the primary outcome of recurrent stroke, MI, or vascular death (AR: 14.7% with ticlopidine *v* 12.3% with aspirin; HR 1.22, 95% CI 0.94 to 1.57). [39]

Clopidogrel plus aspirin versus aspirin alone:
We found one systematic review (15,603 people with clinically evident CVD or multiple risk factors; 5701 of these people had ischaemic stroke or TIA within the last 5 years) comparing clopidogrel (75 mg/day) plus low-dose aspirin (75–162 mg/day) versus placebo plus low-dose aspirin. [40] The RCT found no significant difference between groups in the primary composite end point of MI, stroke, or death from cardiovascular causes at a median of 28 months' follow-up (534/7802 [6.8%] with clopidogrel plus aspirin *v* 573/7801 [7.3%] with aspirin alone; RR 0.93, 95% CI 0.83 to 1.05; P = 0.22). Subgroup analysis in people with a history of previous stroke found no significant difference in the composite outcome of MI, stroke, or death from cardiovascular causes between clopidogrel plus low-dose aspirin and placebo plus low-dose aspirin (results presented graphically; absolute numbers not reported). [40]

Clopidogrel plus aspirin versus clopidogrel plus placebo:
We found one RCT (7599 high-risk people with recent ischaemic stroke or TIA and at least one additional vascular risk factor) comparing clopidogrel plus aspirin versus clopidogrel plus placebo. [41] It found no significant difference between groups after 18 months in the primary composite end point of ischaemic stroke, MI, vascular death, or readmission to hospital for acute ischaemia (596/3797 [16%] with clopidogrel plus aspirin *v* 636/3802 [17%] with clopidogrel plus placebo; RRR +6.4%, 95% CI −4.6% to +16.3%; ARR +1%, 95% CI −0.6% to +2.7%). [41]

Dipyridamole plus aspirin versus aspirin alone:
We found one systematic review (search date 2006; 6 RCTs; 7648 people with previous stroke or TIA), which compared aspirin plus dipyridamole versus aspirin alone. [42] It found that aspirin plus dipyridamole significantly reduced non-fatal stroke and serious vascular events compared with aspirin alone (non-fatal stroke: 294/3823 [8%] with aspirin plus dipyridamole *v* 381/3825 [10%] with aspirin alone; RR 0.77, 95% CI 0.67 to 0.89; stroke, MI, or vascular death: 542/3823 [14%] with aspirin plus dipyridamole *v* 640/3826 [17%] with aspirin alone; RR 0.85, 95% CI 0.76 to 0.94). The review also carried out two subset analyses of RCTs using immediate-release dipyridamole (4 RCTs; 1611 people) and those using predominately extended-release dipyridamole (2 RCTs; 6038 people). A significant reduction in non-fatal stroke and serious vascular events was seen with extended-release dipyridamole plus aspirin compared with aspirin alone (non-fatal stroke: 236/3013 [8%] with dipyridamole plus aspirin *v* 313/3025 [10%] with aspirin alone; RR 0.76, 95% CI 0.65 to 0.89; stroke, MI, or vascular death: 421/3013 [14%] with dipyridamole plus aspirin *v* 513/3025 [17%] with aspirin alone; RR 0.82, 95% CI 0.73 to 0.92). However, there was no significant difference in non-fatal stroke and serious vascular events between immediate-release dipyridamole plus aspirin and aspirin alone (non-fatal stroke: 58/810 [7%] with dipyridamole plus aspirin *v* 68/801 [8%] with aspirin alone; RR 0.83, 95% CI 0.59 to 1.15; stroke, MI, or vascular death: 121/788 [15%] with dipyridamole plus aspirin *v* 127/787 [16%] with aspirin alone; RR 0.95, 95% CI 0.75 to 1.19). [42]

Dipyridamole plus aspirin versus clopidogrel:
We found one RCT (20,332 people with previous stroke or TIA; mean follow-up 2.5 years) comparing extended-release dipyridamole (200 mg) plus aspirin (25 mg) twice daily versus clopidogrel (75 mg) daily. [43] It found no significant difference between dipyridamole plus aspirin and clopidogrel in recurrent stroke or the composite outcome of stroke, MI, or vascular death (recurrent stroke: 916/10,181 [9%] with dipyridamole plus aspirin *v* 898/ 10,151 [9%] with clopidogrel; HR 1.01, 95%

CI 0.92 to 1.11; composite outcome of stroke, MI, or vascular death: 1333/10,181 [13%] with dipyridamole plus aspirin *v* 1333/10,151 [13%] with clopidogrel; HR 0.99, 95% CI 0.92 to 1.07). [43]

Triflusal versus aspirin:
We found one systematic review [7] and two subsequent RCTs [44] [45] comparing triflusal versus aspirin. The systematic review (3 RCTs; 2675 people at high risk of vascular events, 400 of whom had a history of ischaemic stroke or TIA) found no significant difference in vascular events between triflusal and aspirin (10% with triflusal *v* 10% with aspirin; OR 0.93, 95% CI 0.72 to 1.19). [7] The first subsequent RCT (2113 people with a recent ischaemic stroke or TIA) found no significant difference in the primary outcome of ischaemic stroke, MI, or vascular death between triflusal and aspirin (13.1% with triflusal *v* 12.4% with aspirin; HR 1.09, 95% CI 0.85 to 1.38). [44] However, the RCT lacked power to rule out a clinically important difference between treatments. The second subsequent RCT (431 people with a prior ischaemic stroke or TIA, treated for a mean of 586 days) found no significant difference between triflusal (600 mg/day) and aspirin (325 mg/day) in the combined incidence of ischaemic stroke, MI, or vascular death or major haemorrhage (27/213 [13%] with triflusal *v* 30/216 [14%] with aspirin; OR 0.90, 95% CI 0.51 to 1.56). [45] However, the RCT lacked power to rule out a clinically important difference between treatments. [45]

Harms:

Thienopyridines (clopidogrel and ticlopidine) versus aspirin:
The first systematic review gave no information on adverse effects. [7] The second systematic review comparing thienopyridines versus aspirin found that the thienopyridines reduced GI haemorrhage and upper GI symptoms compared with aspirin (GI haemorrhage: 198/11,128 [2%] with thienopyridines *v* 276/11,126 [3%] with aspirin; OR 0.71, 95% CI 0.59 to 0.86; indigestion, nausea, or vomiting: 1648/11,159 [15%] with thienopyridines *v* 1908/11,157 [17%] with aspirin; OR 0.84, 95% CI 0.78 to 0.90). [38] However, thienopyridines increased the incidence of skin rash and diarrhoea compared with aspirin (skin rash: 578/9599 [6%] with clopidogrel *v* 442/9586 [5%] with aspirin; OR 1.3, 95% CI 1.2 to 1.5; 184/1560 [12%] with ticlopidine *v* 86/1571 [5%] with aspirin; OR 2.2, 95% CI 1.7 to 2.9; diarrhoea: 428/9599 [4%] with clopidogrel *v* 322/9586 [3%] with aspirin; OR 1.3, 95% CI 1.2 to 1.6; 318/1560 [20%] with ticlopidine *v* 155/1571 [10%] with aspirin; OR 2.3, 95% CI 1.9 to 2.8). Ticlopidine (but not clopidogrel) increased neutropenia compared with aspirin (ticlopidine 35/1529 [2%] with ticlopidine *v* 12/1540 [1%] with aspirin; OR 2.7, 95% CI 1.5 to 4.8). Observational studies have found ticlopidine to be associated with thrombocytopenia and thrombotic thrombocytopenic purpura. [46] [47] The subsequent RCT comparing aspirin and ticlopidine found similar results. [39] It found that aspirin increased GI tract haemorrhage compared with ticlopidine, but the difference between groups was not significant (0.9% with aspirin *v* 0.4% with ticlopidine; P = 0.39). [39] It also found that ticlopidine increased diarrhoea, thrombocytopenia, and neutropenia compared with aspirin, but the difference was not significant (diarrhoea: 0.3% with ticlopidine *v* 0.2% with aspirin; P = 0.69; thrombocytopenia: 0.3% with ticlopidine *v* 0.2% with aspirin; P = 0.69; neutropenia: 3.4% with ticlopidine *v* 2.2% with aspirin; P = 0.12).

Clopidogrel plus aspirin versus aspirin alone:
The RCT found that the rate of severe bleeding was higher with clopidogrel plus aspirin compared with aspirin alone, although this difference was not significant (130/7802 [2%] with clopidogrel plus aspirin *v* 104/7801 [1%] with aspirin alone; P = 0.09; RR 1.25, 95% CI 0.97 to 1.61). [40]

Clopidogrel plus aspirin versus clopidogrel plus placebo:
The RCT found that life-threatening bleeding was significantly higher with clopidogrel plus aspirin compared with clopidogrel alone (96/3759 [3%] with clopidogrel plus aspirin *v* 49/3781 [2%] with clopidogrel plus placebo; ARI 1.3%, 95% CI 0.6% to 1.9%). [41] It found that major bleeds were also increased in the group receiving aspirin plus clopidogrel (73/3659 [2%] with clopidogrel plus aspirin *v* 22/3781 [1%] with clopidogrel plus placebo; P less than 0.0001). [41]

Dipyridamole plus aspirin versus aspirin alone:
The systematic review did not report harms data. [42] One of the RCTs identified by the review reported fewer major bleeding complications with dipyridamole plus aspirin compared with aspirin alone, although the difference between groups was not significant (35/1363 [3%] with dipyridamole plus aspirin *v* 53/1376 [4%] with aspirin alone; HR 0.67, 95% CI 0.44 to 1.03). [48] The RCT reported that 470/1363 (34%) people taking dipyridamole plus aspirin stopped treatment, mainly because of adverse events (of these, headache was at least one of the reasons in 123 people), and 184/1376 (13%) people taking aspirin stopped treatment, mainly for medical reasons, such as new TIA or stroke, or because oral anticoagulant was indicated. [48]

Dipyridamole plus aspirin versus clopidogrel:
The RCT found no significant difference in major haemorrhagic events between dipyridamole plus aspirin and clopidogrel alone (419/10,181 [4%] with dipyridamole plus aspirin *v* 365/10,151 [4%] with clopidogrel alone; HR 1.15, 95% CI 1.00 to 1.32), although it did report a significantly increased incidence of intracranial haemorrhage with dipyridamole plus aspirin compared with clopidogrel

alone (147/10,181 [1.4%] with dipyridamole plus aspirin *v* 103/10,151 [1.0%] with clopidogrel alone; HR 1.42, 95% CI 1.11 to 1.83). [43]

Triflusal versus aspirin:
The systematic review gave no information on adverse effects. [7] The first subsequent RCT found a significantly lower risk of haemorrhage with triflusal compared with aspirin (intracranial or major extracranial haemorrhage: 20/1055 [2%] with triflusal *v* 42/1052 [4%] with aspirin; HR 0.48, 95% CI 0.28 to 0.82; any haemorrhage: 17% with triflusal *v* 25% with aspirin; absolute numbers not reported; OR 0.76, 95% CI 0.67 to 0.86). [44] The second subsequent RCT also found that triflusal significantly lowered the risk of any haemorrhage compared with aspirin (3% with triflusal *v* 8% with aspirin; P = 0.01). [45] However, this reduction was not significant for intracranial or major extracranial haemorrhages specifically (0.5% with triflusal *v* 3.2% with aspirin; P = 0.07), although the RCT lacked power to rule out a clinically important difference between treatments. [45]

Comment:

We found one systematic review solely in people with previous stroke or TIA comparing aspirin plus dipyridamole versus aspirin alone. [42] As it is more specific to the population of interest, it replaces two previously reported systematic reviews, which were in a broader population of people with high cardiovascular risk and did not report a separate analysis for people with previous stroke or TIA. [7] [49]

Clinical guide:
Adding dipyridamole to aspirin versus aspirin alone:
In clinical practice, the most commonly used combination is aspirin plus dipyridamole, as recommended by National Institute for Health and Clinical Excellence (NICE). There is little support for combining clopidogrel with aspirin and use in routine practice is not recommended. In patients who cannot tolerate aspirin, there is no evidence to support the use of dipyridamole as the sole agent. In such instances, the use of clopidogrel is recommended.

Thienopyridines:
Clopidogrel is the thienopyridine of choice because it has a better safety profile than ticlopidine. Clopidogrel seems as effective as aspirin (and possibly more so), and is probably as safe as aspirin, although their adverse-effect profiles vary. It has been suggested previously that clopidogrel should be used as an alternative to aspirin in people intolerant of, or allergic to, aspirin. However, we have no direct evidence of the relative effectiveness of thienopyridines compared with aspirin in this particular subgroup of people, because they were excluded from the RCTs. Furthermore, in an RCT in people who developed peptic ulcer bleeding while taking aspirin to reduce vascular events, people assigned aspirin plus esomeprazole (a proton pump inhibitor) had a significant reduction in the cumulative incidence of recurrent ulcer bleeding in comparison with people treated with clopidogrel alone. [50] Thus, clopidogrel still seems a reasonable alternative antiplatelet drug for people genuinely allergic to aspirin.

Adding clopidogrel to aspirin versus aspirin alone:
Several large RCTs have assessed the effects of adding clopidogrel to aspirin (versus aspirin alone) in over 60,000 people with acute coronary syndromes (with or without ST segment elevation on ECG) or in people having percutaneous coronary intervention, or both. In this high-risk setting of acute coronary vascular injury, the combination has shown definite reductions in serious vascular events compared with aspirin alone, although this is at the expense of a small increase in the risk of major (but not intracranial or life-threatening) haemorrhage. [51] [52] [53] [54] However, this has not been replicated in the two largest trials in people with stroke, which suggest an increased haemorrhagic risk in this population that outweighs any benefits in vascular end-point reduction. In addition, a randomised trial of clopidogrel plus aspirin versus aspirin alone in 107 people with recently symptomatic carotid stenosis (within the last 3 months) and ongoing asymptomatic emboli detected by transcranial Doppler ultrasound found that the combination was more effective than aspirin alone in reducing asymptomatic emboli. [55] However, this trial was not powered to detect a difference in clinically relevant outcomes.

OPTION DIFFERENT DRUG TREATMENTS TO REDUCE BLOOD PRESSURE VERSUS EACH OTHER

Contributed by Lalit Kalra

Cardiovascular events
Different drug treatments to reduce blood pressure compared with each other We don't know whether one treatment to reduce blood pressure is more effective than the others at reducing stroke in people with a prior stroke or TIA (low-quality evidence).

Mortality

Different drug treatments to reduce blood pressure compared with each other We don't know whether thiazide diuretics are more effective than beta-blockers at reducing mortality in people with a prior stroke or TIA (low-quality evidence).

Note
We found no clinically important results from RCTs comparing different treatments to reduce blood pressure exclusively in people with a prior stroke or TIA.

For GRADE evaluation of interventions for stroke prevention, see table, p 41 .

Benefits:

Different treatments to reduce blood pressure versus each other:
We found no systematic reviews comparing different treatments to reduce blood pressure exclusively in people who have had a prior stroke or TIA. We found three systematic reviews comparing different treatments to reduce blood pressure in people with hypertension or vascular disease. [56] [57] [15] None of the reviews presented results separately for people with a prior stroke or TIA. The first systematic review (search date 1997) compared thiazide diuretics (bendrofluazide 2.5 mg, 5 mg, or 10 mg; hydrochlorthiazide 25 mg or 50 mg) versus beta-blockers (propranolol 80 mg or 160 mg; atenolol 50 mg). [56] The review found no significant difference between thiazide diuretics and beta-blockers in reducing death, stroke, CAD, or total cardiovascular events (5 RCTs; 17,952 people with hypertension; treatment duration between 1 and 10 years; death: 367/8915 [4.1%] with thiazide *v* 387/9037 [4.3%] with beta-blocker; RR 0.97, 95% CI 0.84 to 1.11; stroke: 107/8862 [1.2%] with thiazide *v* 130/8984 [1.4%] with beta-blocker; RR 0.84, 95% CI 0.65 to 1.08; CAD: 285/8862 [3.2%] with thiazide *v* 317/8984 [3.5%] with beta-blocker; RR 0.91, 95% CI 0.78 to 1.07; total cardiovascular events [including stroke, CAD, congestive heart failure, and other vascular events]: 431/8862 [4.9%] with thiazide *v* 495/8984 [5.5%] with beta-blocker; RR 0.88, 95% CI 0.78 to 1.00). [56]

The second systematic review (search date 2003; 16 RCTs; 142,341 people, proportion with previous stroke or TIA not reported) assessed the effects on major cardiovascular outcomes of different treatments to reduce blood pressure (based on ACE inhibitors, calcium channel blockers, diuretics, and beta-blockers) using only direct comparisons. [57] The mean duration of follow-up ranged from 2.0 to 8.4 years. Most people had pre-existing CVD or more than one cardiovascular risk factor at baseline. In the analysis, diuretics and beta-blockers were combined. It found that: calcium channel blockers reduced stroke compared with diuretics or beta-blockers, but the reduction was of borderline significance (RR 0.93, 95% CI 0.86 to 1.00); calcium channel blockers reduced stroke compared with ACE inhibitors, but the reduction was of borderline significance (RR 0.89, 95% CI 0.80 to 0.99); and diuretics or beta-blockers reduced stroke compared with ACE inhibitors, but the reduction was of borderline significance (RR 0.92, 95% CI 0.85 to 1.00). [57]

In the third systematic review, 15 RCTs compared the effects of different types of antihypertensive drugs, with two RCTs including several drug-versus-drug comparisons. [15] There were 96,000 participants in total, and the RCTs recorded almost 3600 stroke events over a mean follow-up time of 4 to 5 years. The number of people with previous stroke or TIA in the included RCTs was not reported. The weighted mean reduction in blood pressure in many of the drug-versus-drug trials was small, often 1 mm Hg systolic blood pressure and diastolic blood pressure. Overall, these RCTs indicated little difference between the drug classes, with relative risk reductions of stroke of 9% with beta-blockers and/or diuretics compared with ACE inhibitors (RR 0.91, 95% CI 0.83 to 0.99), a relative risk increase of stroke of 8% with beta-blockers and/or diuretics compared with calcium antagonists (RR 1.08, 95% CI 0.99 to 1.16), and a risk reduction of stroke of 11% with calcium antagonists compared with ACE inhibitors (RR 0.89, 95% CI 0.80 to 0.99). [15] These results were either not significant or of borderline statistical significance. Three included RCTs including a total of 20,408 people and 384 stroke events, compared more-intensive antihypertensive therapy versus less-intensive regimens. The review suggested that additional benefit in risk of stroke may be gained from a more-intensive treatment regimen compared with a less-intensive regimen (RR 0.80, 95% CI 0.65 to 0.99; P = 0.04). [15] However, it was not reported how many people had had previous stroke or TIA in the analysis.

Harms:

The first systematic review found that a significantly larger proportion of people withdrew from treatment owing to adverse effects with beta-blockers compared with thiazide diuretics (924/8984 [10%] with beta-blockers *v* 624/8862 [7%] with diuretics; RR 1.45, 95% CI 1.32 to 1.59). [56] See harms under blood pressure reduction, p 5 . The second [57] and third [15] systematic reviews reported no information about harms.

Comment:

The relative risk of stroke and of all other major vascular outcomes apart from heart failure seems directly proportional to the blood pressure reduction achieved. [57] [15] Together with the results of the systematic reviews [14] in people with a prior stroke or TIA (see benefits of blood pressure reduction, p 5), these findings suggest that, in general, it is probably the size of the blood pressure reduction rather than the specific drug regimen used that determines the benefit of the treatment.

OPTION HIGH-DOSE VERSUS LOW-DOSE ASPIRIN

Contributed by Lalit Kalra

Cardiovascular events

High compared with low-dose aspirin High-dose aspirin may increase the risk of upper GI upset, and may be no more effective at preventing serious cardiovascular events in people with a previous stroke or TIA (very low-quality evidence).

For GRADE evaluation of interventions for stroke prevention, **see table , p 41 .**

Benefits:

High-dose versus low-dose aspirin:

We found one systematic review [7] and one subsequent RCT. [58] The systematic review (search date 1997; 7225 people at high risk of vascular disease in RCTs comparing different doses of aspirin; about 60,000 people at high risk of vascular disease [excluding those with acute stroke] in RCTs comparing different doses of aspirin versus placebo or no aspirin) compared the effects on serious vascular events of higher- versus lower-dose aspirin. [7] It found no significant difference between aspirin 500 mg to 1500 mg daily and 75 mg to 325 mg daily in serious vascular events (stroke, MI, or vascular death; OR 0.97, 95% CI 0.79 to 1.19). It also found that doses of 75 mg or more did not reduce serious vascular events compared with doses below 75 mg (OR 1.08, 95% CI 0.90 to 1.31). However, the comparison lacked power to detect a clinically important difference. The review also found that different aspirin doses reduced serious vascular events compared with placebo or no antiplatelet treatment by similar amounts for the higher daily doses, but by a smaller amount for very low doses (higher doses: 500–1500 mg/day *v* placebo or no antiplatelet treatment: OR 0.81, 95% CI 0.75 to 0.87; 160–325 mg/day *v* placebo or no antiplatelet treatment: OR 0.74, 95% CI 0.69 to 0.80; 75–150 mg/day *v* placebo or no antiplatelet treatment: OR 0.68, 95% CI 0.59 to 0.79; lower doses: less than 75 mg/day *v* placebo or no antiplatelet treatment: OR 0.87, 95% CI 0.74 to 1.03). See review on secondary prevention of ischaemic cardiac events. People with acute stroke were excluded from these analyses. The results in people with previous stroke or TIA were not presented separately. The subsequent RCT (2849 people scheduled for carotid endarterectomy, most of whom had previous stroke or TIA) compared low-dose aspirin (81 mg/day and 325 mg/day) versus high-dose aspirin (650 mg/day and 1300 mg/day). [58] It found that high-dose aspirin increased the combined outcome of stroke, MI, and death after 3 months compared with low-dose aspirin (AR: 8.4% with high dose *v* 6.2% with low dose; RR 1.34, 95% CI 1.03 to 1.75). [58] However, follow-up was short. A recent review of double-blind controlled studies, meta-analyses, and observational analyses to assess the efficacy of aspirin at doses up to 325 mg daily showed no difference in efficacy across the low-dose range of 75 mg to 325 mg. [59]

Harms:

Extracranial haemorrhage:

The first systematic review found that the proportional increase in the risk of major extracranial haemorrhage was similar with all daily aspirin doses. In direct comparisons, 75 mg to 325 mg aspirin did not increase major extracranial haemorrhage compared with doses lower than 75 mg (AR: 2.5% with 75–325 mg/day *v* 1.8% with less than 75 mg/day; P greater than 0.05). [7] We found one systematic review (search date 1999; 24 RCTs) on the effects of aspirin on GI bleeding. [13] Indirect comparisons in a meta-regression analysis found no association between dose of aspirin and risk of GI bleeds. RCTs directly comparing different daily doses of aspirin have found a trend towards more GI haemorrhage and a significant increase in upper GI symptoms with higher (500–1500 mg) versus lower (75–325 mg) doses (upper GI symptoms: OR 1.3, 95% CI 1.1 to 1.5), but no significant difference in these outcomes between 30 mg and 283 mg daily. [58] [60] [61] We found one systematic review of observational studies (search date 2001; 5 studies) of the effects of different doses of aspirin on the risk of upper GI complications (bleeding, perforation, or upper GI event leading to hospital admission or a visit to a specialist). [62] It found greater risks of upper GI complications with doses of aspirin greater than 300 mg daily. One narrative non-systematic review of double-blind controlled studies, meta-analyses, and observational analyses (assessing the safety of aspirin at doses up to 325 mg daily in people with cardiovascular or cerebrovascular risk in general) reported no difference in safety (based on reported adverse events in included studies) across the low-dose range of 75 mg to 325 mg. [59]

Intracranial haemorrhage:

We found one systematic review (search date 1997; 16 RCTs; 55,462 people) of the effects of aspirin on intracranial haemorrhage. [12] It found no clear variation in risk with the dose of aspirin used. Three RCTs directly compared different daily doses of aspirin and found no significant differences in the risk of intracranial haemorrhage, but they lacked power to detect clinically important differences. [58] [60] [61]

Comment: One narrative non-systematic review of double-blind controlled studies, meta-analyses, and observational analyses to assess the efficacy of aspirin at doses up to 325 mg daily in people with increased cerebrovascular or cardiovascular risk in general, reported that, based on included studies, it found no difference in effectiveness across the low-dose range of 75 mg to 325 mg. [59]

Clinical guide:
Aspirin 75 mg daily seems as effective as doses of 325 mg daily and higher. Observational studies suggested that lower doses of aspirin (less than 75 mg/day) may be associated with a lower risk of haemorrhage than moderate doses (75–325 mg), but RCTs did not confirm this. There seems no significant difference in effectiveness or safety between aspirin doses of 75 mg daily and 325 mg daily. Hence, dosing considerations should include an evaluation of a person's individual clinical status, and an overall benefit-versus-risk assessment.

OPTION ANTICOAGULATION IN PEOPLE IN SINUS RHYTHM

Contributed by Lalit Kalra

Cardiovascular events
Compared with placebo/no treatment Oral anticoagulant treatment (coumarins, phenindione, or low-dose heparin) may be no more effective at reducing serious vascular events (stroke, MI, or vascular death) in people in sinus rhythm and with a previous stroke or TIA (low-quality evidence).

Compared with antiplatelet treatment High- and medium-intensity anticoagulation and antiplatelet treatments seem equally effective at 6 months at preventing recurrent stroke in people with a history of a TIA or minor stroke of presumed non-cardiac origin (moderate-quality evidence).

Mortality
Compared with placebo/no treatment Oral anticoagulant treatment (coumarins, phenindione, or low-dose heparin) may be no more effective at reducing all-cause mortality in people in sinus rhythm and who have had a previous stroke or TIA (low-quality evidence).

Compared with antiplatelet treatment Medium-intensity anticoagulation and aspirin seem equally effective at reducing all-cause and vascular mortality in people with a previous stroke or TIA at 4.6 years (moderate-quality evidence).

Adverse effects
Compared with placebo/no treatment Anticoagulants are more likely to increase the risk of fatal intracranial and extracranial haemorrhage (high-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table, p 41 .

Benefits:

Anticoagulants versus placebo or no treatment:
We found one systematic review (search date 2002; 11 RCTs; 2487 people in sinus rhythm with previous non-embolic presumed ischaemic stroke or TIA, mean duration 1.9 years). [63] It found no significant difference between oral anticoagulant treatment (coumarins, phenindione, or low-dose heparin) and placebo or no treatment for death or dependency, serious vascular events (stroke, MI, or vascular death), or all-cause mortality during follow-up (death or dependency: 2 RCTs; 114/169 [67%] with anticoagulant *v* 111/157 [71%] with control; ARR +4%, 95% CI –6% to +14%; RR 0.95, 95% CI 0.82 to 1.09; serious vascular events: 4 RCTs; 122/294 [41.5%] with anticoagulant *v* 118/281 [42.0%] with control; ARR +1%, 95% CI –7% to +8%; RR 0.98, 95% CI 0.82 to 1.18; all-cause mortality: 10 RCTs; 163/679 [24%] with anticoagulant *v* 161/654 [25%] with control; ARR +1%, 95% CI –4% to +5%; RR 0.97, 95% CI 0.81 to 1.16). [63]

Anticoagulation versus antiplatelet treatment:
We found one systematic review [64] and one subsequent RCT. [65] The systematic review (search date 2004; 5 RCTs; 4076 people) compared long-term (greater than 6 months) treatment with oral anticoagulants (warfarin, phenprocoumarin, or acenocoumarol [nicoumalone]) versus antiplatelet treatment (aspirin or aspirin plus dipyridamole) in people with a history of TIA or minor stroke of presumed arterial (non-cardiac) origin in the past 6 months. [64] The mean duration of follow-up ranged from 12.4 to 24.0 months. The RCTs identified by the review compared different intensities of anticoagulation versus antiplatelet treatment (aspirin). The review found no significant difference between high-intensity (INR 3.0–4.5) or medium-intensity (INR 2.1–3.5) anticoagulation and antiplatelet treatment in rates of recurrent stroke (high-intensity anticoagulation: 1 RCT; 14/651 [2.2%] with anticoagulation *v* 14/665 [2.1%] with antiplatelet treatment; RR 1.02, 95% CI 0.49 to 2.13; ARI 0%, 95% CI –2% to +2%; medium-intensity anticoagulation: 2 RCTs; 8/182 [4%] with anticoagulation *v* 9/194 [5%] with antiplatelet treatment; RR 0.96, 95% CI 0.38 to 2.42; ARR 0%, 95% CI –4% to +4%). [64] The RCT of low-intensity anticoagulation versus aspirin (2206 people) did not report effects

on recurrent stroke. The review also found that high-intensity anticoagulation significantly increased the risk of the composite outcome of vascular death, non-fatal stroke, non-fatal MI, or major bleeding complication compared with aspirin (1 RCT; 81/651 [12%] with anticoagulation *v* 36/665 [5%] with aspirin; RR 2.30, 95% CI 1.58 to 3.35; see harms below). The RCTs of medium- and low-intensity anticoagulation versus aspirin did not report on this outcome. The RCT of low-intensity anticoagulation versus aspirin found no significant difference between treatments in the composite outcome of death or recurrent ischaemic stroke (HR 1.13, 95% CI 0.92 to 1.38). [64] The subsequent RCT (1068 people with previous TIA or minor stroke) compared medium-intensity oral anticoagulants (target INR 2–3) versus aspirin (30–325 mg/day). [65] It found no significant difference between anticoagulants and aspirin in the composite outcome of vascular death, non-fatal stroke, non-fatal MI, or non-fatal bleeding complication (99/536 [18%] with anticoagulants *v* 98/532 [18%] with aspirin; HR 1.02, 95% CI 0.77 to 1.35). There was no significant difference between anticoagulants and aspirin in death from all causes (59/536 [11%] with anticoagulants *v* 44/532 [8%] with aspirin; HR 1.36, 95% CI 0.92 to 2.01), death from vascular causes (31/536 [6%] with anticoagulants *v* 24/532 [4%] with aspirin; HR 1.31, 95% CI 0.77 to 2.23), first ischaemic stroke (41/536 with anticoagulants *v* 53/532 with aspirin; HR 0.76, 95% CI 0.51 to 1.15), and first cardiac event (25/536 [5%] with anticoagulants *v* 33/532 [6%] with aspirin; HR 0.77, 95% CI 0.46 to 1.29). The anticoagulant versus aspirin comparison was ended prematurely after 4.6 years of follow-up, because the same study group had found that the combination of aspirin plus dipyridamole was more effective than aspirin alone. [65]

Harms:

Anticoagulation versus placebo or no treatment:
The systematic review found that anticoagulants significantly increased the risk of fatal intracranial haemorrhage and of major extracranial haemorrhage (fatal and non-fatal) compared with control during follow-up (fatal intracranial haemorrhage: 20/618 [3%] with anticoagulant *v* 7/596 [1%] with control; RR 2.51, 95% CI 1.12 to 5.60; ARI 2%, 95% CI 0% to 4%; all major extracranial haemorrhage: 40/604 [7%] with anticoagulant *v* 10/579 [2%] with control; RR 3.45, 95% CI 1.82 to 6.54; ARI 5%, 95% CI 3% to 7%). [63]

Anticoagulation versus antiplatelet treatment:
The systematic review found that high-intensity anticoagulation significantly increased the risk of a major bleeding complication (intracranial or major extracranial bleeding) compared with aspirin (53/651 [8%] with anticoagulation *v* 6/665 [1%] with aspirin; RR 9.02, 95% CI 3.91 to 20.84; ARI 7%, 95% CI 5% to 9%). [64] It found no significant difference in the risk of intracranial or major extracranial bleeding between either medium- or low-intensity anticoagulation compared with aspirin (medium-intensity anticoagulation *v* aspirin: 15/241 [6%] with anticoagulation *v* 13/252 [5%] with aspirin; RR 1.19, 95% CI 0.59 to 2.41; ARR +1%, 95% CI –4% to +5%; low-intensity anticoagulation versus aspirin: 38/1103 [3.4%] with anticoagulation *v* 30/1103 [2.7%] with aspirin; RR 1.27, 95% CI 0.79 to 2.03; ARI +1%, 95% CI –1% to +2%), but the numbers of events were small and confidence intervals were wide, especially for medium-intensity anticoagulation versus aspirin. The RCT of low-intensity anticoagulation versus aspirin found that low-intensity anticoagulation significantly increased the risk of minor haemorrhage compared with aspirin (RR 1.39, 95% CI 1.17 to 1.64; ARI 7%, 95% CI 3% to 10%). [66] The subsequent RCT found medium-intensity anticoagulants significantly increased the risk of major bleeding complications compared with aspirin (45/536 [8%] with anticoagulants *v* 18/532 [3%] with aspirin; HR 2.56, 95% CI 1.48 to 4.43). [65]

Comment:

Anticoagulation versus placebo or no treatment:
Most trials in the systematic review had major problems with their methods, including poor monitoring of anticoagulation. [63] Most were completed before introducing routine computerised tomography scanning, meaning that people with primary haemorrhagic strokes could have been included. The systematic review could not, therefore, provide a reliable and precise overall estimate of the balance of risk and benefit regarding death or dependency.

Anticoagulation versus antiplatelet treatment:
Oral anticoagulants (target INR range 2.0–3.0) are no more effective than aspirin for secondary prevention after TIA or minor stroke of arterial origin. A possible protective effect against ischaemic events is offset by increased bleeding complications.

OPTION VITAMIN B SUPPLEMENTS (INCLUDING FOLATE)

Contributed by Lalit Kalra

Cardiovascular events
Compared with placebo Vitamin B supplements (including folate) may be no more effective at reducing stroke (low-quality evidence).

Different vitamin B supplement regimens compared with each other We don't know whether high-dose vitamin B supplements are more effective than low-dose vitamin B supplements at reducing further strokes at 2 years in people with an acute ischaemic and non-disabling stroke (high-quality evidence).

Mortality
Compared with placebo Vitamin B supplements (including folate) may be no more effective at reducing mortality (low-quality evidence).

Note
We found no clinically important results comparing vitamin B supplements with placebo exclusively in people with a prior stroke or TIA.

For GRADE evaluation of interventions for stroke prevention, **see table, p 41 .**

Benefits:

Vitamin B supplements (including folate) versus placebo:
We found two systematic reviews, which between them identified 13 RCTs, [67] [68] and we found one subsequent RCT [69] comparing vitamin B supplements (including folate) versus placebo. The first systematic review (12 RCTs; 16,958 people with CHD [7 RCTs], stroke [1 RCT], and ESRD [4 RCTs]) compared folate supplementation (range of doses 0.5–15 mg/day) versus placebo for a minimum duration of 6 months. [67] The review did not present a separate analysis for people with previous stroke or TIA. For the subgroup of people with CVD, the review found no significant difference between folate and placebo in all-cause mortality or stroke (all-cause mortality: RR 0.97, 95% CI 0.88 to 1.06; stroke: RR 0.89, 95% CI 0.74 to 1.07; absolute numbers not reported for this subgroup). [67]

The second systematic review (8 RCTs; 16,841 people with a history of CHD [3 RCTs], stroke [1 RCT], ESRD [3 RCTs], or oesophageal dysplasia [1 RCT]) compared the effects of folate (range of doses 0.5–15 mg/day) versus placebo in stroke prevention. [68] For the subgroup of people with a history of cerebrovascular disease, the review found no significant difference between folate and placebo in the risk of stroke (152/1827 [8%] with folate *v* 148/1853 [8%] with placebo; RR 1.04, 95% CI 0.84 to 1.29). The subsequent RCT (5442 women aged 42 years or older, with a history of CVD or 3 or more coronary risk factors; length of treatment 7.3 years) compared a combination pill containing folate, vitamin B_6, and vitamin B_{12} versus placebo. [69] It found no significant difference between vitamin B supplementation and placebo in the risk of stroke, MI, cardiovascular death, or all-cause mortality (stroke: 79/2721 [3%] with vitamin B supplementation *v* 69/2721 [3%] with placebo; RR 1.14, 95% CI 0.82 to 1.57; MI: 65/2721 [2%] with vitamin B supplementation *v* 74/2721 [3%] with placebo; RR 0.87, 95% CI 0.63 to 1.22; cardiovascular death: 96/2721 [4%] with vitamin B supplementation *v* 94/2721 [4%] with placebo; RR 1.01, 95% CI 0.76 to 1.35; all-cause mortality: 250/2721 [9%] with vitamin B supplementation *v* 256/2721 [9%] with placebo; RR 0.97, 95% CI 0.81 to 1.15). [69]

Different regimens versus each other:
We found one RCT (3680 adults with acute ischaemic non-disabling stroke) comparing a high-dose vitamin supplement (folic acid 2.5 mg plus vitamin B_6 25 mg plus vitamin B_{12} 0.4 mg) versus a lower-dose vitamin supplement (folic acid 20 micrograms plus vitamin B_6 200 micrograms plus vitamin B_{12} 6 micrograms). [70] It found no significant difference between high- and low-dose vitamin supplements for further stroke after 2 years (9.2% with high dose *v* 8.8% with low dose; RR 1.0, 95% CI 0.8 to 1.3; P = 0.8). It also found no significant difference between groups for other outcomes including any cardiovascular event, MI, fatal CHD event, or death. [70]

Harms:

Vitamin B supplements (including folate) versus placebo:
The two systematic reviews [67] [68] and one subsequent RCT [69] did not report on harms.

Different regimens versus each other:
The RCT did not report on harms. [70]

Comment:

In observational studies, lower homocysteine levels are associated with lower rates of CHD and stroke. Vitamins B_6 and B_{12} and folic acid lower homocysteine levels. In a systematic review of folate versus placebo (8 RCTs in people with CVD, ESRD, or oesophageal dysplasia), greatest benefit was seen in those trials with a treatment duration of more than 36 months, decrease in homocysteine concentrations of more than 20%, and no history of previous stroke (treatment duration of more than 36 months: RR 0.71, 95% CI 0.57 to 0.87; decrease in homocysteine concentrations of more than 20%: RR 0.77, 95% CI 0.63 to 0.94; no history of previous stroke: RR 0.75, 95% CI 0.62 to 0.90; absolute numbers not reported). [68]

QUESTION **What are the effects of preventive surgical interventions in people with previous stroke or TIA?**

OPTION CAROTID ENDARTERECTOMY (LESS THAN 30% STENOSIS)

Contributed by Lalit Kalra

Cardiovascular events

Compared with no endarterectomy Carotid endarterectomy is more likely to increase the risk of any stroke or surgical death in people with less than 30% symptomatic carotid artery stenosis (moderate-quality evidence).

Note

The risk of stroke in people with less than 30% carotid artery stenosis is already low, and even the small risk of intra-operative complications exceeds the natural risk of stroke.

For GRADE evaluation of interventions for stroke prevention, **see table, p 41 .**

Benefits:

We found one pooled analysis [71] and one systematic review. [72] The pooled analysis of individual patient data from three large RCTs (4 publications) examined the effects of endarterectomy in people with symptomatic carotid stenosis. [73] [74] [75] [76] The RCTs used different methods to measure the degree of carotid stenosis, studied different populations, and used different definitions of outcome events. However, the pooled analysis adjusted for these differences. The pooled analysis (3 RCTs; 6092 people; 35,000 person-years of follow-up) found that surgery increased the 5-year risk of any stroke or surgical death in people with less than 30% stenosis, although the differences between groups did not reach statistical significance (1746 people: RR 1.17, 95% CI 0.90 to 1.43). [71] This may be because the risk of stroke in people with less than 30% carotid artery stenosis is already low, and even the small risk of intra-operative complications exceeds the natural risk of stroke. The systematic review (search date 2004) did not pool data, and included data from RCTs and previous pooled analysis. [72] It reported the finding of the pooled analysis reported above, [71] and reached similar conclusions, reporting a 2.2% absolute increase in stroke risk (CI not reported; further numerical details not reported). [72]

Harms:

The pooled analysis (3248 people randomised to surgery a median of 6 days after randomisation) reported 229 strokes or deaths within 30 days of surgery (7.1%, 95% CI 6.3% to 8.1%). [71] Operative risk was not related to the degree of stenosis. The risk of death within 30 days of endarterectomy was 1.1% (36/3248; 95% CI 0.8% to 1.5%), and among 209 people who had an operative stroke, 20 people died (9.6%, 95% CI 5.9% to 14.4%). The systematic review did not report on harms. [72] One earlier systematic review (search date 1996; 36 studies) identified several risk factors for operative stroke and death from carotid endarterectomy, including female sex, occlusion of the contralateral internal carotid artery, stenosis of the ipsilateral external carotid artery, and systolic blood pressure greater than 180 mm Hg. [77]

One systematic review (search date 2000; 103 studies, including 6 RCTs, case series, and routinely collected data) examining harms of carotid endarterectomy found that the operative risk of stroke and death was highest in people with cerebral TIA or stroke, and in people with restenosis, and was lowest in people with ocular ischaemic events, and with asymptomatic stenosis (symptomatic stenosis *v* asymptomatic stenosis, 59 studies: OR 1.62, 95% CI 1.45 to 1.81; restenosis *v* primary surgery, 6 studies: OR 1.95, 95% CI 1.21 to 3.16; ocular events only *v* asymptomatic stenosis; 15 studies: OR 0.75, 95% CI 0.50 to 1.14). [78] It found that emergency surgery immediately after a TIA or stroke was associated with a major increase in operative risk compared with elective surgery performed a few days later (OR 4.9, 95% CI 3.4 to 7.1). [78] Endarterectomy is also associated with other postoperative complications, including wound infection (3%), wound haematoma (5%), and lower cranial nerve injury (5%–7%). [79]

We found one systematic review (search date 2004) of all trial data (including surgical case series) investigating gender and age as risk factors for stroke or death or both within 30 days of carotid endarterectomy. [80] The review found significantly higher rates of non-fatal stroke in women compared with men (16 studies: OR 1.28, 95% CI 1.12 to 1.46; P less than 0.001), but found no significant difference in operative mortality between sexes (15 studies: OR 1.05, 95% CI 0.81 to 1.36; P = 0.78). Overall, it found significantly higher combined risk of operative stroke and death in women compared with men (25 studies: OR 1.31, 95% CI 1.17 to 1.47; P less than 0.001). It found that, compared with rates in younger people, mortality was significantly higher in people aged 75 years and older (20 studies; OR 1.36, 95% CI 1.07 to 1.68; P = 0.02), or aged 80 years and older (15 studies: OR 1.80, 95% CI 1.26 to 2.45; P less than 0.001), and in older people overall (35 studies: OR 1.50, 95% CI 1.26 to1.78; P less than 0.001). In contrast, the review found that risk of non-fatal stroke did not significantly increase with age, so that, while there was a small

significant increase in the combined risk of death or stroke in older people overall compared with younger people (36 studies: OR 1.17, 95% CI 1.04 to 1.31; P = 0.01), there was no significant increase in combined death or stroke in people aged 75 years and older (21 studies: OR 1.18, 95% CI 0.94 to 1.44; P = 0.06), or aged 80 years and older (10 studies: OR 1.14, 95% CI 0.92 to 1.36; P = 0.34). [80]

Comment: The RCTs included in the pooled analysis found different results. [73] [74] However, this was due to differences in the methods of measurement of the degree of carotid stenosis on the pre-randomisation catheter angiograms (the method used in one RCT [73] produced higher values than the method used in the other trials), [74] [75] [81] and differences in the definitions of outcome events. Meta-analyses of the overall trial results have been reported, but these took no account of the differences between the trials. [82] [83] The subsequent pooled analysis of individual participant data corrected for these differences in methods, after which there were no clinically or statistically significant differences between the results of the three trials. [71] The degree of carotid stenosis was the single most important factor influencing the effects of endarterectomy. [71]

"Prophylactic" endarterectomy for people having CABG:
It is common practice for endarterectomy for asymptomatic stenosis to be performed as a "prophylactic" procedure either before or during CABG because of the high risk of stroke in this group (stroke after CABG overall: 1.71%; risk of stroke in people with asymptomatic stenosis: 3%). [84] We found no RCTs of endarterectomy for this indication. One systematic review (search date 2002; 97 RCTs) of outcomes after staged and synchronous carotid endarterectomy and CABG reported overall operative risks of stroke and death of 10%. [85] More recently, a Canadian observational study found that adjusted stroke and death rate was 2.67 times greater in all people undergoing combined carotid endarterectomy plus CABG compared with CABG alone. [86]

OPTION CAROTID ENDARTERECTOMY (30%–49% STENOSIS)

Cardiovascular events
Compared with no endarterectomy Carotid endarterectomy is no more effective at reducing the risk of stroke or surgical death in people with moderate (30%–49%) symptomatic carotid artery stenosis (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits: We found one pooled analysis [71] and one systematic review. [72] The pooled analysis of individual patient data from the three large RCTs (4 publications) examined the effects of endarterectomy in people with symptomatic carotid stenosis. [73] [74] [75] [76] The RCTs used different methods to measure the degree of carotid stenosis, studied different populations, and used different definitions of outcome events. However, the pooled analysis adjusted for these differences. The pooled analysis (3 RCTs; 6092 people; 35,000 person-years of follow-up) found that surgery had no significant effect on stroke or surgical death in people with 30% to 49% stenosis (1429 people: RR 0.90, 95% CI 0.75 to 1.04). The systematic review (search date 2004) did not pool data and included data from RCTs and the previous pooled analysis. It reported the finding of the pooled analysis reported above, and reached similar conclusions.

Harms: See harms of carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis, p 18 .

Comment: See comment on carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis, p 18 .

OPTION CAROTID ENDARTERECTOMY IN PEOPLE WITH MODERATELY SEVERE (50%–69%) SYMPTOMATIC CAROTID ARTERY STENOSIS

Contributed by Lalit Kalra

Cardiovascular events
Compared with no endarterectomy Carotid endarterectomy is more effective at reducing the risk of stroke or surgical death in people with moderately severe (50%–69%) symptomatic carotid artery stenosis (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table, p 41 .

Benefits: We found one pooled analysis [71] and one systematic review. [72] The pooled analysis of individual patient data from the three large RCTs (4 publications) examined the effects of endarterectomy in people with symptomatic carotid stenosis. [73] [74] [75] [76] The RCTs used different methods to measure the degree of carotid stenosis, studied different populations, and used different definitions

of outcome events. However, the pooled analysis adjusted for these differences. The pooled analysis (3 RCTs; 6092 people; 35,000 person-years of follow-up) found that surgery was of some benefit in stroke or surgical death in people with 50% to 69% stenosis (1549 people: RR 0.72, 95% CI 0.58 to 0.86). The systematic review (search date 2004) did not pool data, and included data from RCTs and previous pooled analysis. It reported the finding of the pooled analysis reported above. Based on the pooled analysis, the systematic review reported that the benefit in stroke and death for carotid endarterectomy in this group was an absolute risk reduction of 4.6% over 5 years (CI not reported), and the number needed to treat was 22 (CI not reported).

Harms: See harms of carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis, p 18 .

Comment: See comment on carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis, p 18 .

Subgroup analysis of pooled data from the European Carotid Surgery Trial [73] and North American Symptomatic Carotid Endarterectomy Trial [74] (5893 people with 33,000 person-years of follow-up) found that the benefit from surgery was greatest in men, in people aged 75 years and older, and in people randomised within 2 weeks after their last ischaemic event — and that the benefit fell rapidly with increasing delay. [87] For people with 50% or higher stenosis, the number of people needed to undergo surgery to prevent one ipsilateral stroke in 5 years was nine for men compared with 36 for women, five for people aged 75 years and older compared with 18 for younger than 65 years, and five for people randomised within 2 weeks after their last ischaemic event compared with 125 for people randomised after more than 12 weeks. [87] These results were reported to be consistent across the individual trials.

OPTION CAROTID ENDARTERECTOMY IN PEOPLE WITH SEVERE (MORE THAN 70%) SYMPTOMATIC CAROTID ARTERY STENOSIS

Cardiovascular events
Compared with no endarterectomy Carotid endarterectomy is more effective at reducing the risk of stroke or surgical death in people with severe (greater than 70%) symptomatic carotid artery stenosis without near occlusion (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table, p 41 .

Benefits: We found one pooled analysis [71] and one systematic review. [72] The pooled analysis of individual patient data from the three large RCTs (4 publications) examined the effects of endarterectomy in people with symptomatic carotid stenosis. [73] [74] [75] [76] The RCTs used different methods to measure the degree of carotid stenosis, studied different populations, and used different definitions of outcome events. However, the pooled analysis adjusted for these differences. The pooled analysis (3 RCTs; 6092 people; 35,000 person-years of follow-up) found that surgery was highly beneficial in reducing the risk of stroke or surgical death in people with 70% or more stenosis without near occlusion (1095 people: RR 0.52, 95% CI 0.40 to 0.64). The systematic review (search date 2004) did not pool data, and included data from RCTs and previous pooled analysis. It reported the finding of the pooled analysis reported above. Based on this pooled analysis, the review reported that, in people with at least 70% carotid stenosis without near occlusion, carotid endarterectomy reduced stroke or surgical death compared with medical therapy alone (5-year ARR 16%; NNT to prevent 1 stroke: 6.3; CIs not reported). [72]

Harms: See harms on carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis, p 18 .

Comment: See comment on carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis, p 18 .

OPTION CAROTID ENDARTERECTOMY IN PEOPLE WITH SYMPTOMATIC NEAR OCCLUSION OF THE CAROTID ARTERY

Contributed by Lalit Kalra

Cardiovascular events
Compared with no endarterectomy Carotid endarterectomy in people with severe disease (near occlusion of ipsilateral carotid artery) may be no more effective at reducing stroke or surgical death (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits: We found one pooled analysis [71] and one systematic review. [72] The pooled analysis of individual patient data from the three large RCTs (4 publications) examined the effects of endarterectomy in people with symptomatic carotid stenosis. [73] [74] [75] [76] The RCTs used different methods to measure the degree of carotid stenosis, studied different populations, and used different definitions of outcome events. However, the pooled analysis adjusted for these differences. The pooled analysis (3 RCTs; 6092 people; 35,000 person-years of follow-up) found no evidence of benefit from surgery in stroke or surgical death in people with the most severe disease (near occlusion of ipsilateral carotid artery; 262 people: RR compared with control 0.98, 95% CI 0.61 to 1.59). The systematic review (search date 2004) did not pool data and included data from RCTs and the previous pooled analysis. It reported the finding of the pooled analysis reported above. Based on the pooled analysis, the systematic review reported that, in people with near occlusion, carotid endarterectomy was associated with a reduced risk of stroke or death at 2 years compared with medical care (ARR 5.6%; P = 0.19; CI not reported, reported as not significant), and with an increased risk of stroke at 5 years compared with medical care (ARR –1.7%; P = 0.9; CI not reported, reported as not significant). [72]

Harms: See harms of carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis, p 18 .

Comment: See comment on carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis, p 18 .

OPTION CAROTID ENDARTERECTOMY IN PEOPLE WITH ASYMPTOMATIC BUT SEVERE CAROTID ARTERY STENOSIS

Contributed by Lalit Kalra

Cardiovascular events

Compared with medical care Carotid endarterectomy may be more effective at reducing perioperative stroke, death, and subsequent ipsilateral stroke in people with asymptomatic but severe stenosis (moderate-quality evidence).

Note

The risk of stroke without surgery in asymptomatic people is relatively low, and the benefit from surgery is small.

For GRADE evaluation of interventions for stroke prevention, see table, p 41 .

Benefits: We found one systematic review (search date 2004; 3 RCTs; 5223 people) assessing carotid endarterectomy for asymptomatic carotid stenosis (no carotid territory TIA or minor stroke within the previous few months). [88] The review found that carotid endarterectomy reduced the risk of perioperative stroke, death, or subsequent ipsilateral stroke over 3 to 4 years compared with medical treatment only (103/2596 [4%] with endarterectomy *v* 149/2627 [6%] with medical treatment; RR 0.71, 95% CI 0.55 to 0.90; see comment below).

Harms: Given the low prevalence of severe carotid stenosis in the general population, there is concern that screening and surgical intervention in asymptomatic people may result in more strokes than it prevents. [89] The systematic review gave no information on adverse effects. [88] Case series reported that the overall risk of death at 30 days as a result of carotid endarterectomy was 1%, and the that risk of stroke or death at 30 days as a result of surgery was 3.8%. [90]

Comment: Although the risk of perioperative stroke or death from carotid surgery for people with asymptomatic stenosis seems lower than in people with symptomatic stenosis, the risk of stroke or death without surgery in asymptomatic people is low, and so the absolute benefit from surgery is small; and, for most people, the balance of risk and benefit from surgery remains unclear. [88] Subgroup analysis of data from two RCTs comparing endarterectomy versus medical treatment in people with asymptomatic carotid stenosis found that, after a mean follow-up of 2 to 3 years, the benefits of surgery on stroke may be greater in men than in women (stroke in men: 69/1565 [4%] with surgery *v* 38/1570 [2%] with medical treatment; OR 0.49, 95% CI 0.36 to 0.66; stroke in women: 46/820 [5.6%] with surgery *v* 48/824 [5.8%] with medical treatment; OR 0.96, 95% CI 0.63 to 1.45). [91] There is currently no evidence of benefit in women after 5 years. [91]

OPTION EVERSION VERSUS CONVENTIONAL CAROTID ENDARTERECTOMY

Contributed by Lalit Kalra

Cardiovascular events

Eversion compared with conventional carotid endarterectomy We don't know whether eversion carotid endarterectomy performed either with primary closure or patch angioplasty is more effective at reducing the rates of perioperative stroke, or stroke or death (very low-quality evidence).

Mortality

Eversion compared with conventional carotid endarterectomy Eversion carotid endarterectomy seems equally effective at improving long-term survival (moderate-quality evidence).

Adverse effects

Eversion compared with conventional carotid endarterectomy Although eversion carotid endarterectomy may be more effective at reducing restenosis above 50%, we don't know whether it is more effective at reducing local complications such as neck haematoma or cranial nerve injuries (very low-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits:

Eversion versus conventional carotid endarterectomy:
We found one systematic review [92] and one subsequent RCT. [93] The systematic review (search date 2002; 5 RCTs; 2465 people and 2589 carotid arteries) compared eversion carotid endarterectomy versus conventional carotid endarterectomy performed either with primary closure or patch angioplasty. Overall, the review found no significant differences in the rate of perioperative stroke, stroke or death, or stroke during follow-up between eversion and conventional techniques (perioperative stroke: 4 RCTs; 2363 people; 17/1190 [1%] with eversion *v* 24/1173 [2%] with conventional techniques; OR 0.70, 95% CI 0.38 to 1.29; stroke or death or both: 4 RCTs; 2363 people; 20/1190 [2%] with eversion *v* 31/1173 [3%] with conventional techniques; OR 0.44, 95% CI 0.10 to 1.82; stroke during follow-up: 3 RCTs; 2212 people; 16/1115 [1%] with eversion *v* 19/1097 [2%] with conventional techniques; OR 0.84, 95% CI 0.43 to 1.64).

The subsequent RCT (201 people; 52% with previous history of TIA, amaurosis fugax, reversible ischaemic neurological deficit, or stroke) compared eversion versus conventional carotid endarterectomy, with a mean follow-up of 38 months. [93] It found no significant difference in long-term survival between eversion and conventional techniques (average length of survival: 52.6 months with eversion *v* 56.6 months with conventional techniques; P greater than 0.05). In the 7 days after surgery, the RCT found that central neurological complications (stroke, reversible ischaemic neurological deficit, or TIA) were significantly more common with conventional techniques compared with eversion (4/103 [4%] with eversion *v* 12/98 [12%] with conventional techniques; OR 3.45, 95% CI 1.1 to 11.1).

Harms:

Eversion versus conventional carotid endarterectomy:
The review found that eversion carotid endarterectomy was associated with a significantly lower rate of restenosis above 50% compared with conventional carotid endarterectomy during follow-up (5 RCTs; 2557 people: 32/1290 [3%] with eversion *v* 66/1267 [5%] with conventional; OR 0.48, 95% CI 0.32 to 0.72; P = 0.0004). It found no significant difference between groups in MI (2 RCTs; 1663 people; 4/838 [0.5%] with eversion *v* 5/827 [0.6%] with conventional techniques; OR 0.79, 95% CI 0.21 to 2.92), or in local complications such as neck haematoma (4 RCTs; 2389 people; 51/1201 [4%] with eversion *v* 65/1188 [5%] with conventional techniques; OR 0.76, 95% CI 0.52 to 1.11) or cranial nerve injuries (4 RCTs; 2025 people; 39/1017 [4%] with eversion *v* 57/1008 [6%] with conventional techniques; OR 0.52, 95% CI 0.22 to 1.23). [92]

The subsequent RCT found that eversion carotid endarterectomy was associated with a significantly lower rate of haemodynamically significant late restenosis or occlusion (0/103 [0%] with eversion *v* 6/98 [6%] with conventional techniques; reported as significant, further data not reported). [93] There was no significant difference between groups in transient lesions of cranial and cervical nerves (2/103 with eversion *v* 2/98 with conventional techniques; P = 1.00). [93]

Comment:

Studies have not shown significant differences in benefit or risk between the two techniques, but the meta-analysis was limited by heterogeneity among studies and the small number of RCTs included. Further studies are needed to confirm the lower long-term restenosis rate reported by the review and subsequent RCT. [92] [93]

OPTION CAROTID PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

Contributed by Lalit Kalra

Cardiovascular events

Compared with carotid endarterectomy We don't know whether carotid percutaneous transluminal angioplasty (PTA) is more effective at reducing disabling stroke within 30 days of procedure or at 1 year in people with a recent carotid territory TIA or non-disabling ischaemic stroke with stenosis of the ipsilateral carotid artery (low-quality evidence).

Mortality

Compared with carotid endarterectomy We don't know whether carotid PTA is more effective at reducing mortality within 30 days of procedure or at 1 year in people with a recent carotid territory TIA or non-disabling ischaemic stroke with stenosis of the ipsilateral carotid artery (low-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table, p 41 .

Benefits:

Carotid percutaneous transluminal angioplasty (PTA) versus endarterectomy:
We found one systematic review (search date 2003) comparing carotid endarterectomy versus carotid PTA. [94] The review included two completed RCTs (608 people), two RCTs (242 people) that were terminated early, and a fifth RCT (307 people), which had completed randomisation and 30-day follow-up. The review found no significant difference between endarterectomy and angioplasty in stroke or mortality at 30 days or 1 year (death or any stroke within 30 days of procedure: 5 RCTs; 50/578 [9%] with endarterectomy *v* 41/579 [7%] with angioplasty; OR 1.26, 95% CI 0.82 to 1.94; death or disabling stroke within 30 days: 3 RCTs; 19/315 [6%] with endarterectomy *v* 16/316 [5%] with angioplasty; OR 1.22, CI 0.61 to 2.41; death, any stroke, or MI within 30 days: 5 RCTs; 52/578 [9%] with endarterectomy *v* 53/579 [9%] with angioplasty; OR 0.99, CI 0.66 to 1.48; death or any stroke at 1 year after procedure: 2 RCTs; 49/358 [14%] with endarterectomy *v* 38/365 [10%] with angioplasty; OR 1.36, CI 0.87 to 2.13). [94] The largest included RCT (504 people with a recent carotid territory TIA or non-disabling ischaemic stroke with stenosis of the ipsilateral carotid artery) in the review [94] compared "best medical treatment" plus carotid PTA versus "best medical treatment" plus carotid endarterectomy. [95] It found no significant difference between endovascular treatment and surgery for disabling stroke or death within 30 days of first treatment (AR for disabling stroke or death: 6.4% with carotid PTA *v* 5.9% with surgery; AR for stroke lasting over 7 days or death: 10.0% with carotid PTA *v* 9.9% with surgery). The trial found no significant difference between treatments for the primary end point of ipsilateral stroke rate up to 3 years after randomisation (adjusted HR 1.04, 95% CI 0.63 to 1.70; P = 0.9). [95]

Harms:

Carotid PTA versus endarterectomy:
The review found that angioplasty significantly reduced the risk of cranial neuropathy compared with endarterectomy (4 RCTs; 0/471 [0%] with angioplasty *v* 34/467 [7%] with endarterectomy; OR 0.12, CI 0.06 to 0.25). [94] The largest included RCT (reported in 2 publications) [95] [96] found that major groin or neck haematoma occurred less often after angioplasty than after endarterectomy (3 [1%] people with angioplasty *v* 17 [7%] people with endarterectomy; P less than 0.0015). Subsequent analysis of the risk of restenosis found that a higher proportion of people had severe (at least 70%) stenosis of the ipsilateral carotid artery at 1 year in the angioplasty group compared with the endarterectomy group (32/173 [19%] with angioplasty *v* 9/174 [5%] with endarterectomy; P less than 0.0001). [96] At 1 month after endovascular treatment, 6.5% of people had residual severe stenosis . Between 1 month and 1 year, 10.5% of people in the endovascular group had restenosis to at least 70% stenosis. After endarterectomy, 1.7% of people had residual severe stenosis at 1 month, and 2.5% developed severe restenosis. Recurrent transient ipsilateral symptoms were more common in endovascular patients with severe stenosis (5/32 [16%]). There were no recurrent symptoms in the nine people in the endarterectomy group who had at least 70% stenosis at 1 year. [96] A small RCT of 23 people was stopped after 17 people had received allocated treatment because of a high procedural risk of stroke in the angioplasty group compared with the endarterectomy group (5/7 [71%] with angioplasty *v* 0/10 [0%] with endarterectomy; P = 0.03). [97]

Comment:

Several ongoing RCTs are comparing carotid endarterectomy versus primary stenting in people with recently symptomatic severe carotid stenosis.

OPTION VERTEBRAL PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

We found no clinically important results from RCTs about the effects of vertebral percutaneous transluminal angioplasty compared with medical treatment or carotid endarterectomy in people with a recent vertebral territory TIA or non-disabling ischaemic stroke who have severe stenosis of the ipsilateral carotid or vertebral artery.

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits:

Vertebral percutaneous transluminal angioplasty (PTA) versus "best medical treatment":
We found one small RCT (16 people) comparing vertebral angioplasty versus "best medical treatment". [95] The RCT did not provide enough data for reliable estimates of efficacy to be made.

Harms: See harms of carotid percutaneous transluminal angioplasty, p 22 .

Comment: **Clinical guide:**
We found insufficient evidence to assess the effectiveness of vertebral PTA. Treatment of people with vertebral artery stenosis should focus on global reduction of vascular risk until further RCT data are available.

OPTION CAROTID PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY PLUS STENTING

Contributed by Lalit Kalra

Cardiovascular events
Compared with carotid endarterectomy We don't know whether carotid PTA is more effective at reducing stroke or MI at 30 days to 1 year in people with asymptomatic carotid artery stenosis or a previous stroke or TIA (low-quality evidence).

Mortality
Compared with carotid endarterectomy We don't know whether carotid PTA plus stenting is more effective at reducing mortality at 30 days to 1 year in people with asymptomatic carotid artery stenosis or a previous stroke or TIA (low-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits: **Carotid percutaneous transluminal angioplasty (PTA) plus stenting versus endarterectomy:**
We found two systematic reviews, [98] [99] which between them identified nine RCTs, and one subsequent RCT [100] comparing carotid PTA plus stenting versus carotid endarterectomy. The first systematic review (5 RCTs; 2122 people with previous stroke or TIA ascribed to carotid artery stenosis) compared carotid artery stenting (CAS) with carotid endarterectomy (CEA). [98] At 30-day follow-up, it found no significant difference between the two groups in mortality, stroke, or disabling stroke (mortality: RR 0.57, 95% CI 0.22 to1.47; stroke: RR 1.64, 95% CI 0.67 to 4.00; disabling stroke: RR 1.67, 95% CI 0.50 to 5.62; absolute numbers not reported).

The second systematic review (9 RCTs; 3138 people; 89% with symptomatic carotid artery stenosis) compared CAS versus CEA and reported outcomes at 30 days, 6 months, and 1 year after procedure. [99] At 30 days, it found no significant difference between CAS and CEA in mortality (8 RCTs; 12/1467 [1%] with CAS *v* 17/1452 [1%] with CEA; OR 0.75, 95% CI 0.38 to 1.48), stroke (8 RCTs; 90/1467 [6%] with CAS *v* 61/1452 [4%] with CEA; OR 1.46, 95% CI 0.91 to 2.36), or MI (6 RCTs; 11/857 [1%] with CAS *v* 17/856 [2%] with CEA; OR 0.69, 95% CI 0.23 to 2.10). There was no significant difference between the two groups in the composite outcome of stroke or death at 6 months (2 RCTs; 38/343 [11%] with CAS *v* 24/343 [7%] with CEA; OR 1.50, 95% CI 0.69 to 3.23) or after 1 year (3 RCTs; 58/525 [11%] with CAS *v* 51/532 [10%] with CEA; OR 1.25, 95% CI 0.59 to 2.63). [99] The subsequent RCT (334 people; 29% with a history of previous stroke or TIA) compared CAS with use of an emboli-protection device versus CEA, with follow-up at 3 years. [100] It found no significant difference between CAS and CEA in mortality, stroke, or MI (mortality: 31/167 [19%] with CAS *v* 35/167 [21%] with CEA; ARR +2%, 95% CI –10.9% to +6.1%; stroke: 15/167 [9%] with CAS *v* 15/167 [9%] with CEA; ARR 0%, 95% CI –6.1% to +6.1%; MI: 9/167 [5%] with CAS *v* 14/167 [8%] with CEA; ARR +3%, 95% CI –8.4% to +2.4%). [100]

Harms: **Carotid PTA plus stenting versus endarterectomy:**
The first systematic review [98] and the subsequent RCT [100] did not report adverse effects. The second systematic review found the risk of cranial nerve injury was significantly lower with CAS compared with CEA (7 RCTs; 3/868 [0.3%] with CAS *v* 55/868 [6%] with CEA; OR 0.12, 95% CI 0.05 to 0.29). [99] We found one additional systematic review (34 RCTs; 4185 people) of recurrent stenosis after CAS, with follow-up between 6 to 31 months. [101] In studies using a recurrent stenosis threshold of 50% to 70%, it found that cumulative restenosis rates in the first 2 years after CAS were 6% to 7.5%. In studies using a restenosis threshold of 70% to 80%, the restenosis rate was 4% in the first 2 years. The early restenosis rates after CAS compare well with those reported for CEA. [101]

See also harms of carotid percutaneous transluminal angioplasty, p 22 .

Comment: **Clinical guide:**
Angioplasty with or without stenting may be associated with a higher procedural risk than endarterectomy, and a higher rate of restenosis during follow-up. [102] [103] However, improvements in cerebral protection devices may reduce the procedural risks, [104] and several other RCTs comparing angioplasty plus stenting with cerebral protection versus endarterectomy are ongoing. The evidence on

the use of angioplasty remains in equipoise, and the results of further RCTs and analysis of long-term data from existing trials is awaited.

QUESTION **What are the effects of preventive anticoagulant and antiplatelet treatments in people with atrial fibrillation and previous stroke or TIA?**

OPTION **ANTICOAGULANT TREATMENT IN PEOPLE WITH ATRIAL FIBRILLATION AND PREVIOUS STROKE OR TIA**

Cardiovascular events

Adjusted-dose warfarin compared with placebo Adjusted-dose warfarin is more effective at reducing the risk of stroke in people with atrial fibrillation and a previous stroke or TIA (high-quality evidence).

Conventional-intensity warfarin compared with low-intensity or minidose warfarin We don't know whether conventional-intensity warfarin is more effective at reducing ischaemic stroke rates at 1 year in people with atrial fibrillation and an ischaemic stroke within the last 6 months (very low-quality evidence).

Conventional-intensity warfarin compared with other antiplatelet treatments/combinations We don't know whether conventional-intensity warfarin is more effective at preventing recurrence of strokes in people with atrial fibrillation and a previous ischaemic stroke or TIA (very low-quality evidence).

Conventional-intensity warfarin compared with other anticoagulants We don't know whether conventional-intensity warfarin is more effective at preventing stroke in people with atrial fibrillation and previous stroke or TIA (low-quality evidence).

Note

The best time to begin anticoagulation after an ischaemic stroke is unclear. The review provided insufficient evidence to compare warfarin versus aspirin.

For GRADE evaluation of interventions for stroke prevention, see table, p 41 .

Benefits:

Adjusted-dose warfarin versus placebo or control:

We found one systematic review (search date 1999; 1 RCT; [105] 439 people with previous stroke or TIA; see comment below) comparing adjusted-dose warfarin with a control, in which people could self-select to take aspirin (target INR 2.9). [106] The RCT found that adjusted-dose warfarin significantly reduced the risk of stroke compared with control (20/225 [9%] with warfarin *v* 50/214 [23%] with control; ARR 14.5%, 95% CI 7.7% to 21.3%; NNT 7, 95% CI 5 to 13). [105]

Conventional-intensity versus low-intensity or minidose warfarin:

We found one RCT (115 people with ischaemic stroke in the previous 1–6 months). [107] It found no significant difference between conventional-intensity warfarin (target INR 2.2–3.5) and low-intensity warfarin (target INR 1.5–2.1) in ischaemic stroke rate after a mean follow-up of about 1 year (AR: 1/55 [1%] with conventional-intensity *v* 2/60 [2%] with low-intensity warfarin; P value reported as not significant). [107] This result may be due to: insufficient power; premature termination of the trial because of significantly more bleeding complications in the conventional-intensity anticoagulation group (see harms); the low rate of ischaemic stroke observed in both groups in this population, possibly contributed to by different ethnicity from original anticoagulation trial cohorts; or the similar anticoagulation range reached in the two groups (2.2 with conventional-intensity *v* 1.9 with low-intensity warfarin). [108] The RCT was terminated prematurely because of significantly more bleeding complications with conventional-intensity warfarin (see harms and comment below).

Adjusted-dose warfarin versus aspirin:

We found one systematic review (search date 1999), [106] which identified one RCT [105] comparing warfarin with aspirin. However, this comparison was not randomised, and therefore did not meet inclusion criteria for this review.

Conventional-intensity warfarin versus other antiplatelet treatments/combinations:

We found one systematic review [106] and one subsequent RCT. [109] The systematic review (search date 1999; 1 RCT; [108] 916 people within 15 days of stroke onset) compared warfarin (target INR 2.0–3.5) versus indobufen. [106] It found no significant difference in the rate of recurrent stroke between treatments (5% with indobufen *v* 4% with warfarin; ARR +1.0%, 95% CI –1.7% to +3.7%). [106] The subsequent RCT (6706 people with atrial fibrillation plus one or more risk factors for stroke; 1020 people [15%] with previous stroke/TIA) assessed whether clopidogrel (75 mg/day) plus aspirin (75–100 mg/day) was not inferior to adjusted-dose oral anticoagulation therapy (target INR 2–3; the vitamin K antagonist in use in their country) for the prevention of vascular events. [109] The primary composite outcome measure was first occurrence of stroke, non-central nervous system

systemic embolism, MI, or vascular death. The RCT was stopped early because of clear evidence of the superiority of oral anticoagulation treatment compared with clopidogrel plus aspirin for the primary outcome (risk: 5.60% a year with clopidogrel plus aspirin *v* 3.93% a year with oral anticoagulation therapy; RR 1.44, 95% CI 1.18 to 1.76; P = 0.0003). However, it did not separately report results on the subgroup of people with previous stroke or TIA. [109]

Conventional-intensity warfarin versus other anticoagulants:
We found two RCTs. [110] [111] The first RCT (3410 people with atrial fibrillation and at least 1 other risk factor for stroke, 24% with previous stroke or TIA) compared open-label warfarin (INR 2.0–3.0) versus the oral thrombin inhibitor ximelagatran (fixed dose; 36 mg twice daily). [110] It found no significant difference in stroke between warfarin and ximelagatran in a subgroup with previous stroke or TIA after mean follow-up of 17 months (822 people; 5.1% a year with warfarin *v* 3.8% a year with ximelagatran; P = 0.3). [110]

The second RCT (3922 people with atrial fibrillation and at least 1 other risk factor for stroke; 19% with previous stroke or TIA) compared warfarin (INR 2.0–3.0) versus the oral thrombin inhibitor ximelagatran (fixed dose; 36 mg twice daily). [111] It found no significant difference between groups in the proportion of people who experienced at least one primary event (all strokes and systemic embolism) after 20 months (1.6% a year with ximelagatran *v* 1.2% a year with warfarin; absolute difference +0.45% a year, 95% CI –0.13% to +1.03% a year; P less than 0.001 for the predefined non-inferiority hypothesis). [111] Ximelagatran has been voluntarily withdrawn worldwide owing to potential increased risk of liver damage. [112]

Harms:

The major risk associated with anticoagulants and antiplatelet agents was haemorrhage. The first systematic review assessed risk of bleeding in people with atrial fibrillation with or without previous stroke or TIA. [106] It found that the absolute risk of intracranial haemorrhage increased from 0.1% a year with control to 0.3% a year with warfarin, but the difference was not significant. [106] The absolute risks were three times higher in people who had bled previously. Both bleeding and haemorrhagic stroke were more common in people aged over 75 years. The risk of death after a major bleed was 13% to 33%, and the risk of subsequent morbidity in people who survived a major bleed was 15%. The risk of bleeding was associated with an INR greater than 3, fluctuating INRs, and uncontrolled hypertension. In an overview assessing older people with variable risk factors for stroke, the absolute risk of major bleeding was 1.0% for placebo, 1.0% for aspirin, and 1.3% for warfarin. [113]

In another systematic review (search date not reported; 2 RCTs), major extracranial bleeding was more frequent with anticoagulation treatment than with placebo (ARI 4.9%, 95% CI 1.6% to 8.2%; RR 6.2, 95% CI 1.4 to 27.1; NNH 20, 95% CI 12 to 63). [114] The studies lacked power to detect the rate of intracranial haemorrhage (none occurred). In a third systematic review (search date not reported) comparing anticoagulants versus antiplatelet treatment, major extracranial bleeding was more frequent with anticoagulation (ARI 4.9%, 95% CI 1.6% to 8.2%; RR 6.4, 95% CI 1.5 to 28.1; NNH 20, 95% CI 12 to 63). [115] The studies lacked power to detect the rate of intracranial haemorrhage (in 1 RCT, none of the people on anticoagulant and 1 person on aspirin had an intracranial bleed). In the systematic review of oral anticoagulants versus placebo in low-risk people, the number of intracranial haemorrhages was small, with a non-significant increase in the treatment group (5 in the treatment group *v* 2 in the control group). [116]

One systematic review (search date 1999) found no evidence that warfarin significantly increased the risk of major haemorrhage compared with placebo in people with no prior TIA or stroke (5 RCTs; 2415 people: ARI for major haemorrhage warfarin *v* placebo +0.8%, 95% CI –1.3% to +2.9%). [117] However, if people with previous stroke or TIA were included, then warfarin significantly increased major haemorrhage (6 RCTs: ARI for warfarin *v* placebo 1.3%, 95% CI 0.4% to 2.2%; NNH 77, 95% CI 45 to 250). The systematic review found no evidence of a difference in major haemorrhage between warfarin and aspirin, warfarin and any antiplatelet agent, warfarin and low-dose warfarin plus aspirin, and low molecular weight heparin and placebo. However, the review may have lacked power to detect a clinically important difference. [117] One RCT (115 people) found that conventional-intensity warfarin significantly increased major haemorrhagic complications compared with low-intensity warfarin after about 1 year (6/55 [11%] with conventional-intensity *v* 0/60 [0%] with low-intensity warfarin; P = 0.01). [107]

Conventional-intensity warfarin versus other antiplatelet treatments/combinations:
The subsequent RCT found no significant difference in severe or fatal bleeds between clopidogrel plus aspirin compared with oral anticoagulation, although the number of minor and total bleeds was significantly higher with clopidogrel plus aspirin (severe or fatal bleeds: RR 1.10, 95% CI 0.83 to 1.45; P = 0.53; minor bleeds: RR 1.23, 95% CI 1.09 to 1.39; total bleeds: RR 1.21, 95% CI 1.08 to 1.35). [109]

Conventional-intensity warfarin versus other anticoagulants:
The second RCT found no significant difference in major extracerebral bleeds between warfarin and ximelagatran, but found that minor bleeds were significantly more common with warfarin group than with ximelagatran (major bleeds: P = 15; minor bleeds: P less than 0.001). [111] Ximelagatran has been voluntarily withdrawn worldwide owing to potential increased risk of liver damage. [112]

Comment:

We found one systematic review (search date 2005; 5 primary studies, 2 meta-analyses), [118] which was part of the National Institute for Health and Clinical Excellence (NICE) guidelines on atrial fibrillation management (http://guidance.nice.org.uk/CG36), but no meta-analysis was performed. The systematic review for the NICE guideline concluded that anticoagulation with warfarin had a strong beneficial effect in the prevention of recurrent strokes for post-stroke and post-TIA people with atrial fibrillation, when compared with both placebo and aspirin. [118]

Clinical guide:
Timing of anticoagulation:
The best time to start anticoagulation after an ischaemic stroke is unclear, but aspirin reduces the risk of recurrent stroke in these people, with or without atrial fibrillation, suggesting that it is reasonable to use aspirin until it is considered safe to start oral anticoagulants. [119]

See also comment on anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 .

OPTION ANTIPLATELET TREATMENT IN PEOPLE WITH ATRIAL FIBRILLATION AND PREVIOUS STROKE OR TIA

Cardiovascular events
Aspirin compared with placebo Aspirin may be no more effective at preventing stroke in people with atrial fibrillation and previous stroke or TIA (moderate-quality evidence).

Antiplatelet treatments other than warfarin compared with conventional-intensity warfarin We don't know whether antiplatelet treatments/combinations are more effective at preventing recurrence of strokes in people with atrial fibrillation and a previous ischaemic stroke or TIA (very low-quality evidence).

Mortality
Aspirin compared with placebo Aspirin may be no more effective at reducing mortality in people with atrial fibrillation and previous stroke or TIA (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits:

Aspirin versus placebo:
We found one systematic review (search date 1999; 1 RCT; 782 people with atrial fibrillation and previous stroke or TIA; see comment below). [117] The RCT included in the review found no significant difference between aspirin and placebo for stroke or death (stroke: OR 0.89, 95% CI 0.64 to 1.24; death: OR 0.95, 95% CI 0.69 to 1.31).

Aspirin versus adjusted-dose warfarin:
See benefits of anticoagulant treatment in people with atrial fibrillation and previous stroke or TIA, p 25 .

Antiplatelet treatments/combinations versus conventional-intensity warfarin:
See benefits of anticoagulant treatment in people with atrial fibrillation and previous stroke or TIA, p 25 .

Harms:

Aspirin versus placebo:
The first review reported that aspirin was associated with more major bleeds than placebo, but this difference was not significant (OR 0.81, 95% CI 0.37 to1.78). [117]

Aspirin versus adjusted-dose warfarin:
See harms of anticoagulant treatment in people with atrial fibrillation and previous stroke or TIA, p 25 .

Antiplatelet treatments/combinations versus conventional-intensity warfarin:
See harms of anticoagulant treatment in people with atrial fibrillation and previous stroke or TIA, p 25 .

Comment:

Clinical guide:
We found one systematic review (search date 2005; 5 primary studies, 2 meta-analysis), [118] which was part of the National Institute for Health and Clinical Excellence (NICE) guidelines on atrial fibrillation management (http://guidance.nice.org.uk/CG36), but no meta-analysis was performed. The review concluded that antiplatelet therapy did not have a beneficial effect in the prevention of recurrent strokes for people after stroke and after TIA with atrial fibrillation when compared with placebo.

See comment on antiplatelet treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 32 .

QUESTION **What are the effects of preventive anticoagulant and antiplatelet treatment in people with atrial fibrillation and without previous stroke or TIA and with high risk of stroke or TIA?**

OPTION **ANTICOAGULANT TREATMENT IN PEOPLE WITH ATRIAL FIBRILLATION WITHOUT PREVIOUS STROKE OR TIA WITH HIGH RISK OF STROKE OR TIA**

Cardiovascular events
Adjusted-dose warfarin compared with placebo Adjusted-dose warfarin is more effective at reducing stroke in people with atrial fibrillation and at high risk of stroke (moderate-quality evidence).

Adjusted-dose warfarin compared with low-dose warfarin plus aspirin Adjusted-dose warfarin seems more effective at reducing vascular death, disabling stroke, and ischaemic stroke in people with at least one thrombotic risk factor (CHF or left ventricular fractional shortening 25% or less, previous thromboembolism, systolic blood pressure of greater than 60 mm Hg at study enrolment, or being a woman aged over 75 years) at 1.1 years (moderate-quality evidence).

Adjusted-dose warfarin compared with low-intensity or minidose warfarin We don't know whether adjusted-dose warfarin is more effective at reducing the risk of ischaemic stroke (low-quality evidence).

Adjusted-dose warfarin compared with aspirin Adjusted-dose warfarin may be more effective at reducing stroke in people at high risk of stroke (low-quality evidence).

Adjusted-dose warfarin compared with other antiplatelet treatments/combinations Adjusted-dose warfarin is more effective at reducing a composite outcome of first occurrence of stroke, non-central nervous system systemic embolism, MI, or vascular death in people with atrial fibrillation with one or more risk factors for stroke (high-quality evidence).

Oral anticoagulants other than warfarin compared with oral anticoagulant plus aspirin or other antiplatelets Oral anticoagulants other than warfarin may be less effective at reducing a composite outcome of vascular death, TIA, and non-fatal stroke in people with atrial fibrillation and at high to intermediate risk of stroke (low-quality evidence).

Adjusted-dose warfarin compared with other anticoagulants Adjusted-dose warfarin and ximelagatran seem equally effective at preventing ischaemic strokes or systemic emboli, but ximelagatran increases the risk of liver damage (moderate-quality evidence).

Mortality
Adjusted-dose warfarin compared with other anticoagulants Adjusted-dose warfarin and ximelagatran seem equally effective at reducing mortality but ximelagatran increases the risk of liver damage (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits:

Adjusted-dose warfarin versus placebo:
We found three systematic reviews examining the effect of warfarin in different groups of people with atrial fibrillation at high risk of stroke (see comment below). [106] [117] [120] The first systematic review (search date 1999; 6 RCTs; 2900 people at high risk; 80% without previous stroke or TIA, 45% with hypertension) compared adjusted-dose warfarin versus placebo or control. [106] In one RCT (439 people) included in the review, people in the control group could self-select to take aspirin. Target INR varied among RCTs (2.0–2.6 in primary prevention RCTs). The review found that adjusted-dose warfarin significantly reduced the risk of stroke compared with placebo or control (ARR 4.0%, 95% CI 2.3% to 5.7%; NNT 25, 95% CI 18 to 43). For people without previous stroke or TIA (5 RCTs; 2462 people), the relative risk of stroke was reduced by 59% (ARR 2.7% a year). The second systematic review (search date 1999; 14 RCTs) identified the same trials of warfarin compared with placebo and found similar results, [117] as did the third systematic review (search date 2005; 13 RCTs). [120]

Adjusted-dose warfarin versus low-dose warfarin plus aspirin:
We found one RCT (1044 people with at least one thrombotic risk factor [CHF or left ventricular fractional shortening 25% or less, previous thromboembolism, systolic blood pressure of greater than 60 mm Hg at study enrolment, or being a women aged over 75 years]) comparing low-intensity fixed-dose warfarin plus aspirin versus adjusted-dose warfarin. [121] The RCT was stopped after a mean follow-up of 1.1 years when the rate of ischaemic stroke and systemic embolism was significantly higher in people given the combination treatment compared with the adjusted-dose warfarin at an interim analysis (7.9% a year with low-intensity fixed-dose warfarin plus aspirin *v* 1.9% with adjusted-dose warfarin; AR by adjusted-dose warfarin 6.0% a year, 95% CI 3.4% a year to 8.6% a year; P less than 0.0001). The RCT found that annual rates of disabling stroke and vascular death were significantly higher with low-intensity fixed-dose warfarin plus aspirin compared with adjusted-dose warfarin (disabling stroke, P = 0.0007; vascular death, P = 0.002). [121]

Adjusted-dose versus low-intensity or minidose warfarin:
We found two systematic reviews (see comment below). [122] [120] The first review (search date 2005; 13 RCTs; 14,423 people) compared adjusted-dose warfarin versus low-intensity, minidose/low-dose warfarin (with or without low-dose aspirin). It found that adjusted-dose warfarin reduced the risk of ischaemic stroke compared with lower-dose warfarin, although this difference was not significant (RR 0.46, 95% CI 0.20 to 1.07; see comment below). [122] The second review (search date 2005; 4 RCTs) compared adjusted-dose warfarin versus low-dose warfarin in high-risk people. It found that adjusted-dose warfarin significantly reduced the risk of ischaemic stroke or systemic embolism compared with low-dose warfarin (4 RCTs; RR 0.36, 95% CI 0.23 to 0.58). However, it found no significant difference in mortality with different doses (4 RCTs; RR 1.11, 95% CI 0.81 to 1.52). [120]

Adjusted-dose warfarin versus aspirin:
We found two systematic reviews comparing warfarin versus different antiplatelet regimens in people at high risk of stroke, [106] [120] and one subsequent report of a meta-analysis of individual patient data (see comment below). [123] The first systematic review (search date 1999; 4 primary prevention RCTs; 7037 people) compared adjusted-dose warfarin versus aspirin in high-risk people (45% had hypertension). [106] Target INR varied among RCTs (2.0–4.5 in primary prevention RCTs). Adjusted-dose warfarin reduced the overall risk of stroke compared with aspirin (RR 0.64, 95% CI 0.48 to 0.86). The effect varied widely among the four RCTs, none of which were blinded.

The second systematic review (search date 2005; 13 RCTs, including the 4 RCTs identified by the first review; 14,423 people) also compared adjusted-dose warfarin versus aspirin in high-risk people. [120] It also found that adjusted-dose warfarin significantly reduced the risk of ischaemic stroke or systemic embolism compared with aspirin (RR 0.59, 95% CI 0.40 to 0.86). We also found a report that meta-analysed individual patient data (5 RCTs of primary and secondary prevention; 2633 people at high risk of ischaemic stroke; 76% without previous stroke or TIA). [123] It compared full-dose oral anticoagulation (largely coumarin derivatives) versus aspirin 75 mg to 325 mg, and found that anticoagulation significantly decreased strokes compared with aspirin in people at high risk of ischaemic stroke (ARR 3.3% a year).

Adjusted-dose warfarin versus other antiplatelet treatments/combinations:
One RCT (6706 people with atrial fibrillation plus 1 or more risk factor for stroke; 1020 people [15%] with previous stroke/TIA) assessed whether clopidogrel (75 mg/day) plus aspirin (75–100 mg/day) was non-inferior to adjusted-dose oral anticoagulation therapy (target INR 2–3; the vitamin K antagonist in use in their country) for the prevention of vascular events. [109] The primary composite outcome measure was first occurrence of stroke, non-central nervous system systemic embolism, MI, or vascular death. The RCT was stopped early because of clear evidence of the superiority of oral anticoagulation therapy compared with clopidogrel plus aspirin for the primary outcome (risk: 5.60% a year with clopidogrel plus aspirin *v* 3.93% a year with oral anticoagulation therapy; RR 1.44, 95% CI 1.18 to 1.76; P = 0.0003). [109] However, it did not separately report results for the subgroup of people without previous stroke or TIA.

Oral anticoagulant other than warfarin versus oral anticoagulant plus aspirin or other antiplatelet:
One RCT (157 people at high risk) compared oral fluindione (active dose 5–25 mg) versus fluindione plus aspirin 100 mg. [124] It found no significant difference between fluindione alone and fluindione plus aspirin for a combined outcome of stroke, MI, systemic arterial embolism, vascular death, or haemorrhagic complications after a mean follow-up of 8 months (2/81 [2%] with fluindione *v* 5/76 [7%] with fluindione plus aspirin; P = 0.21). The study was insufficiently powered to detect clinically important differences between treatments. [124]

The second RCT (1209 people with atrial fibrillation) compared the COX-2 inhibitor triflusal, the oral anticoagulant acenocoumarol, or a combination of both. [125] Median follow-up time was 2.7

years. The primary outcome was a composite of vascular death, TIA, and non-fatal stroke or systemic embolism (whichever came first). It stratified randomisation by risk group. In the high-risk group (495 people with prior embolism or mitral valve disease), it compared acenocoumarol versus acenocoumarol plus triflusinal. The RCT found that, in the high-risk group, the primary outcome was significantly lower with combined treatment compared with anticoagulant alone (HR 0.51, 95% CI 0.27 to 0.96; P = 0.03). [125] In the intermediate-risk group (714 people; non-valvular atrial fibrillation, excluding people with prior embolism and mitral stenosis with or without prior embolism) it found no significant difference in the occurrence of primary events between anticoagulant alone and antiplatelet alone (HR 0.72, 95% CI 0.37 to 1.39; P = 0.32). The RCT found that anticoagulant plus antiplatelet significantly reduced the occurrence of the primary outcomes compared with anticoagulant alone or antiplatelet alone (combined therapy *v* antiplatelet alone: HR 0.24, 95% CI 0.09 to 0.64, P = 0.001; combined therapy *v* anticoagulant alone: HR 0.33, 95% CI 0.12 to 0.91, P = 0.02). [125]

Adjusted-dose warfarin versus other anticoagulants:
We found one systematic review, which found that the oral direct thrombin inhibitor ximelagatran was as effective as adjusted-dose warfarin in preventing ischaemic strokes or systemic emboli (RR 1.04, 95% CI 0.77 to 1.40), with a lower risk of major bleeding (RR 0.74, 95% CI 0.56 to 0.96). The review found no significant difference in mortality between adjusted-dose warfarin and ximelagatran (RR 1.04, 95% CI 0.86 to 1.26). [120] Ximelagatran has been voluntarily withdrawn worldwide owing to a potential increased risk of liver damage. [112]

Harms:

Adjusted-dose warfarin versus placebo:
The first systematic review assessed bleeding risk in people both with and without previous stroke or TIA (see harms of anticoagulant, p 25 and antiplatelet, p 27 treatment in people with atrial fibrillation and previous stroke or TIA). [106] The third systematic review found that warfarin was associated with significantly more major bleeding than placebo or aspirin (warfarin *v* placebo: RR 0.45, 95% CI 0.25 to 0.82; warfarin *v* aspirin: RR 0.58, 95% CI 0.35 to 0.97; absolute numbers not reported). [120]

Adjusted-dose warfarin versus low-dose warfarin plus aspirin:
The RCT found similar rates of bleeding in both groups (major haemorrhage: 2.1% a year with adjusted-dose warfarin *v* 2.4% a year with low-intensity fixed-dose warfarin plus aspirin; proportion of people with minor bleeding causing discontinuation of treatment: 0.7% a year with adjusted-dose warfarin *v* 1.2% a year with low-intensity fixed-dose warfarin plus aspirin; statistical analysis between groups not reported). [121]

Adjusted-dose versus low-intensity or minidose warfarin:
One systematic review found that adjusted-dose warfarin significantly reduced the risk of any thrombosis compared with low-intensity warfarin at follow-up (RR 0.50, 95% CI 0.25 to 0.97). It found no significant difference between treatments in the risk of major haemorrhage (RR 1.23, 95% CI 0.67 to 2.27). [122]

Adjusted-dose warfarin versus other antiplatelet treatments/combinations:
The RCT found no significant difference between anticoagulation treatment compared with clopidogrel plus aspirin in rates of severe or fatal haemorrhage (93/3335 [3%] with clopidogrel plus aspirin *v* 101/3371 [3%] with oral anticoagulation therapy; RR 1.10, 95% CI 0.83 to 1.45; P = 0.53) [109]

Oral anticoagulant other than warfarin versus oral anticoagulant plus aspirin or other antiplatelets:
The first RCT found that full-dose anticoagulation (target INR 2.0–2.6) plus aspirin significantly increased haemorrhagic complications compared with aspirin alone (13/76 [17%] with fluindione plus aspirin *v* 2/81 [2.5%] with fluindione alone; P = 0.0021). [124] The second RCT found that the prevalence of severe bleeding in the high-risk group was 2.13% with acenocoumarol and 2.09% in the combination-treatment arm (statistical analysis between groups not reported). [125] In the intermediate group, the RCT reported that the incidence of severe bleeding was 0.35% with antiplatelet, 1.8% with anticoagulant, and 0.95% with antiplatelet plus anticoagulant (statistical analysis between groups not reported). [125]

Adjusted-dose warfarin versus other anticoagulants:
The review gave no information on adverse effects. [120] One RCT identified by the review (3410 people; 76% with no previous stroke or TIA) found that ximelagatran (fixed dose; 36 mg twice daily) significantly reduced any haemorrhage (major plus minor) compared with warfarin (INR 2.0–3.0), but found no significant difference between treatments in rates of major haemorrhage (any haemorrhage: 29.8% a year with warfarin *v* 25.8% a year with ximelagatran; P = 0.007; major haemorrhage: 1.8% a year with warfarin *v* 1.3% a year with ximelagatran; P = 0.23; absolute figures not reported). [110] It found that ximelagatran significantly increased the proportion of people with raised

serum alanine aminotransferase (over 3 times normal level) compared with warfarin (107/1704 [6%] with ximelagatran *v* 14/1703 [1%] with warfarin; P less than 0.0001). Ximelagatran has been voluntarily withdrawn worldwide owing to a potential increased risk of liver damage. [112]

See also harms of anticoagulant and antiplatelet treatment in people with atrial fibrillation in people with previous stroke or TIA, p 25 .

Comment:

We found one systematic review (search date 2005; 5 primary studies, 2 meta-analysis), [118] which was part of the National Institute for Health and Clinical Excellence (NICE) guidelines on atrial fibrillation management (http://guidance.nice.org.uk/CG36), but no meta-analysis was performed. The systematic review for the NICE guideline concluded that anticoagulation with warfarin had a strong beneficial effect in the prevention of strokes and thromboembolism in people with atrial fibrillation compared with placebo, low-intensity or minidose warfarin, or antiplatelet therapy, and that antiplatelet therapy had no additional beneficial effect in the prevention of strokes or thromboembolism in people with atrial fibrillation when added to anticoagulation.

Clinical guide:

The three risk strata (high, moderate, low) used have been identified based on evidence derived from one overview of five RCTs [113] and one subsequent RCT. [121] Most reviews have stratified the effects of treatment in terms of these risk categories. However, one systematic review (search date 1999) that did not stratify for perceived risk has suggested that RCTs may be too heterogeneous to determine the effects of long-term oral anticoagulation compared with placebo among people with non-rheumatic atrial fibrillation. [126]

The review (5 RCTs; 3298 people) found results that conflicted with those of previous reviews. The review also questioned the methods, and highlighted the heterogeneity of, RCTs of oral anticoagulation in people with non-rheumatic atrial fibrillation. [127] People in the RCTs were highly selected (less than 10% [range 3%–40%] of eligible people were randomised); many were excluded after assessments for the absence of contraindications and physician's refusal to enter them into the study. Many of the studies were not double blinded, and in some studies there was poor agreement between raters for "soft" neurological end points. The frequent monitoring of warfarin treatment under trial conditions, as well as the motivation of participants and investigators, were probably more than that seen in usual clinical practice. The review suggested that considerable uncertainty remains about the benefits of long-term anticoagulation in people with non-rheumatic atrial fibrillation.

The review has different inclusion and exclusion criteria to those in previously published reviews, having excluded data from two RCTs and included a trial not included in previous reviews. [121] Unlike previous reviews, the recent systematic review did not stratify people for perceived stroke risk, and identified no significant difference between anticoagulant and placebo with either a fixed-effects model or a random-effects model, which was employed to account for heterogeneity of underlying trials (fixed effects: OR 0.74, 95% CI 0.39 to 1.40 for stroke deaths; OR 0.86, 95% CI 0.16 to 1.17 for vascular deaths; random effects: OR 0.79, 95% CI 0.61 to 1.02 for combined fatal and non-fatal events). [127] The publication of this review has led to debate and uncertainty about the clinical effectiveness of long-term anticoagulation in people with non-rheumatic atrial fibrillation. Decisions to treat should be informed by considering trade-offs between benefits and harms, and each person's treatment preferences. [126] [128] [129] [130] [131] [132]

We found net benefit of anticoagulation for people in atrial fibrillation who had had a TIA or stroke, or who were over 75 years of age and at a high risk of stroke. We found less clear-cut evidence for those aged 65 to 75 years and at high risk, and for those with a moderate risk of stroke (aged over 65 years and not in a high-risk group, or aged less than 65 years with clinical risk factors) or for those at low risk (aged less than 65 years with no other risk factors). The benefits of warfarin in the RCTs may not translate into effectiveness in clinical practice. [127] [133] [134] In the RCTs, most strokes in people randomised to warfarin occurred while they were not in fact taking warfarin, or when they were significantly under-anticoagulated. Analyses of the optimal anticoagulation intensity for stroke prevention in atrial fibrillation found that stroke risk was substantially increased at INR levels below 2. [135] [136]

One systematic review (search date not reported; 410 people) identified three trials comparing the outcomes of people treated with anticoagulants in the community versus the pooled results of the RCTs. [137] The authors confirmed that people who have anticoagulation for atrial fibrillation in actual clinical practice are generally older and have more comorbidities than people enrolled in RCTs. However, both groups had similar rates of stroke and major bleeding. This risk of minor bleeding was higher in the community group, and it was suggested that these people may require more intensive monitoring in routine practice.

OPTION ANTIPLATELET TREATMENT IN PEOPLE WITH ATRIAL FIBRILLATION WITHOUT PREVIOUS STROKE OR TIA WITH HIGH RISK OF STROKE OR TIA

Cardiovascular events

Adjusted-dose aspirin compared with placebo Adjusted-dose aspirin may be no more effective at lowering the risk of all strokes, disabling or fatal, in people with atrial fibrillation and at high risk of stroke (low-quality evidence).

Aspirin compared with adjusted-dose warfarin Aspirin may be less effective at reducing stroke in people at high risk of stroke (low-quality evidence).

Antiplatelet treatments/combinations compared with adjusted-dose warfarin Antiplatelet treatments/combinations are less effective at reducing a composite outcome of first occurrence of stroke, non-central nervous system systemic embolism, MI, or vascular death in people with atrial fibrillation with one or more risk factors for stroke (high-quality evidence).

Oral anticoagulants plus aspirin or other antiplatelets compared with oral anticoagulant other than warfarin Oral anticoagulants plus aspirin or other antiplatelets may be more effective at reducing a composite outcome of vascular death, TIA, and non-fatal stroke in people with atrial fibrillation and at high to intermediate risk of stroke (low-quality evidence).

Low-dose warfarin plus aspirin compared with adjusted-dose warfarin Low-dose warfarin plus aspirin seems less effective at reducing vascular death, disabling stroke, and ischaemic stroke in people with at least one thrombotic risk factor (congestive heart failure or left ventricular fractional shortening 25% or less, previous thromboembolism, systolic blood pressure of greater than 60 mm Hg at study enrolment, or being a women aged over 75 years) at 1.1 years (moderate-quality evidence).

Mortality

Adjusted-dose aspirin compared with placebo Adjusted-dose aspirin may be no more effective at lowering all-cause mortality in people with atrial fibrillation and at high risk of stroke (low-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41 .

Benefits:

Adjusted-dose aspirin versus placebo:
We found one systematic review examining the effect of aspirin in different groups of people, which included people with atrial fibrillation at high risk of stroke (see comment below). [138] However, these largely older data also span high-, medium-, and low-risk groups. The review (search date 2004; 3 RCTs; 1965 people without previous stroke or TIA) compared aspirin (75–325 mg/day or 125 mg once every 2 days) versus placebo or control. It found that, at a mean of 1.3 years' follow-up, aspirin lowered the risks of all stroke, ischaemic stroke, all disabling or fatal stroke, and all-cause mortality, although the differences were not significant (all stroke: OR 0.70, 95% CI 0.47 to 1.07; ischaemic stroke: OR 0.70, 95% CI 0.46 to 1.07; disabling or fatal stroke: OR 0.86, 95% CI 0.50 to 1.49; all-cause mortality: OR 0.75, 95% CI 0.54 to 1.04). It found that aspirin significantly reduced the combination of stroke, MI, or vascular death (OR 0.71, 95% CI 0.51 to 0.97). [138] The review found no significant increase in intracranial haemorrhage or major extracranial haemorrhage between aspirin and placebo or control, but numbers were small with wide confidence intervals (see benefits of antiplatelet treatment in people with low to moderate risk of stroke or TIA, p 34).

Aspirin versus adjusted-dose warfarin:
See benefits of anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 .

Antiplatelet treatments/combinations versus adjusted-dose warfarin:
See benefits of anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 .

Aspirin or other antiplatelet plus oral anticoagulant other than warfarin versus oral anticoagulant other than warfarin:
See benefits of anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 .

Low-dose warfarin plus aspirin versus adjusted-dose warfarin:
See benefits of anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 .

Harms:

Adjusted-dose aspirin versus placebo:
The review found no significant increase in intracranial haemorrhage or major extracranial haemorrhage between aspirin and placebo or control, but numbers were small, with wide confidence intervals (no further data reported). [138]

Aspirin versus adjusted-dose warfarin:
See harms of anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 .

Antiplatelet treatments/combinations versus adjusted-dose warfarin:
See harms of anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 .

Aspirin or other antiplatelet plus oral anticoagulant other than warfarin versus oral anticoagulant other than warfarin:
See harms of anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 .

Low-dose warfarin plus aspirin versus adjusted-dose warfarin:
See harms of anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 .

Comment:

We found one systematic review (search date 2005; 5 primary studies, 2 meta-analysis), [118] which was part of the National Institute for Health and Clinical Excellence (NICE) guidelines on atrial fibrillation management (http://guidance.nice.org.uk/CG36), but no meta-analysis was performed. The review concluded that antiplatelet treatment has a marginally beneficial effect in the prevention of strokes of thromboembolism when compared with placebo in people with atrial fibrillation.

Clinical guide:
See comment on anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 . Aspirin is used in people with atrial fibrillation, and when contraindications exist for anticoagulants. Aspirin reduces stroke and major vascular events in people with non-valvular atrial fibrillation to a similar extent as its effect in other people at high risk (by about 25%). For primary prevention among people with atrial fibrillation and an average stroke rate of 4% a year, 10 strokes would probably be prevented each year for every 1000 people given aspirin. Much of the evidence in favour of aspirin in atrial fibrillation [106] [138] is driven by data from one RCT — the latter trial was composed of two separately randomised cohorts, one consisting of people who could not be randomised to warfarin (aspirin *v* placebo), and one for people who could be randomised to warfarin (in this RCT there was also a warfarin arm). In the first cohort, with respect to stroke and thromboembolism, the relative risk reduction afforded by aspirin was 94% (P less than 0.001), while in the second cohort the comparable relative risk reduction was 8% (P = 0.75). The pooled analysis of events in these two cohorts (with the internal inconsistency between the 2 groups) gives the 42% risk reduction with aspirin (P = 0.02) reported for the whole RCT. [139] As atrial fibrillation commonly co-exists with vascular disease, it is likely that we are seeing an effect of aspirin on vascular disease rather than on the atrial fibrillation *per se*, given that the magnitude of stroke reduction (25%) is similar to that seen with antiplatelet treatment use in high-risk people. [140]

QUESTION **What are the effects of preventive anticoagulant and antiplatelet treatment in people with atrial fibrillation and without previous stroke or TIA and with low to moderate risk of stroke or TIA?**

OPTION **ANTICOAGULANT TREATMENT IN PEOPLE WITH ATRIAL FIBRILLATION WITHOUT PREVIOUS STROKE OR TIA WITH LOW TO MODERATE RISK OF STROKE OR TIA**

Contributed by Gregory YH Lip

Cardiovascular events
Anticoagulants compared with placebo Anticoagulants such as warfarin may be no more effective at reducing strokes in people aged under 65 years with atrial fibrillation but no previous stroke or TIA (low-quality evidence).

Minidose warfarin plus aspirin compared with no anticoagulation Minidose warfarin plus aspirin may be no more effective at reducing stroke or stroke and TIA in people with persistent or permanent atrial fibrillation who are at low to moderate risk of stroke (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41

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Benefits:

Anticoagulants versus placebo:
We found one systematic review [138] and one overview [113] comparing warfarin versus placebo in people with atrial fibrillation and a variety of stroke risks (see comment below). The reviews included the same five RCTs. The first systematic review (search date 1999; 5 RCTs; 2313 people with no previous stroke or TIA; mean age 69 years; 20% aged over 75 years, 45% with hypertension, 15% with diabetes, and 15% with a prior history of MI) did not separately analyse people at low risk of stroke. [138] The overview (2461 people; 15% aged at least 65 years) analysed a subgroup of people under 65 years with atrial fibrillation (but no history of hypertension, stroke, TIA, or diabetes). It found that the annual stroke rate was the same with warfarin or placebo (subgroup analysis among 17% of people on warfarin and 15% on placebo; annual stroke rate for both groups 1%, 95% CI 0.3% to 3.0%). [113]

Minidose warfarin plus aspirin versus no anticoagulation:
We found one RCT (668 people with persistent or permanent atrial fibrillation; low to moderate risk defined as risk of stroke 4% or less) comparing warfarin 1.25 mg plus aspirin 75 mg daily versus no anticoagulation. [141] It found that warfarin plus aspirin reduced stroke and stroke or TIA after about 33 months compared with no anticoagulation, but the decrease was not significant (stroke: 32/334 [10%] with warfarin plus aspirin *v* 41/334 [12%] with no treatment; P = 0.28; stroke or TIA: 11.7% with warfarin plus aspirin *v* 16.5% with no anticoagulation; P = 0.09). [141]

Harms:

Anticoagulants versus placebo:
See harms of anticoagulant treatment in people with atrial fibrillation in people with previous stroke or TIA, p 25 .

Minidose warfarin plus aspirin versus no anticoagulation:
One RCT (688 people) found that low-dose warfarin plus aspirin significantly increased bleeding complications after a mean follow-up of 33 months compared with no treatment (19/334 [6%] with warfarin plus aspirin *v* 4/334 [1%] with no treatment; P = 0.003). [141] There were no deaths from bleeding complications.

Comment:

See comment on anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 . We found one systematic review (search date 2005; 5 primary studies, 2 meta-analysis), [118] which was part of the National Institute for Health and Clinical Excellence (NICE) guidelines on atrial fibrillation management (http://guidance.nice.org.uk/CG36), but no meta-analysis was performed. The review concluded that anticoagulant treatment had a beneficial effect in the prevention of strokes of thromboembolism in people with atrial fibrillation compared with placebo.

OPTION ANTIPLATELET TREATMENT IN PEOPLE WITH ATRIAL FIBRILLATION WITHOUT PREVIOUS STROKE OR TIA WITH LOW TO MODERATE RISK OF STROKE OR TIA

Cardiovascular events
Antiplatelet treatment compared with placebo/no treatment We don't know whether antiplatelet treatments are more effective at reducing strokes in people with atrial fibrillation who are at low risk of stroke (very low-quality evidence).

Minidose warfarin plus aspirin compared with no anticoagulation Minidose warfarin plus aspirin is more effective at reducing stroke or stroke and TIA in people with persistent or permanent atrial fibrillation at low to moderate risk of stroke (moderate-quality evidence).

For GRADE evaluation of interventions for stroke prevention, see table , p 41

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Benefits:

Antiplatelet treatment versus placebo or no treatment:
We found two systematic reviews in people with atrial fibrillation at low risk of stroke, [142] [106] and one subsequent RCT (see comment below). [143] However, in the first review, these largely older data also span high-, medium-, and low-risk groups. The first review (search date 2004; 3 RCTs; 1965 people without previous stroke or TIA) compared aspirin (75–325 mg/day or 125 mg once every 2 days) versus placebo or control. [142] It found that, at a mean of 1.3 years' follow-up, aspirin reduced the risks of all stroke, ischaemic stroke, all disabling or fatal stroke, and all-cause mortality, although the reductions were not significant (all stroke: OR 0.70, 95% CI 0.47 to 1.07; ischaemic stroke: OR 0.70, 95% CI 0.46 to 1.07; disabling or fatal stroke: OR 0.86, 95% CI 0.50 to 1.49; all-cause mortality: OR 0.75, 95% CI 0.54 to 1.04). Aspirin significantly reduced the combination of stroke, MI, or vascular death (OR 0.71, 95% CI 0.51 to 0.97). The review found no significant increase in intracranial haemorrhage or major extracranial haemorrhage between aspirin and placebo or control, but numbers were small with wide confidence intervals (see benefits of antiplatelet

treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 32).

The second systematic review (search date 1999; 16 RCTs; 9874 people) included three RCTs of primary prevention. [106] The average rate of stroke among people taking placebo was 5.2% a year. The review found that antiplatelet treatment significantly reduced the risk of stroke compared with placebo after a mean follow-up of 1.2 to 2.3 years (6 RCTs; RR 0.78, 95% CI 0.62 to 0.98). The subsequent RCT (871 people; low-risk atrial fibrillation group in Japan) compared aspirin (150–200 mg/day) versus no treatment. [143] The primary end points were cardiovascular death, symptomatic brain infarction, or TIA. The trial was discontinued early as there were 27 primary end point events with aspirin (3.1% a year, 95% CI 2.1% a year to 4.6% a year) compared with 23 primary end point events with no treatment (2.4% a year, 95% CI 1.5% a year to 3.5% a year) suggesting a low possibility of aspirin superiority for the primary end point. [143]

Minidose warfarin plus aspirin versus no anticoagulation:
See benefits of anticoagulant treatment in people with low to moderate risk of stroke or TIA, p 33 .

Harms:

Antiplatelet treatment versus placebo:
The meta-analysis [106] reported only seven cases of intracranial bleeding (4 people taking aspirin and 3 people taking placebo; rate for aspirin, 0.2% a year) and 28 major extracranial haemorrhages (13 people taking aspirin and 15 people taking placebo) in the six trials. In the subsequent RCT in Japan which was terminated early, there was a marginally increased bleeding rate with aspirin (major bleeding: 7 people [1.6%] with aspirin *v* 2 people [0.4%] with no treatment; P = 0.101), and the RCT suggested that for prevention of stroke in people with lone atrial fibrillation, aspirin at 150 mg to 200 mg daily does not seem either effective or safe. [143]

Minidose warfarin plus aspirin versus no anticoagulation:
See harms of anticoagulant treatment in people with low to moderate risk of stroke or TIA, p 33 .

Comment:

See comment on anticoagulant treatment in people with atrial fibrillation without previous stroke or TIA with high risk of stroke or TIA, p 28 . We found one systematic review (search date 2005; 5 primary studies, 2 meta-analysis), [118] which was part of the National Institute for Health and Clinical Excellence (NICE) guidelines on atrial fibrillation management (http://guidance.nice.org.uk/CG36), but no meta-analysis was performed. The review concluded that antiplatelet therapy has a marginal beneficial effect in the prevention of strokes or thromboembolism in people with atrial fibrillation when compared with placebo, and should only be used where warfarin is not appropriate.

Clinical guide:
The value of aspirin (and the dose used) for atrial fibrillation thromboprophylaxis is subject to some controversy. The stroke relative risk reduction of aspirin in people with atrial fibrillation is similar to that in a general population and the reduction of vascular events for antiplatelet therapy versus control in "high-risk" patients with vascular disease. In trials specifically of people with atrial fibrillation comparing aspirin with placebo, the one trial [144] testing aspirin 75 mg daily did not show a significant benefit for the prevention of stroke in people with permanent atrial fibrillation. Similarly, in another trial, [145] aspirin (most at 325 mg/day) was given in a non-randomised manner, without significant benefit. However, in another RCT [146] using aspirin 325 mg, aspirin was reported to result in a significant 42% reduction in stroke, but was best for those aged under 75 years and did not prevent severe or recurrent strokes, with some internal inconsistency within the trial data (discussed above). The subsequent RCT conducted in Japan reported above found no benefit of aspirin compared with no aspirin in low-risk people. [143] In general, aspirin should be reserved for those patients with atrial fibrillation who cannot take warfarin.

GLOSSARY

Conventional carotid endarterectomy This is more commonly employed and involves a longitudinal arteriotomy of the carotid artery.
Eversion carotid endarterectomy This involves a transverse arteriotomy and reimplantation of the carotid artery.
International normalised ratio (INR) A value derived from a standardised laboratory test that measures the effect of an anticoagulant such as warfarin. The laboratory materials used in the test are calibrated against internationally accepted standard reference preparations, so that variability between laboratories and different reagents is minimised. Normal blood has an INR of 1. Therapeutic anticoagulation often aims to achieve an INR value of 2.0–3.5.
People at high risk of stroke People of any age with a previous transient ischaemic attack or stroke, or a history of rheumatic vascular disease, coronary artery disease, congestive heart failure, and impaired left ventricular function or echocardiography; and people aged 75 years and over with hypertension, diabetes, or vascular disease.
Adjusted-dose warfarin Anticoagulation with warfarin, aiming for a specific target INR range.
Conventional-intensity warfarin Warfarin dose, which is adjusted to a target INR of about 2.0–3.0.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-dose warfarin/minidose warfarin Anticoagulation with a fixed low dose of warfarin (e.g., 1.25 mg/day) without dose adjustment for INR.
Low-intensity warfarin Warfarin dose which is adjusted to a target INR of (usually) less than 1.5.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
People at moderate risk of stroke People aged over 65 years not in the high-risk group; and people aged under 75 years with clinical risk factors, including diabetes, hypertension, and vascular disease (peripheral arterial disease and ischaemic heart disease).
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Alternative antiplatelet regimens to aspirin One systematic review added, which found that aspirin plus dipyridamole significantly reduced incidence of stroke and serious vascular events compared with aspirin alone in people with previous stroke or TIA. [42] One RCT comparing aspirin plus dipyridamole versus clopidogrel added, which found no significant difference between the two groups in recurrent stroke and the composite outcome of stroke, MI, and vascular death. [43] Categorisation unchanged (Beneficial).
Anticoagulation in people in sinus rhythm One already included systematic review updated; [64] one RCT added, which found no significant difference between medium-intensity oral anticoagulants and aspirin on stroke, vascular death, and a composite outcome of vascular death, non-fatal stroke, non-fatal MI, and non-fatal bleeding complications. [65] It found that anticoagulants were associated with a significantly increased risk of major bleeding complications compared with aspirin. Categorisation unchanged (Likely to be ineffective or harmful).
Blood pressure reduction One new RCT added, comparing telmisartan versus placebo in people with a history of ischaemic stroke, which found no significant difference between telmisartan and placebo in recurrent stroke, all-cause mortality, or the composite outcome of cardiovascular events. [16] Categorisation unchanged (Beneficial).
Carotid percutaneous transluminal angioplasty (PTA) plus stenting Two systematic reviews and one RCT added, which showed no significant difference between carotid PTA plus stenting versus endarterectomy. [98] [99] [100] Categorisation unchanged (Unknown effectiveness).
Cholesterol reduction One systematic review added, which found that statins significantly reduced mortality, all-cause stroke, and ischaemic stroke compared with placebo. [27] One new RCT added, which found that atorvastatin reduced the risk of stroke and other major cardiovascular events in people with carotid atherosclerosis. [28] Categorisation unchanged (Beneficial).
Eversion versus conventional carotid endarterectomy One RCT comparing eversion carotid endarterectomy versus conventional techniques added, which found that conventional techniques were associated with a significant increase in central neurological complications in the 7 days after surgery compared with eversion carotid endarterectomy, but reported no significant difference in long-term survival between the two techniques. [93] Categorisation unchanged (Unknown effectiveness).
One systematic review added, which found that antiplatelet therapy for acute ischaemic stroke reduced the incidence of recurrent ischaemic stroke from 21 days' to 6 months' follow-up. [11] Categorisation unchanged (Beneficial).
Vitamin B supplements (including folate) Two systematic reviews and one RCT comparing folate versus placebo added, which all found no significant difference in rates of stroke between folate and placebo. Categorisation changed from Unknown effectiveness to Unlikely to be beneficial.

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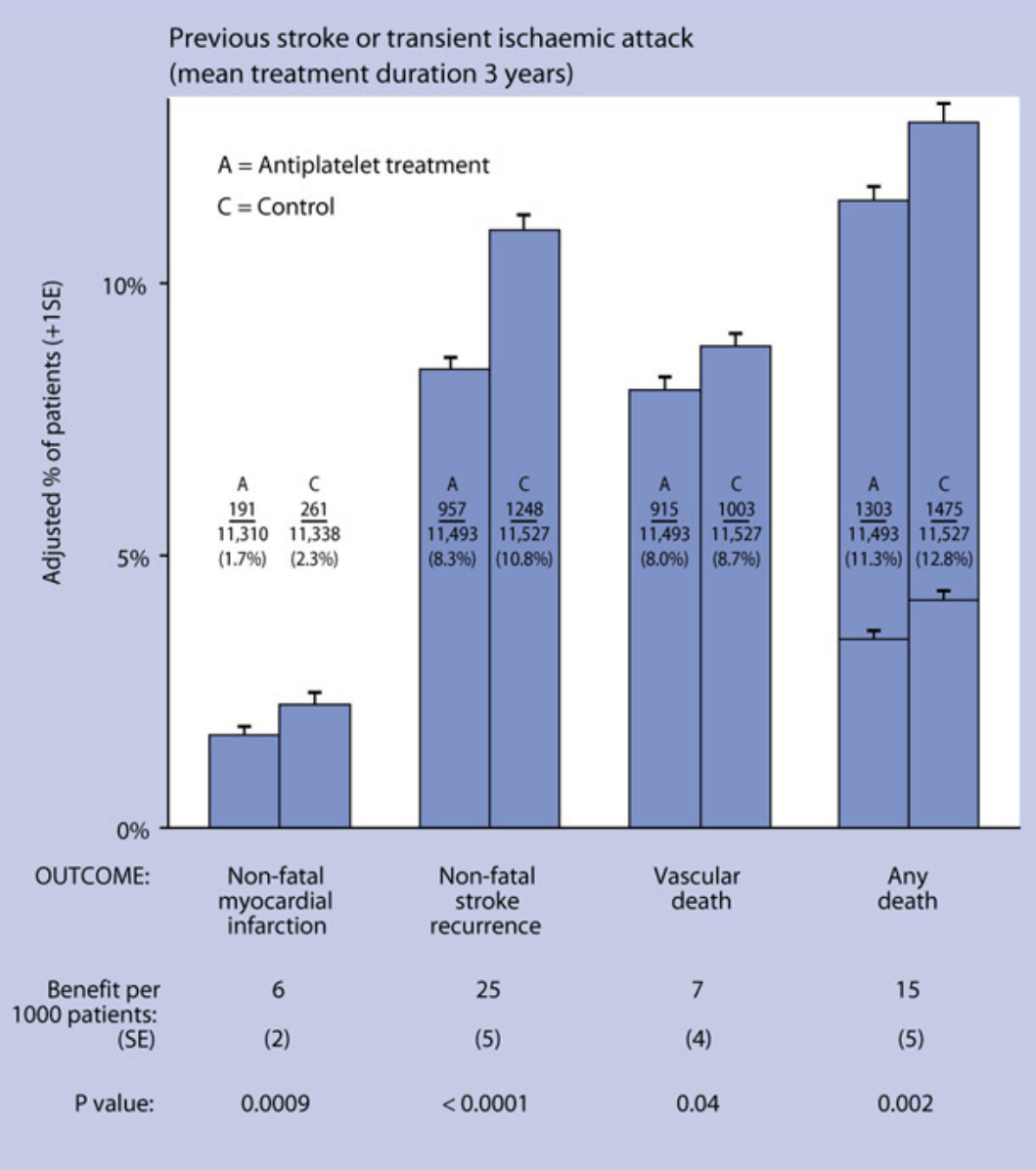

FIGURE 1 **Absolute effects of antiplatelet treatment on various outcomes in 21 trials in people with a prior (presumed ischaemic) stroke or TIA. The columns show the absolute risks over 3 years for each outcome. The error bars represent standard deviations. In the "any death" column, non-vascular deaths are represented by lower horizontal lines. Adapted with permission.**

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TABLE **GRADE evaluation of interventions for stroke prevention**

Important outcomes			Cardiovascular (CV) events, quality of life, mortality, adverse effects						
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of preventive non-surgical interventions in people with previous stroke or TIA?									
33 (61,311) [140] [11]	CV events	Antiplatelet treatment *v* placebo/no antiplatelet treatment	4	0	0	0	0	High	
7 (15,527) [14]	CV events	Any treatment to reduce blood pressure *v* placebo/no treatment	4	0	0	0	0	High	
7 (15,527) [14]	Mortality	Any treatment to reduce blood pressure *v* placebo/no treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (3574) [14]	CV events	ACE inhibitors *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (6216) [14]	CV events	Diuretics *v* placebo/no treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (3544) [14]	CV events	Diuretic plus ACE inhibitor *v* placebo/no treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (2193) [14]	CV events	Beta-blockers *v* placebo/no treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (20,332) [16]	CV events	Angiotensin receptor blockers *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome
1 (20,332) [16]	Mortality	Angiotensin receptor blockers versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome
47 (at least 121,285) [26] [29] [27] [28]	CV events	Statins *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
42 (121,285) [29] [27]	Mortality	Statins *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
14 (33,140) [4] [31] [32]	CV events	Non-statin cholesterol-lowering treatments *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
1 (532) [30]	Mortality	Non-statin cholesterol-lowering treatments *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
9 (at least 24,785 people) [7] [38] [39]	CV events	Thienopyridines (clopidogrel and ticlopidine) *v* aspirin	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
1 (15,603) [40]	CV events	Clopidogrel plus aspirin *v* aspirin alone	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
1 (7599) [41]	CV events	Clopidogrel plus aspirin *v* clopidogrel alone	4	0	0	0	0	High	
6 (7648) [42]	CV events	Dipyridamole plus aspirin *v* aspirin alone	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome
1 (20,332) [43]	CV events	Dipyridamole plus aspirin *v* clopidogrel	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome

Important outcomes			Cardiovascular (CV) events, quality of life, mortality, adverse effects						
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
At least 2 RCTs (at least 2944 people) [140] [44] [45]	CV events	Triflusal *v* aspirin	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome
At least 16 RCTs (at least 142,341 people) [56] [57]	CV events	Different treatments to reduce blood pressure *v* each other	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
5 (17,952) [56]	Mortality	Different treatments to reduce blood pressure *v* each other	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
At least 1 RCT (at least 2849 people) [140] [58]	CV events	High-dose *v* low-dose aspirin	4	–2	+1	–2	0	Very low	Quality points deducted for incomplete reporting of results and for short follow-up in one RCT. Consistency point added for dose effect. Directness points deducted for inclusion of people without a previous ischaemic stroke or TIA and composite outcome
5 (575) [63]	CV events	Anticoagulants *v* placebo/no treatment	4	–1	0	–1	0	Low	Quality point deducted for methodological weaknesses. Directness point deducted for inclusion of people with primary haemorrhagic stroke
At least 10 RCTs (at least 1333) [63]	Mortality	Anticoagulants *v* placebo/no treatment	4	–1	0	–1	0	Low	Quality point deducted for methodological weaknesses. Directness point deducted for inclusion of people with primary haemorrhagic stroke
At least 1314 people [63]	Adverse effects	Anticoagulants *v* placebo/no treatment	4	0	0	0	+1	High	Effect-size point added for RR greater than 2
4 (2760) [64] [65]	CV events	Anticoagulation *v* antiplatelet treatment	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome
1 (1068) [65]	Mortality	Anticoagulation *v* antiplatelet treatment	4	0	0	–1	0	Moderate	Directness point deducted for composite outcome
14 (at least 22,400) [67] [68] [69]	CV events	Vitamin B supplements (including folate) *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting. Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
13 (at least 17,400) [67] [69]	Mortality	Vitamin B supplements (including folate) *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting. Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
1 (3680) [70]	CV events	Different vitamin B supplement regimens *v* each other	4	0	0	0	0	High	
What are the effects of preventive surgical interventions in people with previous stroke or TIA?									
3 (1746) [71] [72]	CV events	Carotid endarterectomy in people with less than 30% symptomatic carotid artery stenosis *v* no endarterectomy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (1429) [71]	CV events	Carotid endarterectomy in people with moderate (30%–49%) symptomatic carotid artery stenosis *v* no endarterectomy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes		Cardiovascular (CV) events, quality of life, mortality, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
3 (1549) [71] [72]	CV events	Carotid endarterectomy in people with moderately severe (50%–69%) symptomatic carotid artery stenosis *v* no endarterectomy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (1095) [71] [72]	CV events	Carotid endarterectomy in people with severe (greater than 70%) symptomatic carotid artery stenosis *v* no endarterectomy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (262) [71] [73] [74] [75] [76]	CV events	Carotid endarterectomy in people with symptomatic near occlusion of the carotid artery *v* no endarterectomy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (5223) [88]	CV events	Carotid endarterectomy in people with symptomatic near occlusion of the carotid artery *v* medical care	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about benefit
5 (2564) [92] [93]	CV events	Eversion carotid endarterectomy *v* conventional carotid endarterectomy	4	–1	–1	–1	0	Very low	Quality point deducted short follow-up. Consistency point deducted for heterogeneity among studies. Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
1 (201) [93]	Mortality	Eversion carotid endarterectomy *v* conventional carotid endarterectomy	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
At least 6 RCTs (at least 2758 people) [92] [93]	Adverse effects	Eversion carotid endarterectomy *v* conventional carotid endarterectomy	4	–1	–1	–1	0	Very low	Quality point deducted for short follow-up. Consistency point deducted for heterogeneity among studies. Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
At least 5 RCTs (at least 1157 people) [95] [94]	CV events	Carotid PTA *v* carotid endarterectomy	4	–2	0	0	0	Low	Quality points deducted for uncertainty about precision of results and short follow-up
At least 5 RCTs (at least 1157 people) [95] [94]	Mortality	Carotid PTA *v* carotid endarterectomy	4	–2	0	0	0	Low	Quality points deducted for uncertainty about precision of results and short follow-up
10 (at least 3472) [98] [99] [100]	CV events	Carotid angioplasty plus stenting *v* carotid endarterectomy	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
10 (at least 3472) [98] [99] [100]	Mortality	Carotid angioplasty plus stenting *v* carotid endarterectomy	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of people without a previous ischaemic stroke or TIA
What are the effects of preventive anticoagulant and antiplatelet treatments in people with atrial fibrillation and previous stroke or TIA?									
1 (439) [105]	CV events	Adjusted-dose warfarin *v* placebo	4	0	0	0	0	High	
1 (115) [107]	CV events	Conventional-intensity warfarin *v* low-intensity or minidose warfarin	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and short follow-up. Directness point deducted for population differences between groups

Important outcomes		Cardiovascular (CV) events, quality of life, mortality, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (6722) [106] [109]	CV events	Conventional-intensity warfarin *v* other antiplatelet treatments/combinations	4	0	–1	–2	0	Very low	Consistency point deducted for conflicting results. Directness points deducted for composite outcome and for not analysing results for population of interest
2 (4744) [110] [111]	CV events	Conventional-intensity warfarin *v* other anticoagulants	4	–1	0	–1	0	Low	Quality point deducted for open label RCT. Directness point deducted for including people with different disease severities
1 (782) [117]	CV events	Aspirin *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (782) [117]	Mortality	Aspirin *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of preventive anticoagulant and antiplatelet treatment in people with atrial fibrillation and without previous stroke or TIA and with high risk of stroke or TIA?									
6 (2900) [106]	CV events	Adjusted-dose warfarin *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (1044) [121]	CV events	Adjusted-dose*v* low-dose warfarin plus aspirin	4	–1	0	0	0	Moderate	Quality point deducted for short follow-up
17 (at least 14,423 people) [120] [122]	CV events	Adjusted-dose*v* low-intensity or minidose warfarin	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
At least 13 RCTs (at least 14,423 people) [106] [120] [123]	CV events	Adjusted-dose warfarin *v* aspirin	4	–2	0	0	0	Low	Quality point deducted for incomplete reporting of results and lack of blinding
1 (6706) [109]	CV events	Adjusted-dose warfarin *v* other antiplatelet treatments/combinations	4	0	0	0	0	High	
3 (1266) [124] [125]	CV events	Oral anticoagulant other than warfarin *v* oral anticoagulant plus aspirin or other antiplatelets	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 SR [112]	CV events	Adjusted-dose warfarin *v* other anticoagulants	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 SR [112]	Mortality	Adjusted-dose warfarin *v* other anticoagulants	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (1965) [138]	CV events	Adjusted-dose aspirin *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of other risk groups
3 (1965) [138]	CV events	Adjusted-dose aspirin *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of other risk groups
What are the effects of preventive anticoagulant and antiplatelet treatment in people with atrial fibrillation and without previous stroke or TIA and with low to moderate risk of stroke or TIA?									
1 (2461) [113]	CV events	Anticoagulants *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for subgroup analysis of overview

Important outcomes		Cardiovascular (CV) events, quality of life, mortality, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (668) [141]	CV events	Minidose warfarin plus aspirin *v* no anticoagulation	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of other risk groups
At least 3 RCTs (at least 1965 people) [142] [106] [143]	CV events	Antiplatelet treatment *v* placebo/no treatment	4	–2	–1	–2	0	Very low	Quality points deducted for incomplete reporting of results and short follow-up. Consistency point deducted for conflicting results. Directness points deducted for inclusion of other risk groups and for composite outcome

Type of evidence: 4 = RCT; 2 = Observational Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio