

**RIJKSINSTITUUT VOOR ZIEKTE- EN  
INVALIDITEITSVERZEKERING**  
**DIENST VOOR GENEESKUNDIGE VERZORGING**  
COMITÉ VOOR DE EVALUATIE VAN DE  
MEDISCHE PRAKTIJK INZAKE GENEESMIDDELEN

**DOELMATIGE MEDICAMENTEUZE AANPAK BIJ PREVENTIE  
EN BIJ BEHANDELING VAN CEREBROVASCULAIRE  
PATHOLOGIEËN IN DE EERSTELIJNSGEZONDHEIDSZORG**

Systematisch onderzoek naar  
de gegevens in de  
wetenschappelijke literatuur:  
syntheserapport

**Consensusvergadering**

10 mei 2012  
AUDITORIUM LIPPENS (KONINKLIJKE BIBLIOTHEEK)  
BRUSSEL

Dit literatuuronderzoek is uitgevoerd door vzw Farmaka asbl en werd opgevolgd door een leescommissie.

## Onderzoekers

Dominique Boudry MD, *vzw Farmaka asbl*  
Hera Decat MD, *vzw Farmaka asbl*  
Griet Goesaert MD, *vzw Farmaka asbl*  
Thérèse Leroy Lic., *vzw Farmaka asbl*  
Joachim Vandenhoven MD, *vzw Farmaka asbl*  
Gerben Vandermeiren MD, *vzw Farmaka asbl*

## Supervisie

Prof. Dr. Dirk Avonts, Vakgroep Huisartsgeneeskunde en  
Eerstelijnsgezondheidszorg, Universiteit Gent

## Leescommissie

Prof. Dr. Em. Marc Bogaert, Heymans Instituut voor Farmacologie, Universiteit Gent  
en *Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI)*  
Dr. Dimitri Hemelsoet, *Dienst Neurologie, UZ Gent*  
Dr. Geert Vanhooren, *Dienst Neurologie, AZ Sint-Jan Brugge*

## Secretariaat en informatica

Stijn Dumon, *vzw Farmaka asbl*  
Tessa Gilliet, *vzw Farmaka asbl*

## Vertaling

Dynamics Translations  
Sophie Vanderdonck

## INHOUDSOPGAVE

<b>1. METHODOLOGIE .....</b>	<b>1</b>
1.1. Inleiding en vraagstelling .....	1
1.2. Selectieprocedure .....	5
1.3. Zoekstrategie .....	6
1.4. Beoordeling van de kwaliteit van de beschikbare evidence .....	8
1.5. Samenvatting van de studieresultaten .....	11
1.6. Lijst van gebruikte afkortingen .....	12
<b>2. KRITISCHE BESCHOUWINGEN VAN HET LEESCOMITÉ EN DE LITERATUURGROEP .....</b>	<b>13</b>
<b>3. SAMENVATTING VAN DE RICHTLIJNEN .....</b>	<b>17</b>
3.1. Criteria for guideline selection .....	17
3.2. Atrial Fibrillation .....	19
3.2.1. Levels of evidence / grades of recommendation .....	19
3.2.2. Included populations – risk stratification .....	21
3.2.3. Recommendations .....	22
3.3. Secondary prevention of stroke .....	24
3.3.1. Levels of evidence / grades of recommendation .....	24
3.3.2. Definitions and patients covered .....	27
3.3.3. Recommendations .....	28
3.4. Carotid artery stenosis .....	32
3.4.1. Levels of evidence / grades of recommendation .....	32
3.4.2. Definitions .....	34
3.4.3. Recommendations .....	34
3.5. Conclusions from guidelines .....	36
3.5.1. Atrial fibrillation .....	36
3.5.2. Secondary prevention stroke .....	36
3.5.3. Carotid artery stenosis .....	36
<b>4. CARDIOVASCULAIRE RISICOREDUCTIE NA CVA/TIA BIJ PERSONEN ZONDER VOORKAMERFIBRILLATIE .....</b>	<b>37</b>
<b>4. SAMENVATTING VAN DE RESULTATEN: RISICOREDUCTIE NA CVA/TIA BIJ PERSONEN ZONDER VOORKAMERFIBRILLATIE .....</b>	<b>39</b>

<b>4.1. Anti-aggregantia na CVA/TIA bij personen zonder voorkamerfibrillatie .....</b>	<b>39</b>
4.1.1. Anti-aggregantia versus placebo/controle .....	39
4.1.2. Laaggedoseerd acetylsalicylzuur vs. placebo .....	40
4.1.3. Anti-aggregantia onderling .....	41
4.1.3.1. Clopidogrel of ticlopidine versus acetylsalicylzuur .....	41
4.1.3.2. Clopidogrel vs. acetylsalicylzuur .....	42
4.1.3.3. Clopidogrel plus acetylsalicylzuur vs. clopidogrel .....	43
4.1.3.4. Dipyridamol plus acetylsalicylzuur vs. acetylsalicylzuur .....	44
4.1.3.5. Dipyridamol plus acetylsalicylzuur vs. clopidogrel .....	45
4.1.3.6. Clopidogrel vs. ticlopidine .....	46
4.1.4. Dosisvergelijkingen: hoge dosis vs. lage dosis acetylsalicylzuur .....	47
<b>4.2. Orale anticoagulantia na CVA/TIA bij personen zonder voorkamerfibrillatie .....</b>	<b>48</b>
4.2.1. Orale anticoagulantia versus placebo of geen behandeling .....	48
4.2.2. Orale anticoagulantia vs. acetylsalicylzuur .....	49
<b>4.3. Antihypertensiva na CVA/TIA bij personen zonder voorkamerfibrillatie .....</b>	<b>50</b>
4.3.1. Antihypertensiva versus placebo .....	50
4.3.1.1. Antihypertensiva als groep versus placebo .....	50
4.3.1.2. ACE-inhibitoren vs. placebo .....	51
4.3.1.3. Diuretica vs. placebo .....	53
4.3.1.4. $\beta$ -blokkers vs. placebo .....	54
4.3.1.5. Sartanen vs. placebo .....	55
4.3.2. Antihypertensiva onderling .....	56
<b>4.4. Cholesterolverlaging na CVA/TIA bij personen zonder voorkamerfibrillatie .....</b>	<b>57</b>
4.4.1. Statines vs. placebo .....	57
 <b>5. HEELKUNDE BOVENOP MEDICAMENTEUZE BEHANDELING VS. MEDICAMENTEUZE BEHANDELING ALLEEN .....</b>	 <b>59</b>
 <b>5. HEELKUNDE BOVENOP MEDICAMENTEUZE BEHANDELING VS. MEDICAMENTEUZE BEHANDELING ALLEEN .....</b>	 <b>61</b>
<b>5.1. Carotis endarterectomie + medicatie versus medicatie alleen bij asymptomatische carotisstenose .....</b>	<b>61</b>
<b>5.2. Carotis endarterectomie + medicatie versus medicatie alleen bij symptomatische carotisstenose .....</b>	<b>62</b>
<b>5.3. Extracraniële-intracraniële bypass + medicatie versus medicatie alleen bij symptomatische carotisocclusie .....</b>	<b>63</b>
<b>5.4. Endovasculaire aanpak + medicatie versus medicatie alleen bij (a)symptomatische carotisstenose .....</b>	<b>64</b>
 <b>6. CARDIOVASCULAIRE RISICOREDUCTIE NA CVA/TIA BIJ PERSONEN MET VOORKAMERFIBRILLATIE .....</b>	 <b>65</b>

## **6. SAMENVATTING VAN DE RESULTATEN: RISICOREDUCTIE NA CVA/TIA BIJ PERSONEN MET VOORKAMERFIBRILLATIE ..... 67**

### **6.1. Orale anticoagulantia na CVA/TIA bij personen met voorkamerfibrillatie..... 67**

6.1.1. Orale anticoagulantia in aangepaste dosis vs. placebo ..... 67

6.1.2. Warfarine in standaarddosis vs. low-intensity of minidosis warfarine ..... 68

6.1.3. Orale anticoagulantia vs anti-aggregantia..... 69

### **6.2. Anti-aggregantia na CVA/TIA bij personen met voorkamerfibrillatie ..... 70**

## **7. CARDIOVASCULAIRE RISICOREDUCTIE BIJ PERSONEN MET VOORKAMERFIBRILLATIE ZONDER VOORGESCHIEDENIS VAN CVA/TIA..... 71**

## **7. SAMENVATTING VAN DE RESULTATEN: RISICOREDUCTIE BIJ PERSONEN MET VOORKAMERFIBRILLATIE ZONDER VOORGESCHIEDENIS VAN CVA/TIA ..... 73**

### **7.1. Risicoreductie bij personen met voorkamerfibrillatie met hoog risico op CVA/TIA..... 73**

7.1.1. Orale anticoagulantia bij personen met voorkamerfibrillatie met hoog risico op CVA/TIA..... 73

7.1.1.1. Warfarine in aangepaste dosis vs. lage dosis warfarine plus ASA..... 73

7.1.1.2. Warfarine in standaarddosis vs. low-intensity of minidosis warfarine ..... 74

7.1.1.2.1. Warfarine in standaarddosis vs. low-intensity of minidosis warfarine ..... 74

7.1.1.2.2. Warfarine in aangepaste dosis lower target INR (1.5-2.0) vs. standard target INR (2.0-3.0) bij hoogbejaarde patiënten (30% high risk en 70% moderate) ..... 75

7.1.1.3 Warfarine in standaarddosis vs. antiaggregantia/associaties..... 76

7.1.1.4. Apixaban vs. acetylsalicylzuur..... 77

7.1.1.5. Apixaban vs. warfarine ..... 78

7.1.1.6. Dabigatran vs. warfarine ..... 79

7.1.1.6.1. Dabigatran 2x110mg/d vs warfarine ..... 79

7.1.1.6.2. Dabigatran 2x150mg/d vs warfarine ..... 80

7.1.1.7. Rivaroxaban vs. warfarine ..... 81

7.1.1.8. Dosisvergelijkingen ..... 82

7.1.1.8.1 Dabigatran 2x150mg/d vs dabigatran 2x110mg/d ..... 82

7.1.2. Anti-aggregantia bij personen met voorkamerfibrillatie met hoog risico op CVA/TIA ..... 83

7.1.2.1. Acetylsalicylzuur + clopidogrel vs. acetylsalicylzuur ..... 83

### **7.2. RISICOREDUCTIE BIJ PERSONEN MET VOORKAMERFIBRILLATIE MET LAAG TOT MATIG RISICO OP CVA/TIA ..... 84**

#### **7.2.1. Orale anticoagulantia bij personen met voorkamerfibrillatie met laag tot matig risico op CVA/TIA..... 84**

7.2.1.1. Orale anticoagulantia vs. placebo ..... 84

7.2.1.2. Warfarine in aangepaste dosis vs. acetylsalicylzuur ..... 85

7.2.1.3. Lage dosis warfarine plus acetylsalicylzuur vs. geen anticoagulantia ..... 86

#### **7.2.2. Anti-aggregantia bij personen met voorkamerfibrillatie met laag tot matig risico van CVA/TIA..... 87**

7.2.2.1. Anti-aggregantia vs. placebo of geen behandeling ..... 87

<b>8. ONGEWENSTE EFFECTEN.....</b>	<b>89</b>
8.1. Belangrijkste ongewenste effecten vitamine K-antagonisten .....	89
8.2. Ongewenste effecten apixaban.....	90
8.3. Ongewenste effecten dabigatran .....	91
8.4. Ongewenste effecten rivaroxaban.....	93
<b>REFERENTIELIJST GEÏNCLUDEERDE STUDIES.....</b>	<b>95</b>
<b>BIJLAGE 1 CLINICAL EVIDENCE .....</b>	<b>105</b>

# 1. Methodologie

## 1.1. Inleiding en vraagstelling

Dit literatuuronderzoek is uitgevoerd in voorbereiding op de consensusvergadering over “De doelmatige medicamenteuze behandeling bij preventie en bij behandeling van cerebrovasculaire pathologieën in de eerstelijnsgezondheidszorg”.

De onderzoeksvragen zijn als volgt geformuleerd door het organiserend comité van het RIZIV:
---------------------------------------------------------------------------------------------

### 1. Spoedgeval: acuut CVA of TIA

- 1.1. Welke zijn nuttige interventies en welke zijn schadelijk in de aanvangsfase van een TIA/CVA?
- 1.2. Een arts oproepen of een ziekenwagen?
- 1.3. Wat doe je beter niet voor ziekenhuisopname?

### 2. Voorkamerfibrillatie en trombo-embolische preventie (geen anti-aritmische behandeling)

- 2.1. Welke risico-evaluatiescore(s) is (zijn) nuttig?
- 2.2. Wat is de (vergelijkende) doeltreffendheid en veiligheid van de bloedplaatjesaggregatieremmers?
- 2.3. Wat is de (vergelijkende) doeltreffendheid en veiligheid van anti-vitamine K behandelingen?
- 2.4. Wat is de (vergelijkende) doeltreffendheid en veiligheid van de nieuwe orale anticoagulantia?
- 2.5. Welke preventieve therapeutische strategie wordt best aanbevolen?
- 2.6. Zijn de gevalideerde interventies dezelfde na een ischemische CVA/TIA?
- 2.7. Zijn de gevalideerde interventies dezelfde na een hemorragische CVA?

### 3. Gedocumenteerde carotisstenose

- 3.1. Asymptomatisch (geen CVA, noch TIA)
  - Welke zijn de argumenten om te kiezen voor een louter medicamenteuze behandeling of eerder een chirurgische (+ medicamenteuze) behandeling?
  - Bestaan er in die indicatie bijzondere aandachtspunten voor de medicamenteuze behandeling versus de klassieke primaire cardiovasculaire preventie?
- 3.2. Symptomatisch (na een CVA of TIA)
  - Welke zijn de argumenten om te kiezen voor een louter medicamenteuze behandeling of eerder een chirurgische (+ medicamenteuze) behandeling?
  - Bestaan er in die indicatie bijzondere aandachtspunten voor de medicamenteuze behandeling versus de klassieke secundaire (post CVA) preventie, zoals beschreven in punt 4?

### 4. Na een CVA of TIA

- 4.1. Bloedplaatjesaggregatieremmers (buiten VKF)
  - Welke zijn doeltreffende behandelingen met aggregatieremmers na een CVA of TIA en zijn ze veilig?
  - Welke zijn aan te bevelen of te vermijden combinaties van aggregatieremmers onderling of met andere geneesmiddelen (in het bijzonder anticoagulantia)?
  - Wat is hun vergelijkbare doeltreffendheid en veiligheid?

#### 4.2. Anticoagulantia (buiten VKF)

- Wat is de doeltreffendheid en de veiligheid van de anti-vitamine K in de onderhoudsbehandeling na een CVA/TIA?
- Wat is de doeltreffendheid en de veiligheid van de nieuwe orale anticoagulantia in de onderhoudsbehandeling na een CVA/TIA?

#### 4.3. Andere behandelingen

- Welke andere geneesmiddelen dan de bloedplaatjesaggregatieremmers en anticoagulantia zijn doeltreffend na een CVA/TIA (statines, antihypertensiva)? Wat is hun veiligheid?

### Onderzoekspopulaties

- Cardiovasculaire risicoreductie na CVA/TIA bij personen zonder voorkamerfibrillatie
- Cardiovasculaire risicoreductie na CVA/TIA bij personen met voorkamerfibrillatie
- Cardiovasculaire risicoreductie bij personen met voorkamerfibrillatie zonder voorgeschiedenis van CVA/TIA

### Eindpunten

- CVA, TIA, perifere embolie
- hemorragisch CVA
- bloedingen: mineur, majeur, fataal, niet-fataal,...
- AMI en andere cardiale eindpunten
- samengestelde CV eindpunten
- mortaliteit: cardiovasculair, totaal
- QoL (levenskwaliteit)
- andere ongewenste effecten behalve bloeding

### Studiecriteria

- Design:
  - o Werkzaamheid: RCT
  - o Minstens single blind
  - o Veiligheid: handboek Meyler's Side Effects of Drugs, Fifteenth Edition (voor de meeste producten hebben we een beroep gedaan op het Gecommentarieerd Geneesmiddelenrepertorium van het BCFI, dat zich o.a. ook baseert op Meyler's)
- Studieduur: minstens 6 maanden behandelingsduur
- Minimum aantal deelnemers per arm: minimum 40 per arm of 40 in totaal voor crossover studies. Een uitzondering hierop kon gemaakt worden indien een studie die niet voldeed aan onze inclusiecriteria, geïnccludeerd was in een meta-analyse.
  - anti-aggregantia: enkel producten met in België geregistreerde indicatie
  - bloeddrukverlagende en lipidenverlagende middelen: enkel producten met in België geregistreerde indicatie
  - anticoagulantia: fenprocoumon, warfarine, acenocoumarol, apixaban, dabigatran, rivaroxaban



Richtlijnen:

- enkel richtlijnen die levels of evidence / recommendation geven
- overzicht overeenkomsten en tegenstrijdigheden
- enkel richtlijnen vanaf 2005.
- geselecteerde richtlijnen (in samenspraak met organisatiecomité):

### 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 attack (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. <a href="http://www.strokefoundation.com.au">www.strokefoundation.com.au</a>
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 attack (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. Selectieprocedure

Volgende inclusiecriteria zijn toegepast bij de selectie van *meta-analyses en systematische reviews*:

- overeenstemming van de onderzoeksvraag in de publicatie met de vraagstelling van dit literatuuronderzoek
- systematische zoekstrategie
- systematische weergave van de resultaten
- inclusie van gerandomiseerde gecontroleerde studies
- vermelding van een klinisch relevante uitkomstmaat

Inclusiecriteria voor *gerandomiseerde gecontroleerde studies (RCT's)* worden hoger vermeld onder puntje 1, waar de relevante interventies, eindpunten en studiecriteria worden opgesomd.

Selectie van relevante referenties is uitgevoerd door twee onderzoekers, onafhankelijk van elkaar. Verschillen zijn na discussie in consensus opgelost. Een eerste selectie van referenties gebeurde op basis van titel en abstract. Wanneer de titel of het abstract onvoldoende uitsluitel konden geven over inclusie, werd de publicatie opgezocht en doorgenomen.

Verschillende publicaties zijn geëxcludeerd omwille van praktische redenen:

- publicaties die niet in Belgische bibliotheken te verkrijgen waren
- publicaties in talen andere dan de West-Europese

## 1.3. Zoekstrategie

### 1.3.1. Principes systematische zoekstrategie

Met behulp van een getrapte zoekstrategie is gezocht naar relevante literatuur.

- In eerste instantie zijn bronnen geraadpleegd die gebruik maken van gegevens uit systematische reviews, meta-analyses en oorspronkelijke studies en hierbij commentaar geven: Clinical Evidence<sup>1</sup>, La Revue Prescrire, Minerva<sup>2</sup>. Richtlijnen werden geraadpleegd om bijkomende relevante referenties op te zoeken.
- In een tweede stap is elektronisch gezocht naar meta-analyses en systematische reviews en werden de referenties van relevante publicaties handmatig gescreend.
- In een derde stap is gezocht naar dubbelblinde gerandomiseerde gecontroleerde studies (RCT's), die verschenen na de zoekdatum van de geselecteerde systematische reviews / meta-analyses.

De volgende *elektronische databanken* zijn geraadpleegd:

- Medline (PubMed)
- Cochrane Library
- Database of Abstracts of Reviews of Effectiveness (DARE)

*Guidelines* zijn gezocht via de link naar "evidence-based guidelines" beschikbaar op de website van vzw Farmaka asbl ([www.farmaka.be](http://www.farmaka.be)).

Verschillende andere bronnen werden handmatig geraadpleegd: relevante publicaties, indexen van tijdschriften beschikbaar in de bibliotheek van vzw Farmaka asbl, vooral de onafhankelijke tijdschriften die lid zijn van de International Society of Drug Bulletins (ISDB) zoals Geneesmiddelenbulletin (Nederland), Folia Pharmacotherapeutica (België), La Revue Prescrire (Frankrijk), Drug & Therapeutics Bulletin (UK), Therapeutics Letter (Canada), Geneesmiddelenbrief (België), Arzneimittelbrief (Duitsland),...

### 1.3.2. Details zoekstrategie

Volgende systematische reviews of meta-analyses werden geselecteerd. Vervolgens werd gezocht naar RCT's in Pubmed die verschenen na de zoekdatum van deze publicaties.

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

Om RCT's terug te vinden die verschenen na de zoekdatum van bovenstaande publicaties, werden volgende zoektermen gebruikt in Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed/> ). In sommige gevallen, waar de systematische reviews / meta-analyses niet volstonden (bvb niet gezocht voor alle producten), werden er ook bijkomende RCT's gezocht, die verschenen voor de zoekdatum van de systematische review / meta-analyse.

```
(
(
(
(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. Beoordeling van de kwaliteit van de beschikbare evidence

Om de kwaliteit van de beschikbare evidence te beoordelen werd het GRADE systeem gebruikt. In andere systemen die "levels of evidence" toekennen, wordt een meta-analyse vaak aanzien als het hoogste niveau van evidentie. In GRADE daarentegen wordt enkel de kwaliteit van het oorspronkelijke studiemateriaal beoordeeld. Of de resultaten van oorspronkelijke studies gepoold werden in een meta-analyse is niet van belang voor de kwaliteit van de evidence. Het GRADE systeem<sup>3,4,5</sup> beoordeelt volgende items:

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

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

\*\* **Directness**: there are two types of indirectness of evidence. The first occurs when considering, for example, use of one of two active drugs. Although randomised comparisons of the drugs may be unavailable, randomised trials may have compared one drug with placebo and the other with placebo. Such trials allow indirect comparisons of the magnitude of effect of both drugs. Such evidence is of lower quality than would be provided by head to head comparisons of the drugs.

The second type of indirectness of evidence includes differences between the population, intervention, comparator to the intervention, and outcome of interest, and those included in the relevant studies.

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

Meer informatie is te vinden op de website <http://www.gradeworkinggroup.org>

In dit literatuuronderzoek werd het item “publication bias” en de items die specifiek bedoeld zijn voor observationele studies uit het GRADE systeem (zie bovenstaande tabel) niet beoordeeld. Deze aangepaste versie van het GRADE systeem beoordeelt dus volgende items:

<b>Study design</b>	+ 4	RCT
<b>Study quality</b>	- 1	Serious limitation to study quality
	- 2	Very serious limitation to study quality
<b>Consistency</b>	- 1	Important inconsistency
<b>Directness</b>	- 1	Some uncertainty about directness
	- 2	Major uncertainty about directness
<b>Imprecision</b>	- 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

Bij de beoordeling van de verschillende items hebben we volgende werkwijze gevolgd:

### **Study design**

In dit literatuuronderzoek zijn per definitie alle studies RCT's (inclusiecriteria). “Study design” wordt daarom niet apart als beoordelingscriterium gerapporteerd in het synthese rapport.

### **Study quality**

Voor de beoordeling van de methodologische kwaliteit van RCT's is de de Jadad score gebruikt, aangevuld met het nakijken of een “intention-to-treat” (ITT) analyse (alle gerandomiseerde patiënten in efficacy analyse) werd toegepast. Indien een meta-analyse of systematische review gebruikt werd, werd zoveel mogelijk de kwaliteit van de opgenomen studies beoordeeld. De kwaliteit van de meta-analyse / systematische review speelt dus geen rol in de GRADE beoordeling, wel de kwaliteit van de RCT's die opgenomen werden in de meta-analyse / systematische review.

Jadad score:

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 with 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

*(Tabel overgenomen van Duke University, Center for Clinical Health Policy Research. Drug Treatments for the Prevention of Migraine. AHCPR February 1999.)*

Toepassing in GRADE: er werd 1 punt voor quality afgetrokken als er een probleem was met puntje 3 van de Jadad score (“was there a description of withdrawals and drop-outs”). Vermits “gerandomiseerd” een inclusiecriteria was, werden hier geen punten afgetrokken, ook al werd de methode (puntje 1a en 2a van Jadad score) niet adequaat beschreven. Behalve de Jadad score werd ook bekeken of er een ITT analyse werd toegepast. Indien dit niet het geval is, werd hier ook een punt voor afgetrokken. Voor ITT werden enkel punten afgetrokken als de follow-up minder dan 80% bedraagt. Indien het follow-up percentage niet bekend was, werd er geen extra punt afgetrokken voor ITT.

### **Consistency**

- Goede “consistency” betekent dat meerdere studies een vergelijkbaar of consistent resultaat hebben. Indien slechts 1 studie beschikbaar is, kan de “consistency” niet beoordeeld worden. Dit wordt in het syntheserapport geformuleerd als “NA” (not applicable).
- Deze “consistency” is beoordeeld door de bibliografiegroep en het leescomité op basis van het geheel aan beschikbare studies. Hierbij werd rekening gehouden met:
  - o statistische significantie
  - o de richting van het effect als er geen statistische significantie bereikt werd: als bijvoorbeeld een statistisch significant effect in 3 studies bevestigd wordt in 2 andere studies door een niet statistisch significant resultaat in dezelfde richting, worden deze resultaten “consistent” genoemd.
  - o klinische relevantie: als bijvoorbeeld 3 studies een niet statistisch significant resultaat vinden, en een 4de studie vindt wel een statistisch significant resultaat, dat echter weinig klinisch relevant is, worden deze resultaten “consistent” genoemd.

### **Directness**

Dit gaat over de generaliseerbaarheid van de gegevens naar de werkelijke populatie (externe validiteit). Als dus studiepopulatie, de bestudeerde interventie en controle groep of de bestudeerde eindpunten niet relevant zijn kunnen hier punten worden afgetrokken.

### **Imprecision**

Als opgenomen systematische reviews of meta-analyses studies opnemen met minder dan 40 patiënten per studie-arm (voor een cross-over studie: minder dan 40 patiënten voor de hele studie), wordt er 1 punt afgetrokken voor “imprecision”.

### **Toepassen GRADE wanneer er veel studies zijn voor één eindpunt:**

Punten worden enkel afgetrokken als de methodologische problemen in belangrijke mate bijdragen tot het resultaat. Als bvb 1 studie van slechte kwaliteit bevestigt wat 2 grote studies van goede kwaliteit al vonden, worden er geen punten afgetrokken.



## 1.5. Samenvatting van de studieresultaten

Het volledig rapport bevat per onderzoeksvraag

- de evidentietabellen (Engelstalig) van de systematische reviews en/of RCT's waarop de antwoorden op de onderzoeksvragen gebaseerd zijn
- een korte samenvatting in tabel- (Engelstalig) en tekstvorm (in Nederlands / Frans) van de resultaten met een kwaliteitsbeoordeling van de gevonden evidentie volgens een aangepaste versie van het GRADE systeem

Het synthese rapport bevat per onderzoeksvraag

- een korte samenvatting in tabel- (Engelstalig) en tekstvorm (in Nederlands / Frans) van de resultaten met een kwaliteitsbeoordeling van de gevonden evidentie volgens een aangepaste versie van het GRADE systeem

Alle conclusies zijn besproken en aangepast in verschillende discussierondes met de auteurs van het literatuuronderzoek en met het leescomité van de bibliografiegroep.

### Referenties

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](http://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

## 1.6. Lijst van gebruikte afkortingen

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

## 2. Kritische beschouwingen van het leescomité en de literatuurgroep

### Aflijning van het onderwerp

- De literatuurgroep heeft zich beperkt tot de producten bepaald door het organiserend comité. Het literatuuronderzoek werd afgelijnd naar de volgende groepen geneesmiddelen:

- Anti-aggregantia, bloeddruk- en lipidenverlagende middelen met een in België geregistreerde indicatie
- Vitamine K-antagonisten
- De nieuwere orale anticoagulantia apixaban, dabigatran en rivaroxaban

- De literatuurgroep heeft in samenspraak met het RIZIV, het literatuuronderzoek afgelijnd tot volgende onderwerpen. Dit werd gedaan om overlap met de Consensusvergadering van 2009 “Het doelmatig gebruik van geneesmiddelen bij de preventie van cardiovasculaire aandoeningen” te vermijden.

- Cardiovasculaire risicoreductie bij patiënten zonder VKF, met voorgeschiedenis van CVA/TIA
- Cardiovasculaire risicoreductie bij patiënten met niet-valvulaire VKF met of zonder voorgeschiedenis van CVA/TIA

- Waar studies bij patiënten met voorgeschiedenis van CVA/TIA ontbreken, verwijzen we naar de conclusies van Clinical Evidence, zie bijlage 1 op het einde van dit document.

- De globale aanpak van cardiovasculaire risicofactoren, al dan niet medicamenteus, zoals rookstop, behandeling van obesitas, stimuleren van gezonde voeding en fysieke activiteit vallen buiten het bestek van dit literatuuronderzoek. Dit mag geenszins betekenen dat deze niet belangrijk zouden zijn. Integendeel, deze maatregelen zijn essentieel in de preventie en behandeling van cardiovasculair lijden. Hierbij verwijzen we naar een recent rapport van de Wereldgezondheidsorganisatie<sup>1</sup>.

- Ook acute interventies zoals trombolysen vallen buiten het bestek van dit literatuuronderzoek.

- De aanpak van de ritmestoornissen bij de patiënt met VKF valt eveneens buiten het bestek van dit literatuuronderzoek.

### Definities

De term ‘preventie’ geeft soms de idee dat de aandoening in kwestie (in dit geval bijvoorbeeld CVA) volledig vermeden zou kunnen worden. Dit is natuurlijk niet het geval. Eigenlijk wordt bedoeld dat men met de voorgestelde interventie het risico op een event probeert te verminderen. Om dit duidelijk te verwoorden hebben we ervoor gekozen om in dit document te spreken over ‘risicoreductie’.

De begrippen ‘primaire preventie’ en ‘secundaire preventie’ zijn soms een bron van discussie. Met primaire preventie wordt bedoeld: het vermijden van een event dat zich nog niet heeft voorgedaan’. Secundaire preventie is dan ‘het vermijden van een nieuw event, nadat een eerste event zich reeds heeft voorgedaan’. Wanneer spreekt men echter van een echt event? Wanneer men op beeldvorming ischemische hersenletsels ziet, zonder dat er ooit klinische tekens werden vastgesteld, moet men dan spreken van secundaire preventie? In studies worden vaak ook verschillende inclusiecriteria voor ‘doorgemaakt CVA’ gehanteerd. In sommige studies is dit puur op basis van klinisch beeld, doorgaans dient dit klinisch beeld bevestigd te worden door beeldvorming. Er zijn geen studies die enkel op basis van ‘ischemische letsels’ patiënten includeren.

Wat betreft de aard van het event zijn eveneens verschillende interpretaties mogelijk. Men kan aan secundaire preventie doen na een CVA of na een ander vasculair event buiten de hersenen (cardiaal of perifeer vaatlijden). Deze literatuurstudie heeft evenwel als onderwerp ‘CVA’, dus daarop zal de focus liggen.

Voor de duidelijkheid zullen we de termen ‘primair’ en ‘secundair’ eerder vermijden. In de bespreking van de verschillende studies zal steeds worden weergegeven welk event werd doorgemaakt en welk event geprobeerd wordt te vermijden.

## Kenmerken van de studies

- Het merendeel van de studies opgenomen in het literatuuronderzoek had een behandelingsduur van meerdere jaren. We hanteerden een minimum behandelingsduur van 6 maanden.
- In veel van de studies worden patiënten met ernstige comorbiditeit of verhoogd bloedingsrisico geëxcludeerd en de geïncludeerde patiënten worden zeer strikt gevolgd. Wat superieur blijkt in deze ideale studie-omstandigheden zal steeds moeten getoetst worden aan de realiteit van de patiënt waarmee de arts geconfronteerd wordt.
  
- Eindpunten in de klinische studies zijn vaak samengestelde eindpunten van verschillende vasculaire aandoeningen of mortaliteit; duidelijke 'harde' eindpunten die een beeld geven van de impact van het product op de geselecteerde populatie. Deze samengestelde eindpunten kunnen sterk verschillen van studie tot studie. Sterk afwezig in de studies zijn de 'functionele eindpunten' die een beeld kunnen geven van de impact van het doorgemaakte CVA op het dagelijks leven van de patiënt. Gezien restletsels van CVA op functioneel vlak een brede waaier vormen van zeer goed functioneren tot volledig zorgbehoevend, wordt het ontbreken van gegevens hierover in studies toch als een gemis ervaren.
- De oudere studies rapporteren vaak heel beperkte uitkomsten en geven weinig informatie over ongewenste effecten.
- Specifiek voor de nieuwere anticoagulantia verschillen de studies wat betreft gerapporteerde eindpunten, bv. definities van bloedingen, gecombineerde eindpunten. Ook de onderzoekspopulaties verschillen: CHADS2 score, TTR (time in treatment range, periode gedurende dewelke patiënten een therapeutische INR hadden met warfarine). Deze verschillen uit zich in verschillende event rates in de groepen behandeld met warfarine zoals 1.69 in de RE-LY studie in vergelijking met 2.4 in de ROCKET studie. Mede hierdoor is het niet mogelijk om de verschillende nieuwere anticoagulantia onderling met elkaar te vergelijken.
  
- De studies met de nieuwere anticoagulantia zijn alle zgn. non-inferiority trials. In een 'non-inferiority trial' wil men niet aantonen dat het nieuwe medicament 'even werkzaam' is als de controlebehandeling, maar dat het '*niet minder werkzaam*' is<sup>2</sup>. Een behandeling X is niet inferieur aan een behandeling Y als het verschil tussen deze twee behandelingen binnen een vastgelegde klinische marge valt. Deze marge voor non-inferioriteit ( $\Delta C$ ) is het resultaat van een afspraak onder experts en is gebaseerd op literatuuronderzoek, bij voorkeur op – indien beschikbaar - een meta-analyse<sup>3</sup>. Met deze complexe methodologie is vaak ook de ervaren lezer nog weinig vertrouwd. Dit maakt het bijgevolg moeilijk de studieresultaten kritisch te beoordelen.
- De studies over heelkundige interventie vergeleken heelkunde met optimale medicamenteuze behandeling werden uitgevoerd in de jaren 90. Ondertussen is de medicamenteuze behandeling geëvolueerd (o.a. meer veralgemeend gebruik van statines) waardoor het voordeel van een heelkundige interventie vermoedelijk lager zal zijn.
- De meeste studies zijn gesponsord door de firma die een van de onderzochte geneesmiddelen produceert.
  
- Vooral van de nieuwe generatie anticoagulantia is nog niet geweten wat het effect en de veiligheid van jarenlange behandeling zullen zijn; dit is nochtans niet onbelangrijk voor geneesmiddelen die jarenlang ingenomen worden, vaak door oudere gepolymediceerde patiënten. We moeten rekening houden met het feit dat bepaalde ongewenste effecten nog niet bekend zijn en farmacovigilantie is dus sterk aan te bevelen.

## Evaluatie van de studies

- Het level of evidence, toegekend via de GRADE methode, moet geïnterpreteerd worden binnen zijn methodologisch kader. Als er voor een bepaald geneesmiddel een hoger "level of evidence" is, betekent dit niet noodzakelijk dat dit geneesmiddel ook werkzaam is dan andere. Het aantal studies voor een bepaalde vergelijking is bv. geen criterium in de GRADE-evaluatie. Eén studie van goede kwaliteit kan leiden tot een "high quality of evidence" label, terwijl voor andere vergelijkingen meerdere studies beschikbaar zijn die kunnen leiden tot een "moderate quality of evidence", als meerdere van die studies methodologische beperkingen hebben.

## 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](http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf)
2. Van Driel M. Editoriaal: Evaluatie van nieuwe geneesmiddelen: 'superieur', 'equivalent' of 'niet-inferieur'? Minerva 2005;4:154.
3. Chevalier P. Non-inferioriteitsstudies: het nut, de beperkingen en de valkuilen. Minerva 2009;8:88.



### 3. Samenvatting van de richtlijnen

#### 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 attack (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 attack (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

<p>European Society of Cardiology</p>	<p><b>Levels of evidence</b>  <b>Level of</b>  A: Data derived from multiple randomized clinical trials or meta-analyses.  B: Data derived from a single randomized clinical trial of large non-randomized studies.  C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</p> <p><b>Classes of recommendations</b></p> <p>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.</p>
<p>European Stroke Organization</p>	<p><b>Levels of evidence</b></p> <p>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</p> <p>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</p> <p>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</p> <p>Class 4: Evidence from uncontrolled studies, case series, case reports, or expert opinion</p> <p><b>Grades of recommendation</b></p> <p>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.</p> <p>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</p>

	<p>evidence.</p> <p>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.</p> <p>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</p>
<p>Canadian Cardiovascular Society</p>	<p><b>Levels of evidence</b></p> <p>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</p> <p><b>Factors determining the strength of recommendations</b></p> <p>Quality of evidence :The higher the quality of evidence, the greater the probability that a strong recommendation is indicated.</p> <p>Difference between desirable: The greater the difference between desirable and undesirable effects, the greater the probability that a strong recommendation is indicated;</p> <p>Values and preferences: The greater the variation or uncertainty in values and preferences, the higher the probability that a conditional recommendation is indicated.</p> <p>Cost: The higher the cost, the lower the likelihood that a strong recommendation is indicated.</p>
<p>American College of Cardiology / American Heart Association</p>	<p><b>Levels of evidence</b></p> <p><b>Level of</b></p> <p>A: Data derived from multiple randomized clinical trials or meta-analyses.  B: Data derived from a single randomized clinical trial or non-randomized studies.  C: Consensus of opinion of the experts and/or small studies, case studies or standard of care</p> <p><b>Classes of recommendations</b></p> <p>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.</p>
<p>American College of Chest Physicians</p>	<p><b>Levels of Evidence</b></p> <p>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</p>

	<p><b>Grades of recommendation</b></p> <p>Strong (1): Desirable effects clearly outweigh undesirable effects, or vice versa</p> <p>Weak (2): Desirable effects closely balanced with undesirable effects</p>
--	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

### 3.2.2. Included populations – risk stratification

European Society of Cardiology (ESC)	<ul style="list-style-type: none"> <li>- Patients with atrial fibrillation (paroxysmal, persistent and permanent)</li> <li>- CHA<sub>2</sub>DS<sub>2</sub>-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’.</li> <li>- 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</li> </ul>
European Stroke Organization	<ul style="list-style-type: none"> <li>- Patients with atrial fibrillation</li> <li>- Risk factors: aged &gt;75y, high blood pressure, left ventricular dysfunction, or diabetes mellitus</li> </ul>
Canadian Cardiovascular Society	<ul style="list-style-type: none"> <li>- Patients with atrial fibrillation (paroxysmal, persistent and permanent) and atrial flutter</li> <li>- CHADS<sub>2</sub>-score</li> <li>- HAS BLED risk stratification for bleeding</li> </ul>
American College of Cardiology Foundation/American Heart Association	<ul style="list-style-type: none"> <li>- Patients with atrial fibrillation (paroxysmal, persistent and permanent). Distinction between atrial flutter and atrial fibrillation</li> <li>- Risk factors: Less Validated or weaker: female, 65-74y, coronary artery disease, thyrotoxicosis Moderate: ≥75y, hypertension, heart failure, LVE fraction &lt;35%, diabetes High-Risk: previous stroke, TIA or embolism, mitral stenosis, prosthetic heart valve</li> <li>- 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.</li> </ul>
American College of Chest Physicians	<ul style="list-style-type: none"> <li>- Patients with atrial fibrillation (persistent, permanent and paroxysmal) and atrial flutter.</li> <li>- 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.</li> <li>- CHADS<sub>2</sub>-score: congestive heart failure, hypertension, age ≥75y, diabetes mellitus, prior stroke or TIA</li> <li>- No risk stratification for bleeding</li> </ul>

### 3.2.3. Recommendations

<p>European Society of Cardiology</p>	<p><u>Antithrombotic management:</u></p> <p><u>CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 2:</u> oral anticoagulant (1A)  <u>CHA<sub>2</sub>DS<sub>2</sub>-VASc score = 1:</u> oral anticoagulant (preferred) (1A) or aspirin (75-325mg) (1B)  <u>CHA<sub>2</sub>DS<sub>2</sub>-VASc score = 0:</u> nothing (preferred) or aspirin (75-325mg) (1B)</p> <p>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.</p> <p>Selection of antitrombotic therapy should be considered irrespective of the pattern of AF (paroxysmal, persistent, or permanent) (2A)</p> <p>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.</p> <p>After cardioversion:          Long term anticoagulation depends on risk of stroke. (2a, B)</p>
<p>European Stroke Organization</p>	<p><u>Antithrombotic management:</u></p> <p>Aspirin may be recommended for patients with non-valvular AF who are younger than 65 years and free of vascular risk factors (<b>Class I, Level A</b>)          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 (<b>Class I, Level A</b>)          Unless contraindicated, an oral anticoagulant (INR 2.0–3.0) is recommended for patients with non-valvular AF who are aged &gt;75, or who are younger but have risk factors such as high blood pressure, left ventricular dysfunction, or diabetes mellitus (<b>Class I, Level A</b>)</p> <p>Oral anticoagulation is not recommended in patients with co-morbid conditions such as falls, poor compliance, uncontrolled epilepsy, or gastrointestinal bleeding (<b>Class III, Level C</b>). Increasing age alone is not a contraindication to oral anticoagulation (<b>Class I, Level A</b>)</p> <p>It is recommended that patients with AF who are unable to receive oral anticoagulants should be offered aspirin (<b>Class I, Level A</b>)          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 (<b>Class II, Level B</b>)</p>
<p>Canadian Cardiovascular Society</p>	<p><u>Antithrombotic management:</u></p> <p><u>Very low risk of stroke (CHADS<sub>2</sub> = 0) :</u> aspirin (75-325 mg/d) (Strong Recommendation, High-Quality Evidence). No antithrombotic may be appropriate in selected young patients with no stroke risk factors</p> <p><u>Low risk of stroke (CHADS<sub>2</sub> = 1) :</u> 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).</p>

	<p><u>Moderate risk of stroke (CHADS<sub>2</sub> = 2)</u> : OAC therapy (either warfarin [INR 2-3] or Dabigatran) (Strong Recommendation, High-Quality Evidence).</p> <p>When OAC therapy is indicated, most patients should receive dabigatran in preference to warfarin. In general, the dose of <i>dabigatran 150 mg</i> by mouth twice a day is preferable to a dose of <i>110 mg</i> by mouth twice a day (Conditional Recommendation, High-Quality Evidence).</p> <p>After cardioversion: Long term anticoagulation depends on risk of stroke. (Strong Recommendation, Moderate Quality Evidence)</p>
<p>American College of Cardiology Foundation/American Heart Association</p>	<p><u>Antithrombotic management:</u></p> <p>Antithrombotic therapy is recommended for all patients with AF, except those with lone AF (younger than 60y with no clinical history or echocardiographic signs 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)</p> <p>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)</p> <p>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)</p> <p>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)</p>
<p>American College of Chest Physicians</p>	<p><u>Antithrombotic management:</u></p> <p>For patients with non-valvular AF, including paroxysmal AF:</p> <p>*low risk of stroke (CHADS<sub>2</sub>-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)</p> <p>*intermediate risk of stroke (CHADS<sub>2</sub>-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)</p> <p>*high risk of stroke (CHADS<sub>2</sub>-score≥2) we recommend oral anticoagulation rather than no therapy (Grade 1A), aspirin (Grade 1B) or combination therapy with aspirin and clopidogrel (Grade 1B)</p> <p>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)</p>

### 3.3. Secondary prevention of stroke

#### 3.3.1. Levels of evidence / grades of recommendation

SIGN	<p><b>Levels of evidence</b></p> <p>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</p> <p><b>Grades of recommendation</b></p> <p>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  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+</p>
CBO	<p><b>Levels of evidence</b></p> <p>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</p> <p><b>Levels of conclusions</b></p> <p>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</p>

<p>Catalan Agency for Health Technology Assessment and Research</p>	<p><b>Levels of evidence</b></p> <p>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</p> <p><b>Grades of recommendation</b></p> <p>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+</p> <p>Good Clinical Practice: Recommended practice based on clinical experience and the consensus of the elaborating team.</p>
<p>American Heart Association/American Stroke Association Council on Stroke</p>	<p><b>Levels of evidence</b></p> <p>Level of</p> <p>A Data derived from multiple randomized clinical trials or meta-analyses.  B Data derived from a single randomized clinical trial or non-randomized studies.  C Consensus of opinion of the experts and/or small studies, case studies or standard of care</p> <p><b>Classes of recommendations</b></p> <p>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.</p>
<p>National Stroke Foundation Australia</p>	<p><b>Grades of recommendation</b></p> <p>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</p> <p>Good Clinical Practice: Recommended practice based on clinical experience and expert opinion</p>

	<p><b>Levels of evidence</b></p> <p>1 A systematic review of level 2 studies  2 A Randomized controlled trial  3-1 A pseudorandomised controlled trial (i.e. alternate allocation or some 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</p>
<p>European Stroke Organization</p>	<p><b>Levels of evidence</b></p> <p>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</p> <p>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</p> <p>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</p> <p>Class 4: Evidence from uncontrolled studies, case series, case reports, or expert opinion</p> <p><b>Grades of recommendation</b></p> <p>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.</p> <p>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.</p> <p>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.</p>



	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	<p>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)</p> <p>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.</p> <p>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.</p> <p>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.</p>
CBO	<p>Stroke: Sudden onset of a focal disorder in the brains, there is no other cause than a vascular disorder.</p> <p>The guideline covers s all stroke patients with or without transient symptoms. Among stroke, this guideline does not include a subarachnoid or subdural hemorrhage</p>
Catalan Agency for Health Technology Assessment and Research	<p>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.</p> <p>The guideline covers stroke (ischemic and hemorrhagic) and transient ischemic attack [TIA].</p>
American Heart Association/American Stroke Association Council on Stroke	<p>Stroke: symptoms lasting &gt;24 hours or imaging of an acute clinically relevant brain lesion in patients with rapidly vanishing symptoms.</p> <p>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.</p> <p>Guideline covers prevention of ischemic stroke among survivors of ischemic stroke or TIA.</p> <p>Hemorrhagic stroke: guideline covers only anticoagulation management after cerebral hemorrhage.</p>
National Stroke Foundation Australia	<p>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.</p> <p>TIA: Stroke-like symptoms that last less than 24 hours.</p> <p>Exclusion of subarachnoid hemorrhage.</p>
European Stroke Organization (1)	<p>Guideline covers Ischemic stroke and TIA. Exclusion of intracerebral hemorrhage and subarachnoid hemorrhage.</p>

### 3.3.3. Recommendations

SIGN	<p><u>Secondary prevention</u></p> <p><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 (&gt;75 years) with ischaemic stroke or TIA who are in atrial fibrillation (B).</p> <p><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).</p> <p><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).</p>
CBO	<p><u>Secondary Prevention</u></p> <p><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).</p> <p><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 &lt;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).</p> <p><u>Antihypertensive drugs:</u>  For patients with hypertension who have a history of TIA or stroke a antihypertensive therapy is initiated or intensified, with a target <math>\leq 130 / \leq 80</math> 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).</p>

<p>Catalan Agency for Health Technology Assessment and Research</p>	<p><u>Secondary Prevention</u>  <u>Antithrombotic treatment:</u>  The combination of aspirin and sustained release dipyridamol 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 dipyridamol (50 and 400 mg/d), triflusal (600 mg/d) or clopidogrel (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++).</p> <p><u>Statins:</u>  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).</p> <p><u>Antihypertensive drugs:</u>  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).</p>
<p>American Heart Association/American Stroke Association Council on Stroke</p>	<p><u>Secondary prevention</u>  <u>Antithrombotic treatment:</u>  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.</p> <p><u>Statins:</u>  Statin agents are recommended, with a target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease is an LDL-C of &lt;100 mg/dL and LDL-C of &lt;70 mg/dL for very-high-risk persons with multiple risk factors (Class I, Level of Evidence A).</p>

	<p>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).</p> <p><u>Antihypertensive drugs:</u> 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).</p>
National Stroke Foundation Australia	<p><u>Secondary prevention</u> <u>Antithrombotic treatment:</u> 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).</p> <p><u>Statins:</u> 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).</p> <p><u>Antihypertensive drugs:</u> All stroke and TIA patients, whether normotensive or hypertensive, should receive blood pressure lowering therapy, unless contraindicated by symptomatic hypotension (A).</p>
European Stroke Organization	<p><u>Secondary Prevention</u> <u>Antithrombotic treatment:</u> 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)</p>

	<p><u>Statins:</u> Statin therapy is recommended in subjects with non-cardioembolic stroke (Class I, Level A)</p> <p><u>Antihypertensive drugs:</u> Blood pressure lowering is recommended after the acute phase, including in patients with normal blood pressure (Class I, Level A)</p>
--	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

### 3.4. Carotid artery stenosis

#### 3.4.1. Levels of evidence / grades of recommendation

European Society of Cardiology	<p><b>Levels of evidence</b></p> <p>Level A: Data derived from multiple randomized clinical trials or meta analyses.</p> <p>Level B: Data derived from a single randomized clinical trial or large non randomized studies.</p> <p>Level C : Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</p> <p><b>Classes of recommendations</b></p> <p>Class 1: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. 'recommended' or 'indicated'</p> <p>Class 2: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</p> <p>Class 2a: Weight of evidence/opinion is in favour of usefulness/efficacy 'should be considered'</p> <p>Class 2b: Usefulness/efficacy is less well established by evidence/opinion. 'may be considered'</p> <p>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'</p>
CBO	<p><b>Levels of evidence</b></p> <p>A1: Systematic review of at least 2 independently conducted studies level A2</p> <p>A2: Randomised double blind controlled trial of good quality and size</p> <p>B: Comparative research, but not with all the characteristics mentioned under A2 (This also includes case-control studies, cohort study)</p> <p>C: non-comparative study</p> <p>D: expert opinion</p> <p><b>Levels of conclusions</b></p> <ol style="list-style-type: none"> <li>1. Conclusion based of level A1 evidence or at least two independently conducted studies level A2</li> <li>2. 1 level A2 study or at least two independently conducted studies level B</li> <li>3. 1 level B or C study</li> <li>4. Expert opinion</li> </ol>
American Heart Association/American Stroke Association Council on Stroke	<p><b>Levels of evidence</b></p> <p><b>Level of</b></p> <p>A: Data derived from multiple randomized clinical trials or meta-analyses.</p> <p>B: Data derived from a single randomized clinical trail or non-randomized studies.</p> <p>C: Consensus of opinion of the experts and/or small studies, case studies or standard or care</p> <p><b>Classes of recommendations</b></p> <p>Class I: Evidence and/or general agreement that a given treatment or</p>

	<p>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.</p>								
<p>European Stroke Organisation</p>	<p><b>Levels of evidence</b></p> <p>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:</p> <ol style="list-style-type: none"> <li>a. randomization concealment</li> <li>b. primary outcome(s) is/are clearly defined</li> <li>c. exclusion/inclusion criteria are clearly defined</li> <li>d. adequate accounting for dropouts and crossovers with numbers sufficiently low to have a minimal potential for bias; and</li> <li>e. relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences</li> </ol> <p>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</p> <p>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</p> <p>Class 4: Evidence from uncontrolled studies, case series, case reports, or expert opinion</p> <p><b>Grades of recommendation</b></p> <table border="0" style="width: 100%;"> <tr> <td style="vertical-align: top; padding-right: 20px;">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 style="vertical-align: top; padding-right: 20px;">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 style="vertical-align: top; padding-right: 20px;">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 style="vertical-align: top; padding-right: 20px;">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> </table>	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
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								

### 3.4.2. 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	<p><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</p> <p><u>Surgery:</u> <u>Symptomatic carotid stenosis:</u> Best Medical Treatment (BMT) vs invasive techniques: Carotid artery stenosis &lt; 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</p> <p><u>Asymptomatic carotid stenosis:</u> Carotid artery stenosis &lt;60%: BMT Carotid artery stenosis 60-99%: revascularization + BMT should be considered when life expectancy &gt;5y, perioperative stroke and death rate &lt;3% and favourable anatomy. (2a, A) Occluded carotid artery: BMT</p>
CBO	<p><u>Medical therapy:</u> No specific recommendations for carotid stenosis</p> <p><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.</p> <p><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,</p>



	<p>a carotid endarterectomy can be considered if the surgical risk of a disabling stroke or death is lower than 3%. (level 1, A1-A2)</p>
<p>American Heart Association/American Stroke Association Council on Stroke</p>	<p><u>Medical therapy:</u> Stroke or TIA patients who undergo interventional procedures also need to be treated with maximal medical therapies.</p> <p><u>Surgery:</u> <u>Symptomatic carotid stenosis:</u> 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 &lt;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 &lt;50%, there is no indication for CEA (Class III, Level of Evidence A)</p> <p><u>Asymptomatic carotid stenosis:</u> No recommendations.</p>
<p>European Stroke Organisation</p>	<p><u>Medical therapy:</u> Low dose aspirin is recommended for patients with asymptomatic internal carotid artery (ICA) stenosis &gt;50% to reduce their risk of vascular events (Class II, Level B)</p> <p><u>Surgery:</u> <u>Symptomatic carotid stenosis:</u> 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)</p> <p>CEA is not recommended for patients with stenosis of less than 50% (Class I, Level A)</p> <p><u>Asymptomatic carotid stenosis:</u> 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)</p>

## **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  $\geq 75$ ) 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 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. Cardiovasculaire risicoreductie na CVA/TIA bij personen zonder voorkamerfibrillatie**



## 4. Samenvatting van de resultaten: risicoreductie na CVA/TIA bij personen zonder voorkamerfibrillatie

### 4.1. Anti-aggregantia na CVA/TIA bij personen zonder voorkamerfibrillatie

#### 4.1.1. Anti-aggregantia versus placebo/controle

<b>Antiplatelet treatment (acetylsalicylic acid, ticlopidine, dipyridamole, sulfapyrazone and associations) vs placebo/control</b> (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 )				
<b>N/n</b>	<b>Duration</b>	<b>Population</b>	<b>Results</b>	
N=21, n= 18.27 0	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
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→High quality of evidence</b>
OK	OK	OK	OK	

- Anti-aggregantia werden uitgebreid onderzocht bij patiënten zonder voorkamerfibrillatie met voorgeschiedenis van CVA of TIA. De meeste studies werden uitgevoerd met acetylsalicylzuur, al dan niet in associatie. Anti-aggregantia bleken werkzaam in de preventie van cardiovasculaire events, waaronder AMI en CVA. Behandeling van 1000 patiënten gedurende 3 jaar kan 36 cardiovasculaire events voorkomen. Ook de mortaliteit was significant lager in de groepen behandeld met anti-aggregantia.

*GRADE: high quality of evidence*

- Bij patiënten behandeld met anti-aggregantia werd een verhoogde incidentie van majeure extracraniale bloedingen vastgesteld. Behandeling van 1000 patiënten gedurende 1 jaar leidt tot 1 à 2 majeure bloedingen extra, vergeleken met controle.

#### 4.1.2. Laaggedoseerd acetylsalicylzuur 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 .96 2	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 infarction	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	

- Acetylsalicylzuur 50-75 mg/d is werkzaam dan placebo voor het voorkomen van recidief CVA bij patiënten zonder voorkamerfibrillatie met een voorgeschiedenis van CVA of TIA.  
De totale mortaliteit en de incidentie van AMI werden niet significant verlaagd.

*GRADE: high quality of evidence*

- Met acetylsalicylzuur werd een hogere incidentie van bloedingen vastgesteld, vergeleken met placebo.

Het Gecommentarieerd Geneesmiddelenrepertorium (BCFI 2012) vermeldt als voornaamste ongewenste effecten van acetylsalicylzuur: een lokaal etsend effect op de maagmucosa, overgevoeligheidsreacties en bloedingsproblemen.

### 4.1.3. Anti-aggregantia onderling

#### 4.1.3.1. Clopidogrel of ticlopidine versus acetylsalicylzuur

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 <b>OR=0.85 (95% CI: 0.75-0.97)</b> ⇒ <b>SS in favour of thienopyridines</b>
			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
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→ Moderate quality of evidence</b>
OK	-1	OK	OK	

- De thiënoopyridines zijn statistisch significant beter dan acetylsalicylzuur voor het voorkomen van ischemische CVA's bij patiënten die reeds een CVA of TIA doormaakten; het klinische voordeel is echter beperkt. Voor de preventie van hemorrhagische CVA's wordt geen verschil gevonden tussen beide groepen. Op het gecombineerd eindpunt van alle CVA's en van CVA, myocardinfarct of dood door vasculair lijden, werd geen significant verschil gevonden in de secundaire preventie door middel van thiënoopyridines of aspirine.

*GRADE: moderate quality of evidence*

- De ongewenste effecten van thiënoopyridines of aspirine bij patiënten met CVA/TIA in hun voorgeschiedenis zijn niet apart bestudeerd.

#### 4.1.3.2. Clopidogrel vs. acetylsalicylzuur

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	

- Deze conclusie is gebaseerd op de resultaten van de CAPRIE-studie, waarin in totaal 19.185 patiënten met recent ischemisch CVA of recent myocardinfarct of symptomatisch perifeer arterieel lijden geïnccludeerd werden. In de totale studiegroep werd een beperkt voordeel gevonden van clopidogrel 75 mg/d vergeleken met acetylsalicylzuur 325 mg/d voor het samengesteld eindpunt ischemisch CVA, AMI of vasculaire mortaliteit (5.32% events/j vs. 5.83% events/j).

In de subgroep van 6.431 patiënten met recent ischemisch CVA werd geen voordeel gevonden van clopidogrel t.o.v. acetylsalicylzuur, noch op het primair samengesteld eindpunt, noch op de secundaire enkelvoudige eindpunten.

*GRADE: moderate quality of evidence*

- Voor de ongewenste effecten beschikken we enkel over gegevens uit het onderzoek bij de totale groep hoogrisicopatiënten met atherosclerotisch vaatlijden. Daaruit blijkt dat acetylsalicylzuur niet significant meer bloedingen veroorzaakt dan clopidogrel met uitzondering van gastro-intestinale bloedingen. Er treedt wel significant meer huiduitslag en diarree op bij het gebruik van clopidogrel. Bij de patiënten die acetylsalicylzuur kregen toegediend, kwamen nausea en abnormale levertesten significant meer voor dan bij de patiënten onder behandeling met clopidogrel.



#### 4.1.3.3. Clopidogrel plus acetylsalicylzuur vs. clopidogrel

Clopidogrel 75 mg/d + acetylsalicylic acid 75 mg/d vs clopidogrel 75 mg/d (Diener 2004)							
N/n	Duration	Population	Results				
N=1, n= 7599	1.5 y	-Ischaemic stroke (79%) or TIA (21%) ≤3months  -at least 1 additional risk factor  - mean age 66 y	<b>Efficacy</b>				
			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)	NS			
			Ischemic stroke	NS			
			Vascular mortality	NS			
			Total mortality	NS			
			Myocardial infarction	NS			
			<b>Harms</b>				
			Primary intracranial haemorrhage	Aspirin+clopidogrel 3% vs 1% clopidogrel <b>SS:</b> ARR = 0.4% (95% CI 0.04 to 0.76) p<0.029			
			Life –threatening bleeding	Aspirin+clopidogrel 3% vs 1% clopidogrel <b>SS:</b> ARR = 1.26% (95% CI 0.64 to 1.88) p<0.0001			
			Major bleeding	Aspirin+clopidogrel 2% vs 1% clopidogrel <b>SS:</b> ARR = 1.36% (95% CI 0.86 to 1.86) p<0.0001			
			Minor bleeding	Aspirin+clopidogrel 3% vs 1% clopidogrel <b>SS:</b> ARR = 2.16% (95% CI 1.51 to 2.81) p<0.0001			
			<b>GRADE assessment</b>				
			<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→High quality of evidence</b>
OK	OK	OK	OK				

- Bij patiënten met een recent ischemisch CVA of TIA en verhoogd cardiovasculair risico leidt het toevoegen van acetylsalicylzuur 75 mg/d aan een behandeling met clopidogrel 75 mg/d niet tot een daling van het aantal cardiovasculaire events vergeleken met monotherapie met clopidogrel 75 mg/d.. Noch voor het primaire samengesteld eindpunt (ischemisch CVA, AMI, vasculaire mortaliteit of ziekenhuisopname wegens acute ischemie), noch voor de afzonderlijke eindpunten werden significante verschillen gevonden tussen beide groepen.

*GRADE: high quality of evidence*

- Bij patiënten behandeld met de combinatietherapie werd een significante stijging vastgesteld van de incidentie van majeure en mineure bloedingen en van het aantal hersenbloedingen.

#### 4.1.3.4. Dipyridamol plus acetylsalicylzuur vs. acetylsalicylzuur

<b>Acetylsalicylic acid 30-1300 mg/d + dipyridamole 150-400 mg/d vs acetylsalicylic acid 30-1300 mg/d</b> (MA Verro 2008: Caneschi 1985, Guiraud-Chaumeil 1982, AICLA Bousser 1983, ACCSG 1985, ESPS-s 1996, ESPRIT 2006 + Uchiyama JASAP 2011)				
<b>N/n</b>	<b>Duration</b>	<b>Population</b>	<b>Results</b>	
N=7, n= 8943	1.3-3.5 y	- patients with a history of recent minor stroke or TIA - no atrial fibrillation - mean age 65 y	<b>Efficacy</b>	
			Non-fatal stroke (both ischemic and hemorrhagic)	- 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
			Recurrent ischemic stroke (fatal or non fatal)	- Reported in 1/7 trials - Event rate 6.9% vs. 5% - NS for non-inferiority: HR = 1.47 (95% CI 0.93 - 2.31)
			TIA	- Reported in 1/7 trials - NS for noninferiority
			Combined vascular events (definition according to trial)	- 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
			<b>Harms</b>	
			Any bleeding	NS
			Major bleeding	NS
Minor bleeding	NS			
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→Moderate quality of evidence</b>
-1 for heterogeneity	OK	OK	OK	

- De associatie van dipyridamol plus acetylsalicylzuur is werkzaamere dan acetylsalicylzuur alleen (mediane dosis 75 mg/d) voor het voorkomen van een recidief CVA bij patiënten met voorgeschiedenis van CVA of TIA. Ook de totale incidentie van cardiovasculaire events was significant lager in de groep behandeld met de associatie. Voor deze beide eindpunten bedroeg de absolute risicoreductie ongeveer 2%. Deze resultaten werden niet bevestigd in een recent verschenen Japanse studie, waar geen significant verschil gevonden werd tussen de associatie en acetylsalicylzuur in monotherapie (50 mg/d).

*GRADE: moderate quality of evidence*

- Er werden geen significante verschillen gevonden tussen de associatie en monotherapie wat betreft het optreden van bloedingen.

#### 4.1.3.5. Dipyridamol plus acetylsalicylzuur 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)	<b>ASA+ER-DP 1.4% vs 1.8% clopidogrel</b> <b>SS for non-inferiority: HR = 0.78 (95% CI 0.62 to 0.96) p=0.02</b>
			Intracranial	<b>ASA+ER-DP 1.4% vs 1.0% clopidogrel</b> <b>SS for non-inferiority: HR = 1.42 (95% CI 1.11 to 1.83) p=0.006</b>
			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	

- De combinatie van dipyridamol en acetylsalicylzuur is niet statistisch significant beter dan clopidogrel voor het verminderen van CVA's (zowel in totaal als enkel de ischemische) en hartinfarcten bij patiënten met een recente voorgeschiedenis van CVA of TIA. Er is evenmin een statistisch significant verschil tussen beide behandelingen wat betreft de eindpunten dood door vasculair lijden, totale mortaliteit en het gecombineerde eindpunt CVA, hartinfarct en/of dood door vasculair lijden. Enkel het aantal gevallen van hartfalen is significant licht verhoogd in de clopidogrel groep.

*GRADE: moderate quality of evidence*

- Er werd geen statistisch significant verschil gevonden in het aantal ernstige bloedingen tussen de twee behandelingsgroepen, alhoewel er met de associatie dipyridamol en acetylsalicylzuur wel een statistisch significant verhoogd aantal intracranieële bloedingen optraden in vergelijking met clopidogrel.

#### 4.1.3.6. 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)	<b>35.0% clopidogrel vs ticlopidine 48.7%</b> <b>SS: HR = 0.610 (95% CI 0.529 to 0.703)</b> <b>p&lt;0.001</b>
		Hepatic dysfunction	<b>13.4% clopidogrel vs ticlopidine 25.6%</b> <b>SS: HR = 0.455 (95% CI 0.367to 0.565)</b> <b>p&lt;0.001</b>	
GRADE assessment				
Quality	Consistency	Directness	Imprecision	→ Moderate quality of evidence
OK	NA	-1 (limited clinical outcomes)	OK	

- In deze studie uit 2009 werd geen statistisch significant verschil gerapporteerd in het voorkomen van CVA, andere vaataandoeningen en mortaliteit tussen de behandeling met clopidogrel in vergelijking met ticlopidine bij patiënten met CVA in de voorgeschiedenis.

*GRADE: moderate quality of evidence*

- Op vlak van veiligheid kunnen we melden dat in deze studie het aantal ernstige bloedingen in beide groepen niet statistisch significant verschillend was. Clopidogrel wordt wel beter verdragen door de patiënten dan ticlopidine. Er werden statistisch significant meer ongewenste effecten waargenomen met ticlopidine : abnormale bloedresultaten (neutropenie, leukopenie, thrombocytopenie) en leverstoornissen.

#### 4.1.4. Dosisvergelijkingen: hoge dosis vs. lage dosis acetylsalicylzuur

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	

- De vergelijking hoog- versus laaggedoseerd acetylsalicylzuur werd slechts beperkt onderzocht bij patiënten met voorgeschiedenis van CVA of TIA. De 2 beschikbare studies vergeleken sterk uiteenlopende dosissen (1200 vs 300 mg/d en 325 vs 30 mg/d). In geen van beide studies werd een significant verschil gevonden in werkzaamheid tussen hoog- en laaggedoseerd acetylsalicylzuur.

*GRADE: low quality of evidence*

- Er werd geen significant verschil gevonden tussen hoog-en laaggedoseerd acetylsalicylzuur wat betreft majeure en mineure bloedingen. Andere ongewenste effecten werden niet statistisch getoetst.

Clinical Evidence besluit als volgt op basis van studies bij personen met verhoogd cardiovasculair risico:

##### 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. Orale anticoagulantia na CVA/TIA bij personen zonder voorkamerfibrillatie

### 4.2.1. Orale anticoagulantia versus placebo of geen behandeling

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	<b>OR= 2.54 (95% CI: 1.19-5.45)</b> <b>=&gt; SS more frequent with anticoagulants</b>
			Fatal extracranial stroke	<b>OR= 4.86 (95% CI: 1.40-16.88)</b> <b>=&gt; SS more frequent with anticoagulants</b>
			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	

- De totale mortaliteit bij patiënten die reeds een CVA of TIA doormaakten is niet statistisch significant verschillend onder behandeling met anticoagulantia in vergelijking met controle. Er is evenmin een significant verschil in het voorkomen van een recidief ischemisch CVA of hartinfarct in beide behandelingsgroepen.

*GRADE: very low quality of evidence*

- Onder behandeling van anticoagulantia treden statistisch significant meer fatale bloedingen op dan onder controle behandeling.

#### 4.2.2. Orale anticoagulantia vs. acetylsalicylzuur

<b>Oral anticoagulants vs acetylsalicylic acid</b> (Olsson 1980, Garde 1983, SPIRIT 1997, Stewart 1998, Mohr 2001, ESPRIT 2007)							
<b>N/n</b>	<b>Duration</b>	<b>Population</b>	<b>Results</b>				
N= 6 n= 5.144	Mean 21m	TIA or minor stroke of presumed arterial origin	<b>High-intensity anticoagulation (INR 3.0-4.5) (N=1, n=1316)</b>				
			Mortality	RR= 2.38 (95% CI 1.31-4.32) <b>SS in favour of ASA</b>			
			Vascular mortality	RR= 2.23 (95% CI 1.10-4.51) <b>SS in favour of ASA</b>			
			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) <b>SS in favour of ASA</b>			
			Major bleeding	RR= 9.02 (95% CI 3.91-20.84) <b>SS in favour of ASA</b>			
			Fatal intracranial or extracranial bleeding	RR= 17.37 (95% CI 2.32-130.11) <b>SS in favour of ASA</b>			
			Intracranial bleeding (fatal or non-fatal)	RR= 9.19 (95% CI 2.80-30.16) <b>SS in favour of ASA</b>			
			<b>Medium-intensity anticoagulation (INR 2.1-3.6) (N=4, n=1561)</b>				
			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 <b>HR= 2.56 (95% CI: 1.48-4.43) SS in favour of ASA</b>			
			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			
			<b>Low-intensity anticoagulation (INR 1.4-2.8) (N=1, n=2206)</b>				
			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			
			<b>GRADE assessment</b>				
			<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→High quality of evidence</b>
			OK	OK	OK	OK	

- Om het risico op een recidief TIA of CVA te verminderen bij patiënten zonder voorkamerfibrillatie blijkt langdurige toediening van acetylsalicylzuur significant beter op bijna alle eindpunten dan orale anticoagulantia met INR>3. Bij minder sterk ontstolde patiënten is het verschil tussen deze twee geneesmiddelen statistisch niet significant.

*GRADE: high quality of evidence*

- Wanneer de INR groter is dan 3, treden er significant meer bloedingen op bij behandeling met orale anticoagulantia dan met acetylsalicylzuur. Zelfs in de groep met matig ontstolde patiënten treden significant meer ernstige bloedingen op in vergelijking met patiënten die acetylsalicylzuur innemen.

### 4.3. Antihypertensiva na CVA/TIA bij personen zonder voorkamerfibrillatie

#### 4.3.1. Antihypertensiva versus placebo

##### 4.3.1.1. Antihypertensiva als groep versus placebo

<b>Antihypertensive treatment</b> (thiazide, deserpidine, atenolol, indapamide, ramipril, perindopril+indapamide) <b>vs control</b> (MA Rashid 2003: Carter 1970, HSCSG 1974, Dutch TIA 1993, PATS 1995, Eriksson 1995, HOPE 2000, PROGRESS 2001)				
<b>N/n</b>	<b>Duration</b>	<b>Population</b>	<b>Results</b>	
N= 7 n= 15.527	2-5 y	-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	Stroke	- 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
			Fatal stroke	Reported in 7/7 trials NS
			Non-fatal stroke	- Reported in 7/7 trials - pooled OR=0.79 (95%CI 0.65-0.95) SS in favour of antihypertensive treatment
			Myocardial infarction	- 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
			Vascular events (stroke, MI or vascular mortality)	- 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
			Vascular mortality	NS
			Total mortality	NS
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→Moderate quality of evidence</b>
-1 for heterogeneity	OK	OK	OK	

- Bij patiënten met voorgeschiedenis van TIA of CVA (trombotisch of hemorragisch) leidt behandeling met antihypertensiva tot een significante daling van de incidentie van recidief CVA, van AMI en totale cardiovasculaire events. In alle studies afzonderlijk werd telkens een voordeel gevonden van antihypertensieve behandeling, maar vaak betrof het hier slechts een trend en werd geen statistische significantie bereikt.

GRADE: moderate quality of evidence

- Deze meta-analyse rapporteert geen gegevens over veiligheid.



### 4.3.1.2. ACE-inhibitoren vs. placebo

Perindopril 4mg + indapamide 2-2.5mg or perindopril 4mg vs placebo (PROGRESS Collaborative Group '01)								
N/n	Duration	Population	Results					
N=1, n=6015	Mean 3.9y	<ul style="list-style-type: none"> <li>- history of stroke or TIA &lt;5y</li> <li>- clinically stable for ≥2w after most recent vascular event</li> <li>- Mean age 64y</li> <li>- Mean BP at baseline: 147/86 mm Hg</li> </ul> <p><u>Exlcusion</u></p> <ul style="list-style-type: none"> <li>- Indication for ACE-I treatment</li> <li>- Contraindication for ACE-I</li> </ul> <p><u>Subgroups</u></p> <p><u>'hypertensive'</u></p> <ul style="list-style-type: none"> <li>- Mean baseline BP: 159/94 mm Hg</li> </ul> <p><u>'non-hypertensive'</u></p> <ul style="list-style-type: none"> <li>- Mean baseline BP: 136/79mm Hg</li> </ul> <p><u>Combination therapy</u></p> <ul style="list-style-type: none"> <li>- Mean age 64y</li> <li>- Age &gt;70y: 22%</li> <li>- Mean baseline BP: 149/87mm Hg</li> <li>- SBP &gt;160mm Hg: 25%</li> </ul> <p><u>Monotherapy</u></p> <ul style="list-style-type: none"> <li>- Mean age: 65y</li> <li>- Age&gt;70y: 31%</li> <li>- Mean baseline BP: 144/84 mm Hg</li> <li>- SBP&gt;160 mm Hg: 17%</li> </ul> <p><i>Choice between combination- or monotherapy by physician (before entry in study)</i></p>	Fatal or nonfatal stroke (ischaemic or haemorrhagic) (PE)	Perindopril 4mg +/- indapamide: 10%	Placebo: 14%	<b>SS: RRR 28% (95%CI 17 to 38), p&lt;0.0001</b>		
				<u>Prespecified SA: Hypertensive patients</u>	Perindopril 4mg +/- indapamide: 11.1%	Placebo: 16.2%	<b>SS: RRR 32% (95%CI 17 to 44)</b>	
				<u>Prespecified SA: Non-hypertensive patients</u>	Perindopril 4mg +/- indapamide: 9.1%	Placebo: 11.5%	<b>SS: RRR 27% (95%CI 8 to 42)</b>	
				<u>Prespecified SA: Combination therapy</u>	Perindopril 4mg +indapamide: 8.5%	Placebo: 12.7%	<b>SS: RRR 43% (95%CI 30 to 54)</b>	
				<u>Prespecified SA: Single drug therapy</u>	Perindopril 4mg : 12.3%	Placebo: 12.9%	NS: RRR 5% (95%CI -19 to 23)	
				Total major vascular events (non-fatal stroke, non-fatal myocardial infarction, death due to any vascular cause, including unexplained sudden death)	Perindopril 4mg +/- indapamide: 15%	Placebo: 20%	<b>SS: RRR 26% (95%CI 16 to 34)</b>	
					<u>Prespecified SA: Hypertensive patients</u>	Perindopril 4mg +/- indapamide: 16.4%	Placebo: 22.8%	<b>SS: RRR 29% (95%CI 16 to 40)</b>
					<u>Prespecified SA: Non-hypertensive patients</u>	Perindopril 4mg +/- indapamide: 13.3%	Placebo: 17%	<b>SS: RRR 24% (95%CI 9 to 37)</b>
					<u>Prespecified SA: Combination therapy</u>	Perindopril 4mg +indapamide: 19.7%	Placebo: 31.3%	<b>SS: RRR 40% (95%CI 29 to 49)</b>
					<u>Prespecified SA: Single drug therapy</u>	Perindopril 4mg : 17.7%	Placebo: 18.5%	NS: RRR 4% (95%CI -15 to 23)
					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>		Average 12.3/5.0 mm Hg (SE 0.5/0.3) reduction		
				<u>Prespecified SA: Single drug therapy</u>		Average 4.9/2.8 mm Hg (SE 0.6/0.3) reduction		
<b>AE</b>								
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					
<b>GRADE assessment</b>								
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→Moderate quality of evidence</b>				
-1 for unclear study design	NA	OK	OK					

- Deze studie vertelt ons dat een bloeddrukverlagend regime gebaseerd op perindopril 4mg (met of zonder toevoeging van indapamide) het risico op CVA doet dalen (RRR 28%). Ook het risico op het totaal aantal vasculaire events (niet-fataal CVA en AMI, vasculair overlijden en onverklaarde plotse dood) daalt met dit regime versus placebo (RRR 26%).

De keuze tussen combinatietherapie of monotherapie werd gemaakt door de behandelende arts voor de start van de studie.

Een voorafbepaalde subgroepanalyse stelt echter enkel bij combinatietherapie (perindopril + indapamide) een significantie daling van CVA (RRR 43%) of totale vasculaire events (RRR 40%) vast. Monotherapie (perindopril alleen) toont geen significant verschil. Het is op basis van deze gegevens niet mogelijk te achterhalen of deze discrepantie te wijten is aan de gebruikte geneesmiddelen, aan het verschil in bloeddrukdaling in beide groepen, of aan verschillen in populatiekenmerken, of eventueel gebrek aan power in de subgroepanalyses.

Een studie-arm met indapamide alleen was nuttig geweest om de rol van indapamide te verduidelijken.

We kunnen op basis van deze gegevens dus niet besluiten dat een bloeddrukverlagend regime perindopril moet bevatten om werkzaam te zijn.

Een andere vooraf bepaalde subgroepanalyse stelt een daling van CVA en totale vasculaire events vast zowel bij "hypertensieve patiënten" (gemiddelde startbloeddruk 159/94mmHg) als bij "niet-hypertensieve patiënten" (gemiddelde startbloeddruk 136/79 mmHg). De definitie 'hypertensie' werd evenwel gesteld op een eemalige meting bij inclusie en als afkapwaarde werd 160/90mm Hg genomen, wat hoger is dan gehanteerd in de klinische praktijk.

*GRADE: moderate quality of evidence*

- Er zijn o.a meer mensen die uit de studie stappen o.w.v. hypotensie (2.1% vs 0.4%), maar voor ongewenste effecten werden geen statistische tests uitgevoerd.

- Het Gecommentarieerd Geneesmiddelenrepertorium (BCFI 2012) vermeldt als belangrijkste ongewenste effecten van ACE-inhibitoren: verslechtering van de nierfunctie, hypotensieve reactie en hoest.

### 4.3.1.3. Diuretica 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
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→ Moderate quality of evidence</b>
-1 for incomplete reporting of results	OK	OK	OK	

- Behandeling met diuretica vermindert bij patiënten met voorgeschiedenis van TIA of CVA (ischemisch of hemorragisch) de incidentie van recidief CVA en de totale incidentie van cardiovasculaire events. Het optreden van AMI wordt niet beïnvloed. Deze resultaten werden vooral gestuurd door de PATS-trial, een Chinese studie waarin indapamide 2.5 mg/d vergeleken werd met placebo. Deze studie werd voortijdig gestopt.

*GRADE: moderate quality of evidence*

- Ongewenste effecten werden niet gerapporteerd.
- Het Gecommentarieerd Geneesmiddelenrepertorium (BCFI 2012) vermeldt als voornaamste ongewenste effecten van thiaziden: kaliumdepletie, hyponatriëmie, hyperuricemie en spierkrampen.

#### 4.3.1.4. $\beta$ -blokkers vs. placebo

Atenolol 50mg vs placebo (Dutch TIA Trial Study Group '93, Eriksson '95)				
N/n	Duration	Population	Results	
N=2, n=2139	Mean 2.6y	- Recent TIA or stroke $\leq$ 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	Mortality from vascular causes, nonfatal stroke or nonfatal myocardial infarction	Reported in 1/2 trials Crude HR=1.04 (95%CI 0.78-1.37) ⇒ NS
			Total mortality, non-fatal stroke, non-fatal myocardial infarction	Reported in 1/2 trials RR= 0.96 (95%CI 0.74-1.25) ⇒ NS
			Mortality	Reported in 2/2 trials ⇒ NS
			Mortality from vascular causes	Reported in 2/2 trials ⇒ NS
			Fatal stroke	Reported in 2/2 trials ⇒ NS
			Cardiac death	Reported in 2/2 trials NS
			Blood pressure	Reported in 2/2 trials 1 trial <b>MD=5.8/2.9mmHg</b> ⇒ <b>SS</b> 1 trial MD=4/3mmHg (NT)
GRADE assessment				
Quality	Consistency	Directness	Imprecision	→ Moderate quality of evidence
-1 for inadequate power and unclear reporting of endpoints	OK	OK	OK	

- Uit deze 2 (oudere) studies blijkt niet dat atenolol 50mg een recidief CVA of ander vasculair event kan voorkomen versus placebo, na een recente TIA of CVA.  
Deze studies zijn echter underpowered om een werkelijk verschil te kunnen aantonen. Ook bekeken deze studies in hoofdzaak het effect van atenolol als molecule (vasodilaterende eigenschappen), waarbij de bloeddrukdaling eerder als een randverschijnsel werd geobserveerd. In 1 studie werden deelnemers die een bloeddruk van <140/80 bereikten zelfs uit de studie gezet.

*GRADE: moderate quality of evidence*

- Uit de summier rapportering van de ongewenste effecten kunnen weinig conclusies getrokken worden.

- Het Gecommentarieerd Geneesmiddelenrepertorium (BCFI 2012) vermeldt als belangrijkste ongewenste effecten van  $\beta$ -blokkers: bradycardie, verminderde inspanningscapaciteit en hartfalen.

#### 4.3.1.5. Sartanen vs. placebo

Telmisartan 80mg vs placebo (Yusuf 2008 PRoFESS)				
N/n	Duration	Population	Results	
N=1, n=20,332	Mean 2.5y	<ul style="list-style-type: none"> <li>- recent ischemic stroke (&lt;90 d or 90-120 d if ≥2 additional risk factors)</li> <li>- mean age: 66y</li> <li>- mean BP at entry: 144/84 mm Hg</li> </ul> Exclusion <ul style="list-style-type: none"> <li>- primary hemorrhagic stroke</li> <li>- severe disability after qualifying stroke</li> <li>- uncontrolled hypertension</li> <li>- severe renal insufficiency</li> <li>- Severe hepatic dysfunction</li> <li>- Severe coronary artery disease</li> </ul>	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% ⇒ <b>SS</b>
			Hypotensive symptoms leading to discontinuation	Telmisartan 80 mg: 3.9% Placebo: 1.8% ⇒ <b>SS</b>
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→High quality of evidence</b>
OK	NA	OK	OK	

- Deze studie toont aan dat telmisartan 80mg/d geen invloed heeft op het vermijden van een recidief CVA of andere cardiovasculaire events bij patiënten met een recent ischemisch CVA. In deze studie, bij patiënten met een gemiddelde bloeddruk bij inclusie van 144/84 mm Hg, was het effect van telmisartan op de bloeddruk eerder klein: gemiddeld 3.2/2.0 mm Hg lager dan met placebo.

*GRADE: high quality of evidence*

- Men zag significant meer uitval door hypotensieve symptomen met telmisartan 80mg (3.9%) dan met placebo (1.8%).  
- Het Gecommentarieerd Geneesmiddelenrepertorium (BCFI 2012) vermeldt als belangrijkste ongewenste effecten van sartanen: verslechtering van de nierfunctie en hypotensieve reactie.

### 4.3.2. Antihypertensiva onderling

<b>Eprosartan 600 mg (+/- dose increase or combination therapy) vs nitrendipine 10 mg (+/- dose increase or combination therapy) (Schrader 2005=MOSES)</b>						
<b>N/n</b>	<b>Duration</b>	<b>Population</b>	<b>Results</b>			
N=1, n=1405	Mean: 2.5y	<ul style="list-style-type: none"> <li>- history of cerebrovascular events:&lt;24 m</li> <li>- treatment requiring hypertension</li> <li>- mean age 68y</li> </ul> <b>Excl</b> <ul style="list-style-type: none"> <li>- Internal carotid artery stenosis &gt;70%</li> <li>- Heart failure NYHA grade III-IV</li> <li>- Age&gt;85y at time of CV event</li> <li>- Anticoagulants for cardiac arrhythmia</li> <li>- High-grade aortic or mitral valve stenosis</li> <li>- Unstable angina pectoris</li> </ul>	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 <b>SS: IDR=0.79 (95%CI 0.66-0.96), p=0.014</b>		
			Total cerebrovascular events	Eprosartan 600mg: 6.56/100 patient years Nitrendipine 10 mg: 8.78/100 patient years <b>SS: IDR= 0.75 (95%CI 0.58-0.97), p=0.026</b>		
			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 <b>SS: HR=0.69 (95%CI 0.50-0.97), p=0.031</b>		
			Mortality	Eprosartan 600mg: 57 Nitrendipine 10 mg: 52 NS: HR=1.07 (95%CI 0.73-1.56), p=0.725		
			Blood pressure	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)		
			<b>AE's</b>			
			dizziness/hypotension		12.9% vs 10.6% (NT : 'comparable')	
<b>GRADE assessment</b>						
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→ Moderate quality of evidence</b>		
OK	NA	-1 for unbalanced composite endpoint	OK			

- Deze studie vergelijkt een bloeddrukverlagend regime met eprosartan met een bloeddrukverlagend regime met nitrendipine. Het samengestelde primaire eindpunt omvat mortaliteit en alle cerebrovasculaire events (ook TIA) en cardiovasculaire events, ook de recurrente events. Men vindt een significant verschil in het voordeel van eprosartan op dit primaire eindpunt.

Het eindpunt 'mortaliteit' of 'het eerste optreden van een cerebrovasculair event' is echter niet significant verschillend. Het is mogelijk dat de vaker voorkomende TIA de resultaten van het primaire eindpunt verklaart.

Het is op basis van deze ene studie niet mogelijk om te besluiten dat een bloeddrukverlagend regime met eprosartan superieur is in het vermijden van CVA of in het verminderen van totale mortaliteit

*GRADE: Moderate quality of evidence*

- Er werden geen statistische tests uitgevoerd in verband met ongewenste effecten. Duizeligheid/hypotensie kwam voor in 12.9% van de eprosartan groep versus 10.6% in de nitrendipine groep. De auteurs beschrijven dit als 'vergelijkbaar'.

## 4.4. Cholesterolverlaging na CVA/TIA bij personen zonder voorkamerfibrillatie

### 4.4.1. Statines 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)	<b>Atorvastatin 11.2% vs 13.1% placebo (p=0.05) HR= 0.84 (95% CI: 0.71-0.99) =&gt; SS</b>
			TIA	<b>Atorvastatin 6.5% vs 8.8% placebo (p=0.004) HR= 0.74 (95% CI: 0.60-0.91) =&gt; SS</b>
			Major coronary event	<b>Atorvastatin 3.4% vs 5.1% placebo (p=0.006) HR= 0.65 (95% CI: 0.49-0.87) =&gt; SS</b>
			Myocardial infarction (non-fatal)	<b>Atorvastatin 1.8% vs 3.5% placebo (p=0.001) HR= 0.51 (95% CI: 0.35-0.74) =&gt; SS</b>
			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	<b>Atorvastatin 2.2% vs 0.5% placebo (p&lt;0.001) =&gt; SS</b>
GRADE assessment				
Quality	Consistency	Directness	Imprecision	→High quality of evidence
OK	OK	OK	OK	

- Bij patiënten die reeds een CVA of TIA doormaakten en die behandeld worden met statines, doen zich significant minder nieuwe CVA's, TIA's of hartinfarcten voor. Er is evenwel geen significant verschil in de mortaliteit tussen de behandelingsgroep met statines of met placebo.

*GRADE: high quality of evidence*

- Zowel bij de behandeling met statines als met placebo, klagen de patiënten van ongewenste effecten, doch dit is niet statistisch getest. Atorvastatine veroorzaakt significant meer verhoogde leverenzymen dan placebo.





## **5. Heelkunde bovenop medicamenteuze behandeling vs. medicamenteuze behandeling alleen**



## 5. Heelkunde bovenop medicamenteuze behandeling vs. medicamenteuze behandeling alleen

### 5.1. Carotis endarterectomie + medicatie versus medicatie alleen bij asymptomatische carotisstenose

Carotid endarterectomy plus medical therapy vs. medical therapy alone for asymptomatic carotid stenosis. (MA Chambers: ACAS '95, ACST '94, Hobson '93 (VACS))				
N/n	Duration	Population	Results	
N=3, n=5223	2.7-4y	-asymptomatic carotid artery stenosis -2 trials > 60% stenosis, 1 trial 50-99% -mostly male -mean age 64.5-67y	Perioperative stroke or death or any subsequent stroke	Reported in 3/3 trials <b>RR 0.69 (95%CI 0.57-0.83) SS in favour of surgery</b> <b>VA-trial: 1% ARR over 4y</b> <b>ACAS-trial: 3% ARR over 2.7y</b> <b>ACST-trial: 3.1% ARR over 3.4y</b> <b>ACST-trial: 4.6% ARR over 10y</b>
			Perioperative stroke or death or subsequent ipsilateral stroke over 3-4 years	Reported in 3/3 trials <b>RR 0.71 (95%CI 0.55-0.90) SS in favour of surgery</b>
			Any stroke or death	Reported in 3/3 trials RR 0.92 (95%CI 0.83-1.02) NS
			Perioperative stroke or death	Reported in 2/3 trials <b>RR 6.49 (95%CI 2.53-16.61) SS in favour of medical treatment</b>
GRADE assessment				
Quality	Consistency	Directness	Imprecision	→Moderate quality of evidence
OK	OK	-1 for no contemporary medical therapy	OK	

Bij patiënten met een asymptomatische carotisstenose (60-99%) vermindert carotisendarterectomie plus medicamenteuze behandeling het risico op een peri-operatief CVA of sterfte of een volgend CVA met 31% gedurende 3 jaar, vergeleken met medicamenteuze behandeling alleen. De resultaten na 10 jaar follow-up in één van de drie studies tonen voor het zelfde eindpunt een absolute risicoreductie van 4.6%; dit betekent een NNT van 22. Voor het eindpunt alle CVA's en sterfte is er geen significant verschil aangetoond.

De medicamenteuze behandeling tijdens de eerste jaren van deze studies was suboptimaal (anti-hypertensiva en statines) waardoor de resultaten niet volledig van toepassing zijn voor de huidige aanpak van carotisstenose. Deze resultaten moeten ook geïnterpreteerd worden rekening houdend met een operatief risico van minder dan 3% op CVA of sterfte.

GRADE: moderate quality of evidence

## 5.2. Carotis endarterectomie + medicatie versus medicatie alleen bij symptomatische carotisstenose

<b>Carotid endarterectomy plus medical therapy vs medical therapy alone for symptomatic carotid stenosis.</b> (MA Rerkasem: Boiten '96 (ECST), Barnett '91 (NASCET), Mayberg '91 (VACSP))				
<b>N/n</b>	<b>Duration</b>	<b>Population</b>	<b>Results</b>	
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)
				<b>50-69% stenosis: RR 0.77 (95%CI 0.63-0.94) (3/3 trials)</b> NNT at 5y to prevent 1 event: 13
				<b>70-99% stenosis: RR 0.53 (95%CI 0.42-0.67) (3/3 trials)</b>
				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
				<b>70-99% stenosis: RR 0.40 (95%CI 0.30-0.54) (3/3 trials)</b> NNT at 5y to prevent 1 event: 6
				Near-occlusion: RR 1.04 (95%CI 0.58-1.86) (2/3 trials)
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→Moderate quality of evidence</b>
-1 for not blinding	OK	OK	OK	

- Deze 3 studies tonen een duidelijk voordeel van carotis endarterectomie plus medicamenteuze behandeling bij patiënten met een symptomatische stenose van 70 tot 99% (NASCET-meting), vergeleken met medicamenteuze behandeling alleen. Men moet 6 patiënten opereren om binnen een opvolgperiode van 5 jaar een ischemisch CVA in het ipsilaterale carotisgebied, een CVA of een peri-operatief overlijden te vermijden. Het voordeel van een ingreep is groter bij mannen, bij hogere leeftijd (>75j) en bij ingrepen uitgevoerd kort (<2 weken) na het ontstaan van de symptomen. Deze resultaten zijn van toepassing in centra met een operatief risico op complicaties van minder dan 7%. Het voordeel is minder uitgesproken voor stenoses van 50 tot 69% (NNT= 22 na 5 jaar).
- Bij andere gradaties van stenose is er geen voordeel aangetoond.

*GRADE: Moderate quality of evidence*

### 5.3. Extracraniële-intracraniële bypass + medicatie versus medicatie alleen bij symptomatische carotisocclusie

Extracraniële-intracraniële bypass plus medicatie versus medicatie alleen. (Powers 2011, COSS)				
N/n	Duration	Population	Results	
N=1, n 195	2y	-mean age 58 -recent symptomatic atherosclerotic internal carotid artery occlusion. -arteriographically 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	

Deze studie toont aan dat heelkunde door middel van een extracraniële-intracraniële bypass bovenop medicamenteuze aanpak geen voordeel biedt vergeleken met een medicamenteuze aanpak alleen bij patiënten met een recente symptomatische occlusie van de arteria carotis interna.

GRADE: Moderate quality of evidence

## 5.4. Endovasculaire aanpak + medicatie versus medicatie alleen bij (a)symptomatische carotisstenose

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	

Deze studie van zwakke kwaliteit toont geen meerwaarde van een endovasculaire ingreep (angioplastie met of zonder stenting) vergeleken met medicatie alleen bij patiënten die niet in aanmerking kwamen voor een carotisendarterectomie.

GRADE: *Very low quality of evidence*

## **6. Cardiovasculaire risicoreductie na CVA/TIA bij personen met voorkamerfibrillatie**





## 6. Samenvatting van de resultaten: risicoreductie na CVA/TIA bij personen met voorkamerfibrillatie

### 6.1. Orale anticoagulantia na CVA/TIA bij personen met voorkamerfibrillatie

#### 6.1.1. Orale anticoagulantia in aangepaste dosis vs. placebo

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

- Bij patiënten met voorkamerfibrillatie en voorgeschiedenis van TIA/CVA leidt behandeling met orale anticoagulantia in aangepaste dosis tot een verlaging van de incidentie van recidief CVA en van het totaal aantal cardiovasculaire events. Behandeling van 1.000 patiënten gedurende een jaar kan 90 cardiovasculaire events, waaronder voornamelijk CVA, voorkomen.

*GRADE :high quality of evidence*

- Vergeleken met controle, hebben patiënten behandeld met orale anticoagulantia een grotere kans op een majeure intracraniale bloeding. Behandeling van 1.000 patiënten gedurende een jaar leidt tot 21 extra majeure hersenbloedingen, vergeleken met geen behandeling.

### 6.1.2. Warfarine in standaarddosering vs. laag-intensiteit of minidosis warfarine

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	

- In een kleine studie bij patiënten met VKF en voorgeschiedenis van ischemisch CVA werd geen significant verschil gevonden tussen warfarine in standaarddosering en lage dosis wat betreft het optreden van recidief ischemisch CVA. Andere eindpunten werden niet gerapporteerd.

*GRADE: low quality of evidence*

- In de groep behandeld met warfarine in standaarddosering was er een significant hogere incidentie van majeure bloedingen. Om deze reden werd de studie voortijdig stopgezet.

### 6.1.3. Orale anticoagulantia vs anti-aggregantia

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

- Orale anticoagulantia zijn statistisch significant beter dan anti-aggregantia in het voorkomen van ernstige vasculaire aandoeningen zoals dood door vaatstoornissen, nieuwe beroerte, hartinfarct of systemische embolen bij patiënten met voorkamerfibrillatie die reeds een CVA of TIA doormaakten. Orale anticoagulantia verminderen significant het risico op recidief CVA's ten opzichte van anti-aggregantia.

*GRADE: moderate quality of evidence*

- Er bestaat significant minder kans op ernstige extracranieële bloedingen onder behandeling van anti-aggregantia in vergelijking met orale anticoagulantia. Voor het aantal intracranieële bloedingen is het verschil tussen beide behandelingsgroepen niet statistisch significant.

## **6.2. Anti-aggregantia na CVA/TIA bij personen met voorkamerfibrillatie**

Er werden geen studies weerhouden voor deze onderzoekspopulatie

## **7. Cardiovasculaire risicoreductie bij personen met voorkamerfibrillatie zonder voorgeschiedenis van CVA/TIA**



## 7. Samenvatting van de resultaten: risicoreductie bij personen met voorkamerfibrillatie zonder voorgeschiedenis van CVA/TIA

### 7.1. Risicoreductie bij personen met voorkamerfibrillatie met hoog risico op CVA/TIA

#### 7.1.1. Orale anticoagulantia bij personen met voorkamerfibrillatie met hoog risico op CVA/TIA

##### 7.1.1.1. Warfarine in aangepaste dosis vs. lage dosis warfarine plus 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	

- Bij patiënten met voorkamerfibrillatie en verhoogd risico van CVA werd warfarine in aangepaste dosis (INR 2-3) vergeleken met laaggedoseerd warfarine (INR 1.5-2) plus acetylsalicylzuur 325 mg/d. Behandeling met de associatie bleek gepaard te gaan met een hogere incidentie van ischemisch CVA en systeemembolen. De gegevens over mortaliteit en fataal CVA werden niet statistisch getoetst.

GRADE: low quality of evidence

- Er was geen significant verschil tussen de associatie en warfarine met INR 2-3 wat betreft de incidentie van majeure bloedingen. Andere veiligheidsuitkomsten werden niet statistisch getoetst.

### 7.1.1.2. Warfarine in standaarddosis vs. low-intensity of minidosis warfarine

#### 7.1.1.2.1. Warfarine in standaarddosis vs. low-intensity of minidosis warfarine

Adjusted-dose warfarin (INR:2-3) vs ow-dose warfarin (1.25mg/d) (SPAF3 1996, Gulløv 1998, Pengo 1998, Hellemons 1999)					
N/n	Duration	Population	Results		
N=4 n=2753	Mean: 1.9y	Nonvalvular chronic AF	Outcomes	With or without aspirin	Without aspirin
			Ischemic stroke	RR=0.46 (95% CI: 0.20-1.07)	RR=0.67 (95% CI: 0.33-1.36)
		Mean age: 73.7y	All thrombotic events (CVA, MI, systemic embolism)	<b>RR=0.50 (95% CI: 0.25-0.97) =&gt; SS in favour of adjusted-dose warfarin</b>	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)	
GRADE assessment					
Quality	Consistency	Directness	Imprecision	→Low quality of evidence	
-1 Incomplete reporting of results	OK	-1 Heterogeneous population	OK		

- Het gebruik van warfarine in een lage dosis leidt tot meer thrombo-embolieën (CVA, hartinfarct en systemische embolen) dan het aanpassen van de dosis warfarine op basis van de INR-bepaling. Voor de preventie van het optreden van CVA bij patiënten met niet-reumatische voorkamerfibrillatie wordt aanbevolen om de INR tussen 2 en 3 te houden.

- Voor het verminderen van het risico op beroertes was er geen significant verschil tussen beide doses.

GRADE: low quality of evidence

- Het bloedingsrisico werd niet significant verminderd door het toedienen van een lage dosis in vergelijking met een aangepaste dosis warfarine.

- Er dient opgemerkt te worden dat deze meta-analyse studies combineerde die klinisch heterogeen en bovendien niet geblindeerd waren. Enkele opgenomen studies bezaten niet voldoende power om een significant verschil tussen de therapiegroepen vast te stellen. In sommige gevallen werd naast warfarine ook preventief acetylsalicylzuur toegediend, waardoor moeilijk vast te stellen is welk effect elke afzonderlijke behandeling had op het uiteindelijke resultaat.



**7.1.1.2.2. Warfarine in aangepaste dosis lower target INR (1.5-2.0) vs. standard target INR (2.0-3.0) bij hoogbejaarde patiënten (30% high risk en 70% moderate)**

Lower target INR (1.5-2.0) vs standard target INR (2.0-3.0) in elderly patients with non-valvular Atrial fibrillation (Pengo 2010)				
N/n	Duration	Population	Results	
N=1, n=267	Mean 5.2y	<ul style="list-style-type: none"> <li>- non-valvular atrial fibrillation</li> <li>- mean age 80y</li> <li>- TTR INR:</li> <li>  lower target group:</li> <li>    TTR(1.5-2) 50%</li> <li>    TTR(2-3) 35%</li> <li>  standard target group:</li> <li>    TTR(1.5-2) 22%</li> <li>    TTR (2-3) 65%</li> </ul> <p><u>Exclusion</u></p> <ul style="list-style-type: none"> <li>- Previous cerebral ischaemia (stroke or TIA)</li> <li>- Uncontrolled BP</li> <li>- Chronic renal failure</li> <li>- Chronic hepatic failure</li> <li>- CHF (III-IV)</li> <li>- AMI &lt;1m</li> <li>- Major bleeding &lt;6 months</li> </ul>	Efficacy	
			Tromboembolism and major bleeding	3.5/100 patient years vs 5.0/100 patient years NS: HR=0.7 (95%CI 0.4-1.1)
			Tromboembolism	1.6/100 patient years vs 2.0/100 patient years NS: HR=0.8 (95%CI 0.4-1.8)
			Major bleeding	1.9/100 patient years vs 3.0/100 patient years NS: HR=0.6 (95%CI 0.3-1.2)
			Median INR	1.86 (IQR 1.58-2.23) vs 2.24 (IQR 1.88-2.67) <b>SS: p&lt;0.001</b>
			AE's	
NR				
GRADE assessment				
Quality	Consistency	Directness	Imprecision	→ Moderate quality of evidence
OK	NA	OK	-1 for inadequate power	

- Deze studie suggereert dat een lagere target INR (1.5-2.0) bij hoogbejaarden geen significant verschil geeft in het samengesteld eindpunt 'tromboembolen en majeure bloedingen' versus de gebruikelijke target INR (2.0-3.0).

Deze studie had echter onvoldoende power om een echt verschil in dit eindpunt en zeker de individuele eindpunten te kunnen aantonen. We kunnen op basis van deze studie dus geen definitieve conclusies trekken

GRADE: moderate quality of evidence

- Zo is er een lager absoluut aantal majeure bloedingen met de lagere target INR, maar deze is dus niet statistisch significant. Verder onderzoek is nodig of deze interessante piste (iets lagere target) bij een kwetsbare populatie kan leiden tot minder majeure bloedingen zonder verhoging van het thromboserisico.

### 7.1.1.3 Warfarine in standaarddosering vs. antiagregantia/associaties

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	

- Orale anticoagulantia (streefwaarde INR 2-3) werden vergeleken met de associatie van clopidogrel 75 mg/d en acetylsalicylzuur 75-100 mg/d bij patiënten met voorkamerfibrillatie en verhoogd risico van CVA (CHADS score gemiddeld 2). Orale anticoagulantia bleken superieur aan anti-aggregantia voor het voorkomen van cardiovasculaire events, waaronder ook ischemisch en hemorragisch CVA. De mortaliteit en de incidentie van AMI werden niet significant beïnvloed.

GRADE: moderate quality of evidence

- Bij patiënten behandeld met anti-aggregantia werd een hogere totale incidentie van bloeding vastgesteld. Het aantal ernstige en intracraniale bloedingen was niet significant verschillend tussen beide groepen.

### 7.1.1.4. Apixaban vs. acetylsalicylzuur

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	<b>Efficacy</b>	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Apixaban: 1.6%/y Aspirin: 3.7%/y <b>Apixaban SS better: HR= 0.45 (95%CI 0.32-0.62), p&lt;0.001</b>
			Ischemic stroke	Apixaban: 1.1%/y Aspirin: 3.0%/y <b>Apixaban SS better: HR= 0.37 (95%CI 0.25-0.55), p&lt;0.001</b>
			Disabling or fatal stroke	Apixaban: 1.0%/y Aspirin: 2.3%/y <b>Apixaban SS better: HR= 0.43 (95%CI 0.28-0.65), p&lt;0.001</b>
			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
			Myocardial infarction	Apixaban: 0.8%/y Aspirin: 0.9%/y NS: HR= 0.86 (95%CI 0.50-1.48), p=0.59
			<b>Harms</b>	
			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
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→Low quality of evidence</b>
-1 for early termination of study (clear benefit of apixaban)	NA	-1 for 36% CHADS 0-1	OK	

Deze studie van lage kwaliteit toont dat bij patiënten met voorkamerfibrillatie die niet in aanmerking kwamen voor een behandeling met vitamine K-antagonisten, apixaban werkzamer is dan aspirine. Apixaban is werkzamer op het gecombineerd eindpunt CVA en systemisch embool (HR 0.45), op het eindpunt ischemisch CVA (HR 0.37) en op het eindpunt invaliderend of fataal CVA (HR 0.43). Op het eindpunt hemorragisch CVA en mortaliteit is er geen statistisch significant verschil. Op het vlak van veiligheid (bloedingen) zijn er geen verschillen aangetoond.

GRADE: low quality of evidence

- Ongewenste effecten: er wordt geen statistische toets gerapporteerd.

### 7.1.1.5. Apixaban vs. warfarine

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	<b>Efficacy</b>	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Apixaban 1.27%/y vs 1.60%/y warfarin <b>Superior: HR= 0.79 (95%CI 0.66-0.95) p&lt;0.001 for noninferiority p = 0.01 for superiority</b>
			Ischemic stroke	Apixaban 1.19%/y vs 1.51%/y warfarin <b>Superior: HR 0.79 (95%CI 0.65-0.95), p = 0.01</b>
			Hemorrhagic stroke	Apixaban 0.24%/y vs 0.47%/y warfarin <b>Superior: HR 0.51 (95%CI 0.35-0.75), p&lt;0.001</b>
			Mortality	Apixaban 3.52%/y vs 3.94%/y warfarin <b>Superior: HR 0.89 (95%CI 0.80-0.998), p=0.047</b>
			Myocardial infarction	Apixaban 0.53%/y vs 0.61%/y warfarin NS: HR 0.37 (95%CI 0.66-1.17), p=0.37
			<b>Harms</b>	
			Intracranial bleeding	Apixaban 0.33%/y vs 0.80%/y warfarin <b>SS less intracranial bleedings with apixaban: HR 0.42 (95%CI 0.30-0.58), p&lt;0.001</b>
			Any bleeding	Apixaban 18.1%/y vs warfarin 25.8%/y <b>SS less any bleedings with apixaban, p&lt;0.001</b>
			ISTH major bleeding	Apixaban 2.13%/y vs warfarin 3.09%/y <b>SS less ISTH major bleedings with apixaban, p &lt;0.001</b>
			Fatal bleeding	NR
			GI-bleeding	Apixaban 0.76%/y vs warfarin 0.86%/y NS, p = 0.37
			AE's	No statistical analysis
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→Moderate quality of evidence</b>
OK	NA	-1 for 34% patients with CHADS2 = 1	OK	

- Deze studie van goede kwaliteit toont een voordeel aan van apixaban 2 keer 5mg vergeleken met warfarine (INR 2-3) op het vlak van werkzaamheid en veiligheid. Op het gecombineerd primair eindpunt CVA (ischemisch of hemorragisch) en systemisch embolus is apixaban werkzaamere dan warfarine met een hazard ratio van 0.79. Het aantal ischemische CVA's, hemorragische CVA's en overlijdens is statistisch significant lager in de apixabangroep. Er is geen verschil in aantal myocardinfarcten. Op het vlak van veiligheid scoort apixaban ook beter: minder totale, intracraniale en majeure bloedingen. Geen verschil in aantal gastro-intestinale bloedingen. De onderzochte populatie bestond voor 34% uit patiënten met een CHADS2-score van 1. Perorale anticoagulantia zijn voornamelijk geïndiceerd vanaf een CHADS2-score vanaf 2.

*GRADE: moderate quality of evidence*

- Ongewenste effecten: er wordt geen statistische toets gerapporteerd.

### 7.1.1.6. Dabigatran vs. warfarine

#### 7.1.1.6.1. Dabigatran 2x110mg/d vs warfarine

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	<b>Efficacy</b>	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Dabigatran 110mg: 1.53%/y Warfarine: 1.69%/y <b>Non-inferior: RR 0.91 (95%CI 0.74-1.11), p&lt;0.001 for noninferiority, Not superior (p=0.34)</b>
			Ischemic or unspecified stroke	Dabigatran 110mg: 1.34%/y Warfarine: 1.20%/y NS: RR 1.11 (95%CI 0.89-1.40) (p=0.35)
			Hemorrhagic stroke	Dabigatran 110mg: 0.12%/y Warfarine: 0.38%/y <b>Superior: RR 0.31 (95%CI 0.17-0.56), p&lt;0.001</b>
			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)
			<b>Harms</b>	
			Intracranial bleeding	Dabigatran 110mg 0.23%/y vs warfarine 0.74%/y <b>SS less intracranial bleedings with dabigatran 110mg: RR 0.31 (95%CI 0.20-0.47), p&lt;0.001</b>
			Major life threatening bleeding	1.22%/y vs 1.80%/y <b>SS less major life threatening bleedings with dabigatran 110mg: RR 0.68 (95%CI 0.55-0.83), p&lt;0.001</b>
			Major or minor bleeding	14.62%/y vs 18.15%/y <b>SS less major or minor bleedings with dabigatran 110mg: RR = 0.78 (95%CI 0.74-0.83), p&lt;0.001</b>
			Minor bleeding	13.16%/y vs 16.37%/y <b>SS less minor bleedings with dabigatran 110mg RR = 0.79 (95%CI 0.74-0.84), p&lt;0.001</b>
			GI-bleeding	1.66%/y vs 1.76%/y NS: RR 0.94 (95%CI 0.78-1.15), p=0.56
Dyspepsia	<b>SS more dyspepsia 11.8% vs 5.8% (p&lt;0.001)</b>			
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→Moderate quality of evidence</b>
-1 for not blinding	NA	OK	OK	

- Deze studie van matige kwaliteit toont aan dat dabigatran 2x110mg/d niet inferieur is aan warfarine op het gecombineerd eindpunt CVA (ischemisch en hemorragisch) en systemisch embol. Op het eindpunt hemorragische CVA's is dabigatran 2x110mg superieur aan warfarine (RR 0.31) . Op de eindpunten ischemische CVA's en mortaliteit is aangetoond dat dabigatran 2x110mg niet inferieur is aan warfarine.

Dabigatran 2x110mg leidt niet tot meer myocardinfarcten.

- Op het vlak van bloedingen zijn er met dabigatran 2x110mg significant minder intracraniale (RR 0.31) en levensbedreigende bloedingen (RR 0.68). Ook het aantal majeure of mineure bloedingen (RR 0.78) en het aantal mineure bloedingen (RR 0.79) zijn lager met dabigatran 110mg. Wat gastro-intestinale bloedingen betreft is er geen statistisch significant verschil.

*GRADE: Moderate quality of evidence*

- Dabigatran 2x110mg geeft vergeleken met warfarine meer aanleiding tot dyspepsie.

### 7.1.1.6.2. Dabigatran 2x150mg/d vs warfarine

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	<b>Efficacy</b>	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Dabigatran 150mg: 1.11%/y Warfarin: 1.69%/y <b>Superior: RR 0.66 (95%CI 0.53-0.82), p&lt;0.001</b>
			Ischemic or unspecified stroke	Dabigatran 150mg: 0.92%/y Warfarin: 1.20%/y <b>Superior: RR 0.76 (95%CI 0.60-0.98), p=0.03</b>
			Hemorrhagic stroke	Dabigatran 150mg: 0.10%/y Warfarin: 0.38%/y <b>Superior: RR 0.26 (95%CI 0.14-0.49), p&lt;0.001</b>
			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 <b>SS more MI in dabigatran group: RR 1.38 (95%CI 1.00-1.91) p = 0.048</b>
			<b>Harms</b>	
			Intracranial bleeding	Dabigatran 150mg 0.30%/y vs warfarin 0.74%/y <b>SS less intracranial bleedings with dabigatran: RR 0.40 (95%CI 0.27-0.60), p&lt;0.001</b>
			Major life threatening bleeding	1.45%/y vs 1.80%/y <b>SS less major life threatening bleedings with dabigatran: RR 0.81 (95%CI 0.66-0.99), p = 0.04</b>
			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 <b>SS more GI-bleeding in dabigatran group: RR 1.50 (95%CI 1.19-1.89), p&lt;0.001</b>			
Dyspepsia	SS more in dabigatran group <b>11.3% vs 5.8% (p&lt;0.001)</b>			
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→Moderate quality of evidence</b>
-1 for not blinding	NA	OK	OK	

- Deze studie van matige kwaliteit toont aan dat dabigatran 2x150 mg/d superieur is aan warfarine op het gecombineerd eindpunt CVA (ischemisch en hemorragisch) en systemisch embol (NNT= 172 gedurende 2 jaar). Dit wordt voornamelijk gerealiseerd door een vermindering in aantal hemorragische CVA's (RR 0.26). Ook op het eindpunt ischemische of niet gespecificeerde CVA's is aangetoond dat dabigatran 2x150mg net significant superieur is aan warfarine (RR 0.76). Op het eindpunt mortaliteit is er geen significant verschil.

- Levensbedreigende bloedingen komen minder voor in de dabigatran 2x150mg-groep (RR 0.81). Gastro-intestinale bloedingen komen daarentegen meer voor (RR 1.50). Ook het aantal myocardinfarcten ligt hoger in de dabigatran 2x150mg groep (RR1.38).

*GRADE: moderate quality of evidence*

- Dabigatran 2x150mg geeft vergeleken met warfarine meer aanleiding tot dyspepsie.

### 7.1.1.7. Rivaroxaban vs. warfarine

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 <sub>2</sub> ≥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	<b>Efficacy</b>	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Rivaroxaban: 2.1%/y vs warfarin: 2.4%/y <b>Not inferior: HR 0.88 (95%CI 0.74 – 1.03)</b> <b>p&lt;0.001 for noninferiority, p = 0.12 for superiority (IIT)</b>
			Ischemic stroke	Rivaroxaban 1.34% vs warfarin 1.42% NS: HR 0.94; 95%CI 0.75-1.17, p=0.581
			Hemorrhagic stroke	<b>Rivaroxaban 0.26% vs warfarin 0.44%</b> <b>Superior: HR 0.59 (95%CI 0.37-0.93)</b> <b>p=0.024</b>
			Mortality	Rivaroxaban 1.87% vs 2.21% warfarin NS: HR 0.85 (95%CI 0.70 – 1.02) p=0.073
			Myocardial infarction	Rivaroxaban 0.91% vs 1.12% warfarin NS: HR 0.81 (95%CI 0.63 – 1.06) p=0.121
			<b>Harms</b>	
			Intracranial bleeding	<b>Rivaroxaban 0.5% vs 0.7% warfarin</b> <b>SS less intracranial bleeding with rivaroxaban: HR 0.67 (95% CI 0.47-0.93)</b> <b>(p=0.02)</b>
			Major bleeding	3.6% vs 3.4% (NS: p=0.58)
			Decrease in Hb ≥ 2g/dl	<b>2.8% vs 2.3%</b> <b>SS more decrease in Hb ≥ 2g/dl with rivaroxaban: HR 1.22 (95%CI 1.03-1.44)</b> <b>(p=0.02)</b>
			Fatal bleeding	<b>0.2% vs 0.5%</b> <b>SS less fatal bleeding with rivaroxaban: HR 0.50 (95%CI 0.31-0.79), p=0.003</b>
			Transfusion	<b>1.6% vs 1.3%</b> <b>SS more need of transfusion with rivaroxaban : HR 1.25 (95%CI 1.01-1.55), p = 0.04</b>
			GI-bleeding	<b>3.2% vs 2.2%</b> <b>SS more GI-bleeding with rivaroxaban ( p&lt;0.001)</b>
			<b>AE</b>	
			<b>Epistaxis (10.14% vs 8.55%, SS: p&lt;0.05) and hematuria (4.16% vs 3.420%, SS: p&lt;0.05) SS more frequent in rivaroxaban group</b>	
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	<b>→Moderate quality of evidence</b>
OK	NA	-1 for low TTR warfarin group	OK	

Deze studie toont aan dat rivaroxaban niet inferieur is aan warfarine voor de preventie van CVA en systemisch embol bij patiënten met voorkamerfibrillatie en een CHADS<sub>2</sub>-score ≥2. Rivaroxaban geeft geen significante daling in aantal ischemische CVA's, wel in aantal hemorrhagische CVA's (HR 0.59). Mortaliteit en aantal myocardinfarcten verschillen niet significant.

Op het vlak van veiligheid geeft rivaroxaban minder aanleiding tot intracranieële (0.5% vs 0.7%, NNT 246) en fatale bloedingen (0.2% vs 0.5%, NNT 254). In de rivaroxabangroep komen daarentegen meer gastro-intestinale bloedingen voor (3.2% vs 2.2%, NNH 101). Ook zijn er meer dalingen in het hemoglobine van meer dan 2g/dl (2.8% vs 2.3%, NNH 138) en vaker nood aan transfusie (1.6% vs 1.3%, NNH 207).

*GRADE: moderate quality of evidence*

- Er wordt vaker epistaxis en hematurie gerapporteerd met rivaroxaban vergeleken met warfarine.

### 7.1.1.8. Dosisvergelijkingen

#### 7.1.1.8.1 Dabigatran 2x150mg/d vs dabigatran 2x110mg/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	<b>Efficacy</b>	
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Dabigatran 150mg: 1.11%/y Dabigatran 110mg: 1.53%/y <b>SS: RR 0.73 (95%CI 0.58-0.91), p = 0.005</b>
			Ischemic or unspecified stroke	Dabigatran 150mg: 0.92%/y Dabigatran 110mg: 1.34%/y <b>SS: RR 0.69 (95%CI 0.54-0.88), p=0.002</b>
			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: RR 1.02 (95%CI 0.76-1.38), p=0.88
			<b>Harms</b>	
			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 <b>SS more minor bleeding with 150 mg: RR 1.16 (95%CI 1.08-1.24), p&lt;0.001</b>
			Major or minor bleeding	Dabigatran 150mg 16.42%/y vs 14.62%/y 110mg <b>SS more major or minor bleeding with 150 mg: RR 1.16 (95%CI 1.09-1.23), p&lt;0.001</b>
			GI-bleeding	1.51%/y vs 1.12%/y <b>SS more GI-bleeding with 150mg: RR 1.36 (95%CI 1.09-1.70), p=0.007</b>
<b>GRADE assessment</b>				
<b>Quality</b>	<b>Consistency</b>	<b>Directness</b>	<b>Imprecision</b>	→High quality of evidence
OK	NA	OK	OK	

- Deze studie toont aan dat dabigatran 2x150 mg/d werkzamer is dan dabigatran 2x110 mg/d op het primair eindpunt CVA (ischemisch en hemorragisch) en systemisch embol (RR 0.73). Dit verschil wordt voornamelijk gerealiseerd door een daling in het aantal ischemische CVA's (RR 0.69). Op het vlak van hemorragische CVA's, mortaliteit en myocardinfecten is er geen verschil. Deze verhoogde werkzaamheid gaat wel ten koste van meer gastro-intestinale bloedingen (RR 1.36), meer mineur bloedingen (RR 1.16) en meer majeure of mineure bloedingen (RR 1.16).

GRADE: high quality of evidence

- Er wordt geen statistische toets voor ongewenste effecten gerapporteerd.



## 7.1.2. Anti-aggregantia bij personen met voorkamerfibrillatie met hoog risico op CVA/TIA

### 7.1.2.1. Acetylsalicylzuur + clopidogrel vs. acetylsalicylzuur

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 heterogeneo us study population	OK	

- De associatie van clopidogrel en acetylsalicylzuur vergeleken met acetylsalicylzuur alleen werd onderzocht bij patiënten met voorkamerfibrillatie die ongeschikt waren voor behandeling met vitamine K-antagonisten. Ongeveer 2/3 van de onderzoekspopulatie had een verhoogd risico van CVA. De associatie bleek werkzaamere dan acetylsalicylzuur in monotherapie voor de preventie van majeure vasculaire events, vnl. CVA. Op mortaliteit en AMI werd geen effect gevonden. De NNT voor het primaire samengesteld eindpunt bedroeg 125.

GRADE: moderate quality of evidence

- In de groep behandeld met de associatie traden significant meer majeure bloedingen op (NNH=143).

## 7.2. Risicoreductie bij personen met voorkamerfibrillatie met laag tot matig risico op CVA/TIA

### 7.2.1. Orale anticoagulantia bij personen met voorkamerfibrillatie met laag tot matig risico op CVA/TIA

#### 7.2.1.1. Orale anticoagulantia 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 <b>OR=0.39 (95% CI 0.26-0.59)</b> in favour of treatment with OACs
			Ischemic strokes	Reported in 5/5 trials <b>OR=0.34 (95% CI 0.23-0.52)</b> in favour of treatment with OACs
			Disabling or fatal strokes	Reported in 5/5 trials <b>OR=0.47 (95% CI 0.28-0.80)</b> 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 <b>OR=0.57 (95% CI 0.42-0.76)</b> in favour of treatment with OACs
			All cause mortality	Reported in 5/5 trials <b>OR=0.69 (95% CI 0.50-0.94)</b> in favour of treatment with OACs
GRADE assessment				
Quality	Consistency	Directness	Imprecision	→Moderate quality of evidence
-1 for methodological weakness	OK	OK	OK	

- Bij chronische voorkamerfibrillatie patiënten met een laag tot matig risico op CVA of TIA en zonder voorgeschiedenis van CVA of TIA reduceren orale anticoagulantia significant het risico op beroertes (OR=0.39, 95% BI 0.26-0.59). De dosis orale anticoagulantia wordt individueel aangepast tot de INR zich tussen 2 en 3 bevindt. De mortaliteit ten gevolge van alle mogelijke oorzaken daalt tevens significant bij het gebruik van orale anticoagulantia.

*GRADE: moderate quality of evidence*

- Er zijn meer intracranieële of majeure bloedingen bij behandeling met orale anticoagulantia ten opzichte van placebo, maar het verschil is niet significant.

### 7.2.1.2. Warfarine in aangepaste dosis vs. acetylsalicylzuur

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

- Bij patiënten met chronische voorkamerfibrillatie zonder voorgeschiedenis van CVA of TIA reduceert warfarine significant het risico op beroertes in vergelijking met acetylsalicylzuur in een lage dosis (minder dan 300 mg per dag). Deze statistische significantie verdwijnt wanneer de dosis acetylsalicylzuur verhoogd wordt tot meer dan 300 mg per dag. Op vlak van mortaliteit werd geen significant verschil gerapporteerd tussen de behandeling met acetylsalicylzuur of orale anticoagulantia.

*GRADE: low quality of evidence*

- In bovenstaande meta-analyse uit 2010 worden de ongewenste effecten van orale anticoagulantia en acetylsalicylzuur niet besproken.

### 7.2.1.3. Lage dosis warfarine plus acetylsalicylzuur vs. geen anticoagulantia

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 ( $\leq 4\%/y$ ) 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	

- De associatie van laaggedoseerd warfarine plus acetylsalicylzuur 75 mg/d werd vergeleken met controle bij personen met voorkamerfibrillatie en laag tot matig risico van CVA ( $\leq 4\%/jaar$ ). Er werden geen statistisch significante verschillen gevonden tussen beide groepen voor de incidentie van CVA of TIA. Evenmin werd de mortaliteit significant beïnvloed.

*GRADE: moderate quality of evidence*

- Bij patiënten behandeld met de associatie van warfarine plus acetylsalicylzuur traden significant vaker bloedingen op. De auteurs van deze studie berekenden dat met actieve behandeling 18 CVA's konden voorkomen worden, maar dit ten koste van 15 bloedingen die behandeling behoeften.

## 7.2.2. Anti-aggregantia bij personen met voorkamerfibrillatie met laag tot matig risico van CVA/TIA

### 7.2.2.1. Anti-aggregantia vs. placebo of geen behandeling

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 <b>OR=0.71 (95% CI 0.51-0.97) =&gt; SS</b> 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	

- Bij chronische voorkamerfibrillatie patiënten met een laag tot matig risico op CVA of TIA en zonder voorgeschiedenis van CVA of TIA reduceert acetylsalicylzuur niet significant het risico op beroertes. De onderzochte doseringen van acetylsalicylzuur gaan van 75 mg tot 325 mg per dag. Het risico op het optreden van een hartinfarct is eveneens niet statistisch significant verschillend bij patiënten die acetylsalicylzuur kregen toegediend ten opzichte van patiënten die geen behandeling ondergingen. Enkel op het samengestelde eindpunt beroertes en/of hartinfarct en/of dood door vasculair lijden is acetylsalicylzuur randsignificant voordeliger dan geen behandeling voor VKF-patiënten met een laag risico.

*GRADE: high quality of evidence*

- Wat ongewenste effecten betreft, werd in een studie gemeld dat er meer gastro-intestinale last optrad bij gebruik van acetylsalicylzuur doch dit was niet significant.

- Er dient opgemerkt te worden dat in de studie uit 2006 gemiddeld 45% VKF patiënten werden geïncludeerd met een hoog risico op CVA of TIA.



## 8. Ongewenste effecten

### 8.1. Belangrijkste ongewenste effecten vitamine K-antagonisten

- Bloeding is het belangrijkste ongewenste effect van de vitamine K-antagonisten. De jaarlijkse incidentie van ernstige bloedingen in de AFFIRM-studie (4060 patiënten over 3.5 jaar) was 2% per jaar. Het verband tussen de intensiteit van de ontstollende behandeling en het bloedingsrisico is heel sterk. Uit gerandomiseerde studies blijkt dat de kosten-baten balans het beste is bij een INR tussen 2 en 3.
- Allergische reacties zijn erg zeldzaam. Onder de behandeling van vitamine K-antagonisten treedt wel een verminderde reactie op huidtesten op.
- Uricosurie werd gemeld bij dicoumarol.
- Uitzonderlijk kan huidnecrose ontstaan door gebruik van vitamine K-antagonisten, dit is het geval in 0.01 tot 0.1% van de patiënten. De morbiditeit van deze complicatie is echter groot: ondanks een adequate behandeling, moet de helft van deze patiënten een operatie ondergaan waarbij al dan niet huidtenten noodzakelijk zijn. Preventie van coumarine-geïnduceerde huidnecrose kan gebeuren door voorzichtig de dosis op te bouwen, in het bijzonder bij ouderen.
- Vitamine K-antagonisten hebben een vasodilaterend effect op coronairen, perifere venen en capillairen, met het fenomeen van paarse tenen als gevolg. De perifere vasodilatatie kan ook verantwoordelijk zijn voor het koudegevoel dat sommige patiënten ervaren.
- Er zijn slechts enkele gevallen van leverschade gerapporteerd. Gewoonlijk presenteert zich dit als een cholestatisch ziektebeeld, ongeveer tien dagen na aanvang van de behandeling met vitamine K-antagonisten.
- Antitrombotische behandeling tijdens de zwangerschap brengt een gekend hoog risico met zich mee, zowel voor de moeder als voor het kind. Zwangere vrouwen hebben een verhoogde kans op miskramen en perinatale bloedingen. Vitamine K-antagonisten zijn bovendien teratogeen. Ze worden ook gesecreteerd in de moedermelk, maar dit zou geen effect hebben op de baby. Toch wordt door sommige experts aangeraden om bij baby's van moeders die borstvoeding geven onder behandeling van vitamine K-antagonisten, regelmatig de prothrombine tijd te bepalen en ze eventueel wekelijks 1 mg vitamine K per os toe te dienen.

#### Bron

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

## 8.2. Ongewenste effecten apixaban

Opmerking: momenteel niet verkrijgbaar in België, wel Europees geregistreerd sinds 18 mei 2011

- Zoals alle anticoagulantia is het risico op bloedingen ook met apixaban verhoogd en mag men dit geneesmiddel enkel toedienen wanneer hemostase bereikt is. Bloedingen, anemie en ecchymosen maken 1-10% uit van alle gekende ongewenste effecten. Gastro-intestinale bloedingen komen minder frequent voor (1-0.1%) In de ARISTOTLE studie was het totale bloedingspercentage 18% per jaar bij de behandeling van patiënten met voorkamerfibrillatie met apixaban.
- Voorzichtigheid is geboden bij het gecombineerd gebruik van apixaban met aspirine wegens het mogelijk verhoogde bloedingsrisico.
- Apixaban wordt afgeraden bij patiënten met ernstige nierinsufficiëntie waarbij de creatinineklaring <15ml/min bedraagt of bij dialysepatiënten.
- Er bestaat slechts een beperkte klinische ervaring met apixaban bij ouderen, doch dit geneesmiddel mag volgens de producent toegediend worden aan patiënten ouder dan 65 jaar. Er bestaat evenmin een beperking voor het gebruik bij afwijkend lichaamsgewicht (<50kg of >120kg).
- Apixaban is gecontra-indiceerd bij patiënten met leveraandoeningen die gepaard gaan met stollingsstoornissen en een klinisch relevant bloedingsrisico. Er hoeft geen dosisaanpassing doorgevoerd te worden bij patiënten met mild tot matig ernstige leverfunctiestoornissen.
- Over pediatrisch gebruik van apixaban zijn geen gegevens beschikbaar, daarom wordt afgeraden om apixaban aan kinderen <18 jaar toe te dienen.
- Apixaban wordt niet aangeraden tijdens de zwangerschap of borstvoeding aangezien het effect onbekend is in deze omstandigheden.

### Bronnen

- European Medicines Agency. Accessed February 6, 2012. [www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002148/WC500107728.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf)
- Granger CB, Alexander JH, McMurray JJ, et al. for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.



### 8.3. Ongewenste effecten dabigatran

- Het meest voorkomende ongewenste effect van dabigatran is bloeding. Bloedingen kwamen in totaal bij ongeveer 14% van de patiënten voor. De frequentie van ernstige bloedingen (inclusief wondbloedingen) bedroeg minder dan 2%. Epistaxis en gastro-intestinale bloedingen kwamen vaak voor, bij 1 tot 10 van de 100 behandelde patiënten. Deze bloedingen kunnen leiden tot anemie en een afname van de hoeveelheid hemoglobine.
- Buikpijn, diarree en nausea worden eveneens vaak gemeld. Uit de RE-LY studie blijkt dat dyspepsie significant meer voorkomt bij behandeling met dabigatran vergeleken met warfarine. Er was geen significante stijging van de leverenzymen, doch waakzaamheid is aangewezen. Het Amerikaans geneesmiddelenagentschap (FDA) oordeelde dat in één geval van leverschade het oorzakelijk verband met dabigatran waarschijnlijk was.
- Het Europees Geneesmiddelenagentschap (EMA) beveelt aan de nierfunctie te meten alvorens een behandeling op te starten met dabigatran, en die regelmatig op te volgen gedurende de behandeling. Bij ernstige nierinsufficiëntie (creatinineklaring <30ml/min) is dabigatran gecontra-indiceerd.
- In een recente meta-analyse van Uchino en Hernandez (Arch Int Med 2012; doi:10.1001) wordt het gebruik van dabigatran in verband gebracht met een verhoogd risico op myocardinfarct en acuut coronair syndroom in vergelijking met andere antitrombotica.
- In de RE-LY studie traden overgevoeligheid, angio-oedeem en anafylactische reacties op bij minder dan 0,1% van de behandelde patiënten.
- Gebruik van dabigatran bij kinderen jonger dan 18 jaar wordt niet aanbevolen vanwege het ontbreken van gegevens over veiligheid en werkzaamheid.
- Er zijn geen toereikende gegevens over het gebruik van dabigatran bij zwangere vrouwen en er zijn geen klinische gegevens over het effect van dabigatran op zuigelingen die borstvoeding krijgen.
- Er bestaat geen antidotum, wat een nadeel is bij een ernstige bloeding. Bovendien is er tot op heden geen laboratoriumtest beschikbaar om het antistollende effect van dabigatran na te gaan.

#### Bronnen

- Belgisch Centrum voor Farmacotherapeutische Informatie. De Transparantiefiches: een update. Folia Farmacotherapeutica 2011;38:100-104.
- Chevalier P. Online themadossier. Orale anticoagulatie: nieuwe geneesmiddelen. 04.01.2012. [www.minerva-ebm.be](http://www.minerva-ebm.be)
- European Medicines Agency. Accessed February 6, 2012. [www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000829/WC500041059.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf)
- US Food and Drug Administration. Accessed February 6, 2012. [www.fda.gov/Drugs/DrugSafety/ucm282724.htm#hcp](http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm#hcp)
- Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events. Meta-analysis of noninferiority randomized controlled trials. Arch Int Med 2012; published online January 9, 2012. doi:10.1001/archinternmed.2011.1666
- Rédaction Prescrire. Dabigatran et fibrillation auriculaire (Pradaxa®). Une alternative à la warfarine dans certains cas. Revue Prescrire 2012;31:888-92.

- Connolly SJ, Ezekowitz MD, Yusuf S, et al. for the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.

## 8.4. Ongewenste effecten rivaroxaban

- Het meest voorkomende ongewenste effect van rivaroxaban is bloeding, eventueel postoperatoir, met soms anemie en trombocytopenie tot gevolg. Deze bloedingen uiten zich onder de vorm van epistaxis, gastro-intestinale en urologische bloedingen en hematomen. Klinisch relevante bloedingen gebeurden bij ongeveer 15% van de behandelde patiënten per jaar in de ROCKET studie.
- De levertesten van patiënten onder behandeling van rivaroxaban moeten regelmatig opgevolgd worden. Er kan immers een stijging optreden van cGT en transaminasen, alsook van LDH en alkalisch fosfatase. Soms verhoogt het bilirubinegehalte in het bloed; er wordt zelden een vermeerdering van het geconjugeerd bilirubine gerapporteerd.
- Nausea, koorts en perifeer oedeem komen voor bij 1-10% van de patiënten die rivaroxaban innemen.
- Minder vaak voorkomende ongewenste effecten bij het gebruik van rivaroxaban zijn duizeligheid, hoofdpijn, tachycardie, hypotensie, constipatie, diarree, buikpijn, dyspepsie, braken, droge mond, algehele vermindering van kracht en energie, pijn in de ledematen, verhoging amylase/lipase en meer secretie van wondvocht.
- In uitzonderlijke gevallen kan door rivaroxaban syncope optreden. Dermatitis of urticaria komen eveneens zelden voor.
- Rivaroxaban mag niet toegediend worden aan zwangere vrouwen of vrouwen die borstvoeding geven.
- Andere contra-indicaties volgens het Europees Geneesmiddelenagentschap (EMA) zijn actieve bloedingen of leveraandoeningen die gepaard gaan met een verhoogd risico op bloedingen. Rivaroxaban wordt best vermeden in geval van ernstige nierinsufficiëntie (creatinineklaring <30ml/min); indien creatinineklaring <50ml/min, wordt een aangepaste dosis aangeraden.
- Er bestaat geen antidotum, wat een nadeel is in geval van ernstige bloeding.

### Bronnen

- Belgisch Centrum voor Farmacotherapeutische Informatie. De Transparantiefiches: een update. Folia Farmacotherapeutica 2011;38:100-104.
- European Medicines Agency. Accessed February 6, 2012. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000944/WC500057108.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf)
- Patel MR, Mahaffey KW, Garg J, et al. for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.



## Referentielijst geïnccludeerde studies

AATAFS. Antithrombotic Therapy in Atrial Fibrillation Study Group. The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin. *Zhonghua Xin Xue Guan Bing Za Zhi* 2006;34:295–8.

ACAS. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421–8.

ACCSG. American-Canadian Cooperative Study Group. Persantin aspirin trial in cerebral ischemia, part II: endpoint results. *Stroke* 1985;16:406-15.

ACST. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. *Lancet* 2004;363:1491–502.

AFASAK 1. Petersen P, Boysen G, Godtfredsen J, et al. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet* 1989;1:175-9.

AFASAK 2. Gullov AL, Koefoed BG, Petersen P, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study. *Arch Int Med* 1998;158:1513-21.

Aguilar MI, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD001925. DOI: 10.1002/14651858.CD001925.pub2.

Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD001927. DOI: 10.1002/14651858.CD001927.pub2.

AICLA. Bousser MG, Eschwège E, Haguenu M, Lefauconnier JM, Thibault N, Touboul D, et al. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of atherothrombotic cerebral ischaemia. *Stroke* 1983;14:5-14.

AITA. Fields WS, Lemak NA, Frankowski RF, Hardy RJ. Controlled trial of aspirin in cerebral ischemia. *Stroke* 1977;8:301-14. + Fields WS, Lemak NA, Frankowski RF, Hardy RJ. Controlled trial of aspirin in cerebral ischemia. Part II: surgical group. *Stroke* 1978;9:309-18.

Algra A, De Schryver ELLM, van Gijn J, Kappelle LJ, Koudstaal PJ. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD001342. DOI: 10.1002/14651858.CD001342.pub2.

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ* 2002;32:171-80.

BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation) Investigators. The effect of low-dose warfarin on the risk of stroke in nonrheumatic atrial fibrillation. *N Engl J Med* 1990;323:1505-11.

BAFTA. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370:493-503.

Baker RN, Schwartz WS, Rose MD. Transient ischemic strokes. A report of a study of anticoagulant therapy. *Neurology* 1966;16: 841-7.

Birmingham-B. Roden S, Low-Beer T, Carmalt M, Cockel R, Green I. Transient cerebral ischaemic attacks - management and prognosis. *Postgrad Med J* 1981;57:275-8.

Blakely JA. A prospective trial of sulfinpyrazone and survival after thrombotic stroke. In: *Proceedings of VII International Congress on Thrombosis and Haemostasis* 1979;42:161(Abstract 0382).

Bousser MG, Eschwege E, hagenau M, et al. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of atherothrombotic cerebral ischemia. *Stroke* 1983;14:5-14.

Bradshaw P, Brennan S. Trial of long-term anticoagulant therapy in the treatment of small stroke associated with a normal carotid angiogram. *J Neurol Neurosurg Psychiatry* 1975;38:642-7.

Britton M, Helmers C, Samuelsson K. High-dose acetylsalicylic acid after cerebral infarction. A Swedish co-operative study. *Stroke* 1987;18:325-34.

Canadian Co-op. Canadian Co-operative Study Group. A randomised trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med* 1978;299:53-9. + Gent M, Barnett HJM, Sackett DL, Taylor DW. A randomized trial of aspirin and sulfinpyrazone in patients with threatened stroke. Results and methodologic issues. *Circulation* 1980;62(suppl V):97-105.

Caneshi S, Bonaventuri C, Finzi F. Ischemic cerebrovascular disease: treatment with various anti-platelet aggregation drugs. Clinical follow-up of 80 patients (22-34 months). *Minerva Med* 1985;76:1933-43.

CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.

Carter A. Hypotensive therapy in stroke survivors. *Lancet*. 1970;1:485-489.

CATS. Gent M, Easton JD, Hachinski VC, Panak E, Sicurella J, Blakely JA, et al. The Canadian American ticlopidine study (CATS) in thromboembolic stroke. *Lancet* 1989;i:1215-20.

Chambers BR, Donnan G. Carotid endarterectomy for asymptomatic carotid stenosis. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD001923. DOI: 10.1002/14651858.CD001923.pub2.

Charing Cross. Gawel M, Rose FC. Use of sulphinpyrazone in the prevention of re-stroke and stroke in man. In: Rose FC. Advances in stroke therapy. New York: Raven Press, 1982:158.

Connolly SJ, Eikelboom J, Joyner C, et al. for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364:806-17.

Connolly SJ, Ezekowitz MD, Yusuf S, et al. for the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.

Connolly SJ, Iapacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. J Am Coll Cardiol 1991;18:349-55.

Danish Co-op. Sorensen PS, Pedersen H, Marquardsen J, Petersson H, Heltberg A, Simonsen N, et al. Acetylsalicylic acid in the prevention of stroke in patients with reversible cerebral ischemic attacks. A Danish cooperative study. Stroke 1983;14:15-22.

Danish low-dose. Boysen G, Soelberg-Sørensen P, Juhler M, Andersen AR, Boas J, Olsen JS, et al. Danish very-low-dose aspirin after carotid endarterectomy trial. Stroke 1988;19:1211-5.

Diener HC, Bogousslavsky J, Brass LM, et al. on behalf of the MATCH Investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. Lancet 2004;364:331-7.

Diener HC, Connolly SJ, Ezekowitz MD, for the RE-LY study group. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-Ly trial. Lancet Neurol 2010;9:1157-63.

Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1-13.

Diener HC, Eikelboom J, Connolly SJ, et al. for the AVERROES steering committee and investigators. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomized trial. Lancet Neurology Early Online Publication, 1 February 2012. doi:10.1016/S1474-4422(12)70017-0

EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in nonrheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342:1255-62.

EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255–62.

ECST. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379-87.

Ederle J, Featherstone RL, Brown MM, on behalf of the CAVATAS collaborators. Long-term outcome of endovascular treatment versus medical care for carotid artery stenosis in patients not suitable for surgery and randomized in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). *Cerebrovasc Dis* 2009;28:1-7.

Edvardsson N, Jull-Möller S, Omblus R, Perhrsson K. Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation. *J Int Med* 2003;254:95-101.

Eikelboom JW, Wallentin L, Connolly SJ, et al; Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial. *Circulation* 2011;123:2363-72.

Enger E, Boyesen S. Long-term anticoagulant therapy in patients with cerebral infarction: a controlled clinical study. *Acta Med Scand Suppl* 1965;438:7-61.

Eriksson S, Olofsson BO, Wester PO, for the TEST study group. Atenolol in secondary prevention after stroke. *Cerebrovasc Dis* 1995;5:21-5.

ESPS-1. ESPS Group. European stroke prevention study. *Stroke* 1990;21:1122-30.

Ezekowitz MD, Wallentin L, Connolly SJ, et al. Dabigatran and warfarin in vitamin K antagonist-naïve and -experienced cohorts with atrial fibrillation. *Circulation* 2010;122:2246-53.

Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011;32:2387-94.

Garde A, Samuelsson K, Fahlgren H, et al. Treatment after transient ischemic attacks: a comparison between anticoagulant drug and inhibition of platelet aggregation. *Stroke* 1983;14(5):677-81.

Gent-stroke. Gent M, Blakely JA, Hachinski VC, Roberts RS, Barnett HJM, Bayer NH, et al. A secondary prevention randomized trial of suloctidil in patients with a recent history of thromboembolic stroke. *Stroke* 1985;16:416-24.

Gorelick PB, Richardson DJ, Kelly M, et al. for the African American Antiplatelet Stroke Prevention Study (AAASPS) Investigators. Aspirin and ticlopidin for prevention of recurrent stroke in black patients. *JAMA* 2003;289:2947-57.



Granger CB, Alexander JH, McMurray JJ, et al. for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.

Guiraud-Chaumeil B, Rascol A, David J, et al. Prévention des récives des accidents vasculaires cérébraux ischémiques par les anti-aggrégants plaquettaires: résultats d'un essai thérapeutique contrôlé de 3 ans. *Rev Neurol* 1982;138:367-85.

Halliday A, Harrison M, Hayter E, et al. on behalf of the Asymptomatic Carotid Surgery Trial (AVST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomized trial.

Hass WK, Easton JD, Adams HP, et al. A randomised trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med* 1989;321:501-7.

HOPE. The Heart Outcome Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145–153.

Howard FA, Cohen P, Hickler RB, Locke S, et al. Survival following stroke. *JAMA* 1963;183:921-5.

HSCSG. Hypertension-Stroke Cooperative Study Group. Effect of antihypertensive treatment on stroke recurrence. *JAMA*. 1974;229:409–418.

HSPS. Fortini A, Bonechi G, Carnovali M, et al. Multi-centric study on ischemic cerebral reinfarct prevention with low-dose heparin: the informatic system [Sistema informatico dello studio clinico controllato multicentrico sulla prevenzione del reinfarto cerebrale ischemico con eparina a basso dosaggio]. *Rivista di Neurobiologica* 1990;36:219–21. + Neri Serneri GG, Gensini GF, et al. Low-dose heparin stroke prevention study: preliminary efficacy analysis. *Cerebrovasc Dis* 1999;9 Suppl 1:67.

Li Y, Li D, Wang L. A prospective randomized control study on ticlopidine with aspirin for the prevention of ischaemic cerebral stroke. *J Clin Neurol* 2000;13:146–8. + Li Y-Z, Wang L, Yu P-X. A randomized trial comparing ticlopidine with aspirin for the prevention of ischaemic cerebral stroke. *Acta Pharmacologica Sinica* 1999;20:476.

Liu L, Wang Z, Gong L, et al. for the Post-stroke Antihypertensive Treatment Study (PATS) Investigators. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. *Hypertens Res* 2009;32:1032-40.

McDevitt E, Groch SN, Wright IS. A cooperative study of cerebrovascular disease. *Circulation* 1959;20:215–23. + Groch SN, McDevitt E, Wright IS. A long-term study of cerebral vascular disease. *Annals of Internal Medicine* 1961;55:358–67. + McDowell F, McDevitt E, Wright IS. Anticoagulant therapy: five years experience with the patient with an established cerebrovascular accident. *Arch Neurol* 1963;8:209–14.

McKenna-III. Graham A. A trial of ticlopidine hydrochloride for the prevention of deep vein thrombosis in high risk (post CVA) medical patients. Guildford: Sanofi Winthrop, 1987: (Sanofi internal report 001.6.188).

Memphis. Robertson JT, Dugdale M, Salky N, Robinson H. The effect of a platelet inhibiting drug (sulfipyrazone) in the therapy of patients with transient ischemic attacks (TIAs) and minor strokes. *Thromb et Diathesis Haemorrhagica* 1975;34:598.

Mohr JP, for the WARSS Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345:1444–51.

Morocutti C, Amabile G, Fattaposta F, et al. Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. *Stroke* 1997;28:1015-21.

MWNAF. Pengo V, Zasso A, Barbero F, et al. Effectiveness of minidose warfarin in the prevention of thromboembolism and vascular death in nonrheumatic atrial fibrillation. *Am J Cardiol* 1998;82:433-7.

NASCET. North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445-53.

Nat-Coop. Baker RN, Broward JA, Fang HC, et al. Anticoagulant therapy in cerebral infarction. Report on co-operative study. *Neurology* 1962;12:823-9. + Fisher CM. Anticoagulant therapy in cerebral thrombosis and cerebral embolism. A national cooperative study interim report. *Neurology* 1961;11:119–31.

North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991; 325:445-53.

Olsson JE, Brechter C, Bäcklund H, et al. Anticoagulant vs anti-platelet therapy as prophylactic against cerebral infarction in transient ischemic attacks. *Stroke* 1980;11:4-9.

Owen A. Antithrombotic treatment for the primary prevention of stroke in patients with non valvular atrial fibrillation: a reappraisal of the evidence and network meta analysis. *Int J Cardiol* 2010;142:218-23.

PATAF. Hellemons BS, Langenberg M, Lodder J, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *BMJ* 1999;319:958-64.

Patel MR, Mahaffey KW, Garg J, et al. for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.

PATS Collaborating Group. Post-Stroke Antihypertensive Treatment Study: a preliminary result. *Chin Med J.* 1995;108:710–717.

Pengo V, Cucchini U, Denas G, et al. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation. *Thromb Haemost* 2010;103:442-9.

Perret-Guillaume C, Wahl DG. Low-dose warfarin in atrial fibrillation leads to more thromboembolic events without reducing major bleeding when compared to adjusted-dose. *Thromb Haemost* 2004;394:402.

Posada IS, Puebla V, Barriales V, et al. on behalf of the LASAF Pilot Study. Alternate-day dosing of aspirin in atrial fibrillation. *Am Heart J* 1999;138 (1 Pt 1): 137-43.

Powers WJ, Clarke WR, Grubb RL, et al. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study randomized trial. *JAMA* 2011;306:1983-92.

PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033-41.

Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. *Stroke* 2003;34:2741-8.

Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database of Systematic Reviews* 2011, Issue 4. Art. No.: CD001081. DOI: 10.1002/14651858.CD001081.pub2.

Reuther R, Dorndorf W. Aspirin in patients with cerebral ischaemia and normal angiograms or non-surgical lesions. In: Breddin HK, Dorndorf W, Loew D, Marx R (eds). *Acetylsalicylic acid in cerebral ischaemia and coronary heart disease*. Stuttgart: Schattauer, 1978:97-106

Ross Russell RW. The effect of ticlopidine in patients with amaurosis fugax. Guildford: Sanofi Winthrop, 1985:(Sanofi internal report 105062-0051).

Sacco RL, Diener HC, Yusuf S, et al. for the PROFESS study group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;359:1238-51.

SALT. The SALT Collaborative Group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *Lancet* 1991;338:1245-9.

Sandercock PAG, Gibson LM, Liu M. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD000248. DOI: 10.1002/14651858.CD000248.pub2.

Sato H, Ishikawa K, Kitabatake A, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan atrial fibrillation stroke trial. *Stroke* 2006;37:447-51.

Saxena R, Koudstaal PJ. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischaemic attack. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD000185. DOI:10.1002/14651858.CD000185.pub2.

Saxena R, Koudstaal PJ. Anticoagulants versus antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD000187. DOI: 10.1002/14651858.CD000187.pub2.

Schrader J, Lüders S, Kulschewski A, et al. for the MOSES study group. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). Stroke 2005;36:1218-24.

Sillescu H, Amarencu P, Hennerici MG, et al. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 2008;39:3297-302.

SPAF (Stroke Prevention in Atrial Fibrillation) Investigators. The stroke prevention in atrial fibrillation study: final results. Circulation 1991;84:527-39.

SPAF 2. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation. Stroke Prevention in Atrial Fibrillation II Study. Lancet 1994;343:687-91.

SPAF 3. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation.: Stroke Prevention in Atrial Fibrillation III randomized clinical trial. Lancet 1996;348:633-8.

SPIRIT. The Stroke Prevention In Reversible Ischemia Trial (SPIRIT) study group. A randomised trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. Ann Neurol 1997;42:85-65.

Stroke. Acheson J, Danta G, Hutchinson EC. Controlled trial of dipyridamole in cerebral vascular disease. BMJ 1969;i:614-5.

Sudlow CLM, Mason G, Maurice JB, Wedderburn CJ, Hankey GJ. Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD001246. DOI: 10.1002/14651858.CD001246.pub2.

SWAT. Stewart B, Shuaib A, Veloso F. Stroke Prevention with Warfarin or Aspirin Trial (SWAT). Stroke 1998;29:304 (Abst.P9).

The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066-78.

The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomized controlled trial. *Lancet* 2006;367:1903-12.

The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischaemic attack or minor ischemic stroke. *N Engl J Med* 1991;325:1261-6.

The Dutch TIA Trial Study Group. Trial of secondary prevention with atenolol after transient ischaemic attack or nondisabling ischemic stroke. *Stroke* 1993;34:543-8.

The ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomized controlled trial. *Lancet* 2006;367:1665-73.

The ESPRIT Study Group. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurology* 2007;6:115-24.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355: 549-59.

Thygesen P, Christensen E, Dyrbye M, et al. Cerebral apoplexy: a clinical, radiological, electroencephalographic and pathological study with special reference to the prognosis of cerebral infarction and the result of long-term anticoagulant therapy. *Dan Med Bull* 1964;11:233-57.

Tohgi H, Murakami M. The effect of ticlopidine on TIA compared with aspirin - a double-blind, twelve-month and open 24-month follow-up study. *Jpn J Med* 1987;26:117-9.

Toulouse-TIA. Guiraud-Chaumeil B, Rascol A, David J, Boneu B, Clanet M, Bierme R. Prévention des récurrences des accidents vasculaires cérébraux ischémiques par les anti-agrégants plaquettaires. *Rev Neurol (Paris)* 1982;138:367-85.

Uchiyama S, Fukuuchi Y, Yamaguchi T. The efficacy and safety of clopidogrel versus ticlopidine in Japanese stroke patients: combined results of two phase III, multicenter, randomized clinical trials. *J Neurol* 2009;256:888-97.

Uchiyama S, Ikeda Y, Urano Y, et al. The Japanese Aggrenox (extended-release dipyridamole plus aspirin) stroke prevention versus aspirin programme (JASAP) study: a randomized, double-blind controlled trial. *Cerebrovasc Dis* 2011;31:601-13.

UK-TIA study group. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol, Neurosurg Psychiatry* 1991;54:1044-54.

VA Study. Baker RN. An evaluation of anticoagulant therapy in the treatment of cerebrovascular disease. Report of the Veterans Administration Cooperative Study of atherosclerosis, Neurology Section. *Neurology* 1961;11:132–8.

VACS. Hobson RW, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *New England Journal of Medicine* 1993;328:221–7.

VA-SPINAF. Ezekowitz MD, Bridgers SL, James KE, et al. for the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med* 1992;327:1406–12.

Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. *Stroke* 2008;39:1358-63.

Wallace DC. Cerebral vascular disease in relation to long-term anticoagulant therapy. *Journal of Chronic Diseases* 1964;17:527–37.

Wallentin L, Yusuf S, Ezekowitz MD, et al. for the RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;376:975-83.

Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. *Stroke* 2000;31:817-21.

Yusuf S, Diener HC, Sacco R, et al for the PROFESS study group. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008;359:1225-37.

## **Bijlage 1 Clinical evidence**





## 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

What are the effects of preventive non-surgical interventions in people with previous stroke or TIA? . . . . .	4
What are the effects of preventive surgical interventions in people with previous stroke or TIA? . . . . .	18
What are the effects of preventive anticoagulant and antiplatelet treatments in people with atrial fibrillation and previous stroke or TIA? . . . . .	25
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? . . . . .	28
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? . . . . .	33

### INTERVENTIONS

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

##### Beneficial

Alternative antiplatelet regimens to aspirin (adding dipyridamole to aspirin shows benefit in reducing composite vascular end points and stroke compared with aspirin alone; no evidence that any other regimen alone has any major advantages over aspirin alone) . . . . . 9

Antiplatelet treatment (better than no antiplatelet treatment) . . . . . 4

Blood pressure reduction (better than placebo or no treatment) . . . . . 5

Cholesterol reduction (better than placebo or no treatment) . . . . . 7

##### Unknown effectiveness

Different treatments to reduce blood pressure (no evidence that any regimen is more or less effective than any other) . . . . . 12

##### Unlikely to be beneficial

High-dose versus low-dose aspirin (no additional benefit but may increase harms) . . . . . 14

Vitamin B supplements (including folate) . . . . . 16

##### Likely to be ineffective or harmful

Anticoagulation in people in sinus rhythm (may be no more effective than placebo or no treatment) . . . . . 15

#### IN PEOPLE WITH PREVIOUS STROKE OR TIA: SURGICAL PREVENTION

##### Beneficial

Carotid endarterectomy in people with moderately severe (50%–69%) symptomatic carotid artery stenosis . . . 19

Carotid endarterectomy in people with severe (greater than 70%) symptomatic carotid artery stenosis . . . 20

##### Likely to be beneficial

Carotid endarterectomy in people with asymptomatic but severe carotid artery stenosis . . . . . 21

##### Unknown effectiveness

Carotid percutaneous transluminal angioplasty . . . 22

Carotid percutaneous transluminal angioplasty plus stenting (no evidence that one intervention is more or less effective than the other) . . . . . 24

Eversion carotid endarterectomy (no more effective than conventional carotid endarterectomy) . . . . . 21

Vertebral percutaneous transluminal angioplasty . . 23

<p><b>Unlikely to be beneficial</b></p> <p>Carotid endarterectomy in people with moderate (30%–49%) symptomatic carotid artery stenosis . . . 19</p> <p>Carotid endarterectomy in people with symptomatic near occlusion of the carotid artery . . . . . 20</p> <p><b>Likely to be ineffective or harmful</b></p> <p>Carotid endarterectomy in people with symptomatic carotid artery stenosis (less than 30%) . . . . . 18</p> <p><b>IN PEOPLE WITH ATRIAL FIBRILLATION AND PREVIOUS STROKE OR TIA</b></p> <p><b>Beneficial</b></p> <p>Oral anticoagulants . . . . . 25</p> <p><b>Unknown effectiveness</b></p> <p>Aspirin . . . . . 27</p>	<p><b>IN PEOPLE WITH ATRIAL FIBRILLATION WITHOUT PREVIOUS STROKE OR TIA: HIGH RISK OF STROKE OR TIA</b></p> <p><b>Beneficial</b></p> <p>Oral anticoagulant treatment (adjusted-dose warfarin may be more effective than placebo, low-intensity fixed-dose warfarin, and antiplatelet treatments) . . . . . 28</p> <p><b>Unlikely to be beneficial</b></p> <p>Antiplatelet treatment (aspirin in people with contraindications to anticoagulants) . . . . . 32</p> <p><b>IN PEOPLE WITH ATRIAL FIBRILLATION WITHOUT PREVIOUS STROKE OR TIA: LOW TO MODERATE RISK OF STROKE OR TIA</b></p> <p><b>Unknown effectiveness</b></p> <p>Antiplatelet treatment (aspirin in people with contraindications to anticoagulants) . . . . . 34</p> <p>Oral anticoagulation . . . . . 33</p>
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

### 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.

<b>DEFINITION</b>	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. <b>Stroke:</b> 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. <b>TIA:</b> This is similar to a mild ischaemic stroke, except that symptoms last for less than 24 hours. <sup>[1]</sup> For management of stroke in the acute phase, see review on stroke management.
<b>INCIDENCE/ PREVALENCE</b>	See incidence/prevalence under review on stroke management.
<b>AETIOLOGY/ RISK FACTORS</b>	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. <sup>[2]</sup> <sup>[3]</sup> <sup>[4]</sup> However, two of the overviews found that higher cholesterol increased the risk of ischaemic stroke, but reduced the risk of haemorrhagic stroke. <sup>[3]</sup> <sup>[4]</sup>
<b>PROGNOSIS</b>	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]). <sup>[5]</sup> <sup>[6]</sup> <sup>[7]</sup> 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. <sup>[8]</sup> <sup>[9]</sup> 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). <sup>[10]</sup>
<b>AIMS OF INTERVENTION</b>	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.
<b>OUTCOMES</b>	Stroke, MI, mortality, disability, dependency, and adverse effects.
<b>METHODS</b>	<i>Clinical Evidence</i> 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 <i>Clinical Evidence</i> 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](http://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. <sup>[7]</sup> <sup>[11]</sup> 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. <sup>[7]</sup> 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). <sup>[7]</sup> 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. <sup>[11]</sup> 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. <sup>[11]</sup>

### 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). <sup>[7]</sup> The estimated excess risk of bleeding was about one to two additional major extracranial bleeds per 1000 people a year. <sup>[7]</sup> 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). <sup>[11]</sup>

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. <sup>[12]</sup> The second review (search date 1999; 24 RCTs) assessed the effects of aspirin on GI bleeding. <sup>[13]</sup> 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. <sup>[7]</sup> 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**

### 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. <sup>[14]</sup> <sup>[15]</sup> <sup>[16]</sup>

#### 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) <sup>[14]</sup> 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). <sup>[14]</sup> 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). <sup>[15]</sup> 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). <sup>[15]</sup>

#### 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). <sup>[14]</sup>

**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).<sup>[14]</sup>

**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).<sup>[14]</sup>

**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).<sup>[14]</sup>

**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.<sup>[16]</sup> 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).<sup>[16]</sup>

**Harms:**

The systematic reviews gave no information on adverse effects.<sup>[14]</sup> <sup>[15]</sup> 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).<sup>[17]</sup> <sup>[18]</sup> 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).<sup>[19]</sup> 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.<sup>[20]</sup> 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).<sup>[16]</sup> 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).<sup>[16]</sup>

**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.<sup>[14]</sup> 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.<sup>[14]</sup> 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.<sup>[15]</sup> 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).<sup>[15]</sup> 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).<sup>[14]</sup> 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).<sup>[19]</sup> 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).<sup>[19]</sup>

#### 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.<sup>[3] [21] [22] [23]</sup> 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.<sup>[24]</sup> 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.<sup>[25]</sup>

## 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,<sup>[26] [27]</sup> and we found one subsequent RCT.<sup>[28]</sup> 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.<sup>[26]</sup> 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).<sup>[26]</sup>

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.<sup>[27]</sup> 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).<sup>[27]</sup> 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.<sup>[29]</sup> 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).<sup>[28]</sup> 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).<sup>[28]</sup>

#### 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.<sup>[4]</sup> 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).<sup>[4]</sup> We found one additional RCT<sup>[30]</sup> and two subsequent RCTs<sup>[31]</sup> <sup>[32]</sup> 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).<sup>[30]</sup> 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%).<sup>[31]</sup> 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).<sup>[32]</sup>

#### 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).<sup>[26]</sup> 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).<sup>[27]</sup> One RCT reported by the second systematic review looked specifically at treatment with statins for secondary prevention of stroke.<sup>[29]</sup> 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).<sup>[29]</sup>

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).<sup>[28]</sup>

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%).<sup>[33]</sup> 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).<sup>[33]</sup>

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).<sup>[34]</sup> 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.<sup>[34]</sup> Less-severe adverse events,



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

#### 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). <sup>[33]</sup> 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). <sup>[30]</sup> 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). <sup>[31]</sup> The RCT comparing bezafibrate with placebo found similar adverse effect rates for treatments (no further data reported). <sup>[32]</sup>

#### 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](http://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). <sup>[27]</sup> 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. <sup>[35]</sup> 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. <sup>[29]</sup> Cholesterol lowering with statins is associated with a low adverse-event profile. <sup>[3] [36] [33] [37]</sup>

## 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*).

*Triflusal 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<sup>[7]</sup> and 1999)<sup>[38]</sup> and one subsequent RCT<sup>[39]</sup> 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).<sup>[7]</sup> 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%).<sup>[38]</sup> 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).<sup>[39]</sup>

##### 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.<sup>[40]</sup> 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).<sup>[40]</sup>

##### 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.<sup>[41]</sup> 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%).<sup>[41]</sup>

##### 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.<sup>[42]</sup> 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).<sup>[42]</sup>

##### 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.<sup>[43]</sup> 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).<sup>[43]</sup>

#### Triflusal versus aspirin:

We found one systematic review<sup>[7]</sup> and two subsequent RCTs<sup>[44]</sup> <sup>[45]</sup> 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).<sup>[7]</sup> 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).<sup>[44]</sup> 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).<sup>[45]</sup> However, the RCT lacked power to rule out a clinically important difference between treatments.<sup>[45]</sup>

#### Harms:

##### Thienopyridines (clopidogrel and ticlopidine) versus aspirin:

The first systematic review gave no information on adverse effects.<sup>[7]</sup> 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).<sup>[38]</sup> 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.<sup>[46]</sup> <sup>[47]</sup> The subsequent RCT comparing aspirin and ticlopidine found similar results.<sup>[39]</sup> 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).<sup>[39]</sup> 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).<sup>[40]</sup>

##### 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%).<sup>[41]</sup> 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).<sup>[41]</sup>

##### Dipyridamole plus aspirin versus aspirin alone:

The systematic review did not report harms data.<sup>[42]</sup> 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).<sup>[48]</sup> 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.<sup>[48]</sup>

##### 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).<sup>[43]</sup>

#### Triflusal versus aspirin:

The systematic review gave no information on adverse effects.<sup>[7]</sup> 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).<sup>[44]</sup> 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).<sup>[45]</sup> 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.<sup>[45]</sup>

#### Comment:

We found one systematic review solely in people with previous stroke or TIA comparing aspirin plus dipyridamole versus aspirin alone.<sup>[42]</sup> 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.<sup>[7] [49]</sup>

#### 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.<sup>[50]</sup> 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.<sup>[51] [52] [53] [54]</sup> 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.<sup>[55]</sup> 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. <sup>[56]</sup> <sup>[57]</sup> <sup>[15]</sup> 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 (bendroflumazide 2.5 mg, 5 mg, or 10 mg; hydrochlorothiazide 25 mg or 50 mg) versus beta-blockers (propranolol 80 mg or 160 mg; atenolol 50 mg). <sup>[56]</sup> 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). <sup>[56]</sup>

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. <sup>[57]</sup> 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). <sup>[57]</sup>

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. <sup>[15]</sup> 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). <sup>[15]</sup> 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). <sup>[15]</sup> 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). <sup>[56]</sup> See [harms under blood pressure reduction, p 5](#) . The second <sup>[57]</sup> and third <sup>[15]</sup> 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. <sup>[57]</sup> <sup>[15]</sup> Together with the results of the systematic reviews <sup>[14]</sup> 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<sup>[7]</sup> and one subsequent RCT.<sup>[58]</sup> 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.<sup>[7]</sup> 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).<sup>[58]</sup> 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).<sup>[58]</sup> 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.<sup>[59]</sup>

#### 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).<sup>[7]</sup> We found one systematic review (search date 1999; 24 RCTs) on the effects of aspirin on GI bleeding.<sup>[13]</sup> 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.<sup>[58] [60] [61]</sup> 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).<sup>[62]</sup> 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.<sup>[59]</sup>

##### Intracranial haemorrhage:

We found one systematic review (search date 1997; 16 RCTs; 55,462 people) of the effects of aspirin on intracranial haemorrhage.<sup>[12]</sup> 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.<sup>[58] [60] [61]</sup>

**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. <sup>[59]</sup>

**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). <sup>[63]</sup> 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). <sup>[63]</sup>

**Anticoagulation versus antiplatelet treatment:**

We found one systematic review <sup>[64]</sup> and one subsequent RCT. <sup>[65]</sup> 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. <sup>[64]</sup> 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%). <sup>[64]</sup> 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).<sup>[64]</sup> 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).<sup>[65]</sup> 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.<sup>[65]</sup>

**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%).<sup>[63]</sup>

**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%).<sup>[64]</sup> 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%).<sup>[66]</sup> 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).<sup>[65]</sup>

**Comment:****Anticoagulation versus placebo or no treatment:**

Most trials in the systematic review had major problems with their methods, including poor monitoring of anticoagulation.<sup>[63]</sup> 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, <sup>[67]</sup> <sup>[68]</sup> and we found one subsequent RCT <sup>[69]</sup> 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. <sup>[67]</sup> 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). <sup>[67]</sup>

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. <sup>[68]</sup> 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<sub>6</sub>, and vitamin B<sub>12</sub> versus placebo. <sup>[69]</sup> 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). <sup>[69]</sup>

#### 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<sub>6</sub> 25 mg plus vitamin B<sub>12</sub> 0.4 mg) versus a lower-dose vitamin supplement (folic acid 20 micrograms plus vitamin B<sub>6</sub> 200 micrograms plus vitamin B<sub>12</sub> 6 micrograms). <sup>[70]</sup> 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. <sup>[70]</sup>

### Harms:

#### Vitamin B supplements (including folate) versus placebo:

The two systematic reviews <sup>[67]</sup> <sup>[68]</sup> and one subsequent RCT <sup>[69]</sup> did not report on harms.

#### Different regimens versus each other:

The RCT did not report on harms. <sup>[70]</sup>

### Comment:

In observational studies, lower homocysteine levels are associated with lower rates of CHD and stroke. Vitamins B<sub>6</sub> and B<sub>12</sub> 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). <sup>[68]</sup>

**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<sup>[71]</sup> and one systematic review.<sup>[72]</sup> The pooled analysis of individual patient data from three large RCTs (4 publications)<sup>[73] [74] [75] [76]</sup> examined the effects of endarterectomy in people with symptomatic carotid stenosis. 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).<sup>[71]</sup> 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.<sup>[72]</sup> It reported the finding of the pooled analysis reported above,<sup>[71]</sup> and reached similar conclusions, reporting a 2.2% absolute increase in stroke risk (CI not reported; further numerical details not reported).<sup>[72]</sup>

**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%).<sup>[71]</sup> 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.<sup>[72]</sup> 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.<sup>[77]</sup>

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).<sup>[78]</sup> 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).<sup>[78]</sup> Endarterectomy is also associated with other postoperative complications, including wound infection (3%), wound haematoma (5%), and lower cranial nerve injury (5%–7%).<sup>[79]</sup>

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.<sup>[80]</sup> 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 to 1.78; 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;  $P = 0.34$ ).<sup>[80]</sup>

**Comment:** The RCTs included in the pooled analysis found different results.<sup>[73] [74]</sup> 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<sup>[73]</sup> produced higher values than the method used in the other trials),<sup>[74] [75] [81]</sup> 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.<sup>[82] [83]</sup> 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.<sup>[71]</sup> The degree of carotid stenosis was the single most important factor influencing the effects of endarterectomy.<sup>[71]</sup>

#### "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%).<sup>[84]</sup> 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%.<sup>[85]</sup> 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.<sup>[86]</sup>

### 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<sup>[71]</sup> and one systematic review.<sup>[72]</sup> 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.<sup>[73] [74] [75] [76]</sup> 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<sup>[71]</sup> and one systematic review.<sup>[72]</sup> 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.<sup>[73] [74] [75] [76]</sup> 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 <sup>[73]</sup> and North American Symptomatic Carotid Endarterectomy Trial <sup>[74]</sup> (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. <sup>[87]</sup> 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. <sup>[87]</sup> 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 <sup>[71]</sup> and one systematic review. <sup>[72]</sup> 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. <sup>[73]</sup> <sup>[74]</sup> <sup>[75]</sup> <sup>[76]</sup> 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). <sup>[72]</sup>

**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<sup>[71]</sup> and one systematic review.<sup>[72]</sup> 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.<sup>[73] [74] [75] [76]</sup> 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).<sup>[72]</sup>
- 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).<sup>[88]</sup> 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.<sup>[89]</sup> The systematic review gave no information on adverse effects.<sup>[88]</sup> 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%.<sup>[90]</sup>
- 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.<sup>[88]</sup> 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).<sup>[91]</sup> There is currently no evidence of benefit in women after 5 years.<sup>[91]</sup>

#### 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<sup>[92]</sup> and one subsequent RCT.<sup>[93]</sup> 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.<sup>[93]</sup> 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).<sup>[92]</sup>

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).<sup>[93]</sup> 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).<sup>[93]</sup>

### 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.<sup>[92]</sup> <sup>[93]</sup>

## 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.<sup>[94]</sup> 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).<sup>[94]</sup> 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<sup>[94]</sup> compared "best medical treatment" plus carotid PTA versus "best medical treatment" plus carotid endarterectomy.<sup>[95]</sup> 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).<sup>[95]</sup>

### 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).<sup>[94]</sup> The largest included RCT (reported in 2 publications)<sup>[95] [96]</sup> 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).<sup>[96]</sup> 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.<sup>[96]</sup> 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).<sup>[97]</sup>

### 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".<sup>[95]</sup> 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, <sup>[98]</sup> <sup>[99]</sup> which between them identified nine RCTs, and one subsequent RCT <sup>[100]</sup> 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). <sup>[98]</sup> 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 to 1.47; 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. <sup>[99]</sup> 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). <sup>[99]</sup> 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. <sup>[100]</sup> 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%). <sup>[100]</sup>

**Harms:** **Carotid PTA plus stenting versus endarterectomy:**  
The first systematic review <sup>[98]</sup> and the subsequent RCT <sup>[100]</sup> 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). <sup>[99]</sup> We found one additional systematic review (34 RCTs; 4185 people) of recurrent stenosis after CAS, with follow-up between 6 to 31 months. <sup>[101]</sup> 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. <sup>[101]</sup>

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. <sup>[102]</sup> <sup>[103]</sup> However, improvements in cerebral protection devices may reduce the procedural risks, <sup>[104]</sup> 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; <sup>[105]</sup> 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). <sup>[106]</sup> 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). <sup>[105]</sup>

#### Conventional-intensity versus low-intensity or minidose warfarin:

We found one RCT (115 people with ischaemic stroke in the previous 1–6 months). <sup>[107]</sup> 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). <sup>[107]</sup> 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). <sup>[108]</sup> 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), <sup>[106]</sup> which identified one RCT <sup>[105]</sup> 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 <sup>[106]</sup> and one subsequent RCT. <sup>[109]</sup> The systematic review (search date 1999; 1 RCT; <sup>[108]</sup> 916 people within 15 days of stroke onset) compared warfarin (target INR 2.0–3.5) versus indobufen. <sup>[106]</sup> 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%). <sup>[106]</sup> 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. <sup>[109]</sup> 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.<sup>[109]</sup>

#### Conventional-intensity warfarin versus other anticoagulants:

We found two RCTs.<sup>[110] [111]</sup> 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).<sup>[110]</sup> 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).<sup>[110]</sup>

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).<sup>[111]</sup> 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).<sup>[111]</sup> Ximelagatran has been voluntarily withdrawn worldwide owing to potential increased risk of liver damage.<sup>[112]</sup>

#### 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.<sup>[106]</sup> 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.<sup>[106]</sup> 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.<sup>[113]</sup>

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).<sup>[114]</sup> 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).<sup>[115]</sup> 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).<sup>[116]</sup>

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%).<sup>[117]</sup> 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.<sup>[117]</sup> 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).<sup>[107]</sup>

#### 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).<sup>[109]</sup>

**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).<sup>[111]</sup> Ximelagatran has been voluntarily withdrawn worldwide owing to potential increased risk of liver damage.<sup>[112]</sup>

**Comment:**

We found one systematic review (search date 2005; 5 primary studies, 2 meta-analyses),<sup>[118]</sup> 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.<sup>[118]</sup>

**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.<sup>[119]</sup>

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).<sup>[117]</sup> 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 to 1.78).<sup>[117]</sup>

**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),<sup>[118]</sup> 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).<sup>[106] [117] [120]</sup> 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.<sup>[106]</sup> 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,<sup>[117]</sup> as did the third systematic review (search date 2005; 13 RCTs).<sup>[120]</sup>

**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.<sup>[121]</sup> 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).<sup>[121]</sup>

**Adjusted-dose versus low-intensity or minidose warfarin:**

We found two systematic reviews (see comment below).<sup>[122]</sup> <sup>[120]</sup> 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).<sup>[122]</sup> 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).<sup>[120]</sup>

**Adjusted-dose warfarin versus aspirin:**

We found two systematic reviews comparing warfarin versus different antiplatelet regimens in **people at high risk of stroke**,<sup>[106]</sup> <sup>[120]</sup> and one subsequent report of a meta-analysis of individual patient data (see comment below).<sup>[123]</sup> 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).<sup>[106]</sup> 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.<sup>[120]</sup> 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).<sup>[123]</sup> 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.<sup>[109]</sup> 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).<sup>[109]</sup> 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.<sup>[124]</sup> 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.<sup>[124]</sup>

The second RCT (1209 people with atrial fibrillation) compared the COX-2 inhibitor triflusal, the oral anticoagulant acenocoumarol, or a combination of both.<sup>[125]</sup> 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 triflusal. 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;  $P = 0.03$ ).<sup>[125]</sup> 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,  $P = 0.02$ ).<sup>[125]</sup>

#### 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).<sup>[120]</sup> Ximelagatran has been voluntarily withdrawn worldwide owing to a potential increased risk of liver damage.<sup>[112]</sup>

### 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).<sup>[106]</sup> 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).<sup>[120]</sup>

#### 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).<sup>[121]</sup>

#### 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).<sup>[122]</sup>

#### 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;  $P = 0.53$ )<sup>[109]</sup>

#### 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;  $P = 0.0021$ ).<sup>[124]</sup> 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).<sup>[125]</sup> 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).<sup>[125]</sup>

#### Adjusted-dose warfarin versus other anticoagulants:

The review gave no information on adverse effects.<sup>[120]</sup> 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).<sup>[110]</sup> 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.<sup>[112]</sup>

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),<sup>[118]</sup> 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<sup>[113]</sup> and one subsequent RCT.<sup>[121]</sup> 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.<sup>[126]</sup>

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.<sup>[127]</sup> 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.<sup>[121]</sup> 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).<sup>[127]</sup> 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.<sup>[126] [128] [129] [130] [131] [132]</sup>

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.<sup>[127] [133] [134]</sup> 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.<sup>[135] [136]</sup>

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.<sup>[137]</sup> 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.

<b>OPTION</b>	<b>ANTIPLATELET TREATMENT IN PEOPLE WITH ATRIAL FIBRILLATION WITHOUT PREVIOUS STROKE OR TIA WITH HIGH RISK OF STROKE OR TIA</b>
---------------	---------------------------------------------------------------------------------------------------------------------------------

**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).<sup>[138]</sup> 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).<sup>[138]</sup> 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).<sup>[138]</sup>

**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),<sup>[118]</sup> 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<sup>[106] [138]</sup> 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.<sup>[139]</sup> 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.<sup>[140]</sup>

**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

**Benefits:****Anticoagulants versus placebo:**

We found one systematic review <sup>[138]</sup> and one overview <sup>[113]</sup> 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. <sup>[138]</sup> 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%). <sup>[113]</sup>

**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. <sup>[141]</sup> 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). <sup>[141]</sup>

**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 (668 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). <sup>[141]</sup> 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), <sup>[118]</sup> 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

**Benefits:****Antiplatelet treatment versus placebo or no treatment:**

We found two systematic reviews in people with atrial fibrillation at low risk of stroke, <sup>[142]</sup> <sup>[106]</sup> and one subsequent RCT (see comment below). <sup>[143]</sup> 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. <sup>[142]</sup> 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.<sup>[106]</sup> 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.<sup>[143]</sup> 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.<sup>[143]</sup>

**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<sup>[106]</sup> 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.<sup>[143]</sup>

**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),<sup>[118]</sup> 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<sup>[144]</sup> 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,<sup>[145]</sup> aspirin (most at 325 mg/day) was given in a non-randomised manner, without significant benefit. However, in another RCT<sup>[146]</sup> 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.<sup>[143]</sup> 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/mini-dose 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.<sup>[42]</sup> 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.<sup>[43]</sup> Categorisation unchanged (Beneficial).

**Anticoagulation in people in sinus rhythm** One already included systematic review updated;<sup>[64]</sup> 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.<sup>[65]</sup> 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.<sup>[16]</sup> 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.<sup>[98]</sup><sup>[99]</sup><sup>[100]</sup> 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.<sup>[27]</sup> One new RCT added, which found that atorvastatin reduced the risk of stroke and other major cardiovascular events in people with carotid atherosclerosis.<sup>[28]</sup> 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.<sup>[93]</sup> 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.<sup>[11]</sup> 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.

## REFERENCES

- Hankey GJ, Warlow CP. *Transient ischaemic attacks of the brain and eye*. London: WB Saunders, 1994.
- Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet* 1995;346:1647–1653.[\[PubMed\]](#)
- Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet* 1998;352:1801–1807.[\[PubMed\]](#)
- Di Maschio R, Marchioli R, Tognoni G. Cholesterol reduction and stroke occurrence: an overview of randomized clinical trials. *Cerebrovasc Dis* 2000;10:85–92. Search date not reported.[\[PubMed\]](#)
- Warlow CP, Dennis MS, Van Gijn J, et al. Predicting recurrent stroke and other serious vascular events. In: *Stroke. A practical guide to management*. Oxford: Blackwell Science, 1996:545–552.
- Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81–106. Search date 1990.[\[PubMed\]](#)
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86. Search date 1997.[\[PubMed\]](#)
- Rothwell PM, Warlow CP. Timing of TIAs preceding stroke: Time window for prevention is very short. *Neurology* 2005;64:817–820.[\[PubMed\]](#)
- Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005;366:29–36.[\[PubMed\]](#)
- Hart RG, Pearce LA, Rothbart RM, et al. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial fibrillation Investigators. *J Am Coll Cardiol* 2000;35:183–187.[\[PubMed\]](#)
- Sandercock PAG, Counsell C, Gubitz GJ, et al. Antiplatelet therapy for acute ischaemic stroke. In: *The Cochrane Library*, Issue 3, 2008. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.[\[PubMed\]](#)
- He J, Whelton PK, Vu B, et al. Aspirin and risk of hemorrhagic stroke. A meta-analysis of randomised controlled trials. *JAMA* 1998;280:1930–1935. Search date 1997.[\[PubMed\]](#)
- Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000;321:1183–1187. Search date 1999.[\[PubMed\]](#)
- Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events. A systematic review. *Stroke* 2003;34:2741–2749.[\[PubMed\]](#)
- Lawes C, Bennett DA, Feigin VL, et al. Blood pressure and stroke. An overview of published reviews. *Stroke* 2004;35:1024–1033.[\[PubMed\]](#)
- Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Eng J Med* 2008;359:1225–1237.
- Eriksson S, Olofsson BO, Wester PO for the TEST study group. Atenolol in secondary prevention after stroke. *Cerebrovasc Dis* 1995;5:21–25.
- Dutch TIA Trial Study Group. Trial of secondary prevention with atenolol after transient ischaemic attack or non-disabling ischaemic stroke. *Stroke* 1993;24:543–548.
- PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033–1041.[\[PubMed\]](#)

20. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *New Engl J Med* 2000;342:145–153.[PubMed]
21. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913. Search date not reported. [PubMed]
22. Rodgers A, MacMahon S, Gamble G, et al, for the United Kingdom Transient Ischaemic Attack Collaborative Group. Blood pressure and risk of stroke in patients with cerebrovascular disease. *BMJ* 1996;313:147.[PubMed]
23. Neal B, Clark T, MacMahon S, et al, on behalf of the Antithrombotic Trialists' Collaboration. Blood pressure and the risk of recurrent vascular disease. *Am J Hypertension* 1998;11:25A–26A.
24. Staessen JA, Wang J. Blood-pressure lowering for the secondary prevention of stroke. *Lancet* 2001;358:1026–1027.[PubMed]
25. Rothwell PM, Howard SC, Spence JD, for the Carotid Endarterectomy Trialists' Collaboration. Relationship between blood pressure and stroke risk in patients with symptomatic carotid occlusive disease. *Stroke* 2003;34:2583–2592.[PubMed]
26. Amarenco P, Labreuche J, Lavallee P, et al. Statins in stroke prevention and carotid atherosclerosis. Systematic review and up-to-date meta-analysis. *Stroke* 2004;35:2902–2909.[PubMed]
27. O'Regan C, Wu P, Arora P, et al. Statin therapy in stroke prevention: a meta-analysis involving 121,000 patients. *Am J Med* 2008;121:24–33.[PubMed]
28. Sillesen H, Amarenco P, Hennerici MG, et al. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke* 2008;39:3297–3302.[PubMed]
29. Amarenco P, Bogousslavsky J, Callahan A III, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355:549–559.[PubMed]
30. Anonymous. The treatment of cerebrovascular disease with clofibrate. Final report of the Veterans' Administration Cooperative Study of Atherosclerosis, neurology section. *Stroke* 1973;4:684–693.[PubMed]
31. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410–418.[PubMed]
32. The BIP Study Group. Secondary prevention by raising HDL-cholesterol and reducing triglycerides in patients with coronary artery disease. The Bezafibrate Infarction Prevention (BIP) Study. *Circulation* 2000;102:21–27.[PubMed]
33. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423–1427. Search date 2002.[PubMed]
34. Silva MA, Swanson AC, Gandhi PJ, et al. Statin-related adverse events: A meta-analysis. *Clin Ther* 2006;28:26–35.[PubMed]
35. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22.[PubMed]
36. Cholesterol Treatment Trialists' Collaboration. Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. *Am J Cardiol* 1995;75:1130–1134.[PubMed]
37. Josan K, Majumdar SR, McAlister FA, et al. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. *CMAJ* 2008;178:576–584.[PubMed]
38. Hankey GJ, Sudlow CLM, Dunbabin DW. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. In: *The Cochrane Library*, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 1999.[PubMed]
39. Gorelick PB, Richardson D, Kelly M, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients. A randomized trial. *JAMA* 2003;289:2947–2957.[PubMed]
40. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706–1717.[PubMed]
41. Diener H-C, Bogousslavsky J, Brass LM, et al, on behalf of the MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. *Lancet* 2004;364:331–337.[PubMed]
42. Verro P, Gorelick PB, Nguyen D, et al. Aspirin plus dipyridamole versus aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. *Stroke* 2008;39:1358–1363.[PubMed]
43. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;359:1238–1251.[PubMed]
44. Matias-Guiu J, Ferro JM, Alvarez-Sabin J, et al. Comparison of triflusal and aspirin for prevention of vascular events in patients after cerebral infarction. The TACIP study: a randomized, double-blind, multicenter trial. *Stroke* 2003;34:840–848.
45. Culebras A, Rotta-Escalante R, Vila J, et al. Triflusal versus aspirin for prevention of cerebral infarction. A randomized stroke study. *Neurology* 2004;62:1073–1080.[PubMed]
46. Moloney BA. An analysis of the side effects of ticlopidine. In: Hass WK, Easton JD, eds. *Ticlopidine, platelets and vascular disease*. New York: Springer, 1993:117–139.
47. Bennett CL, Davidson CJ, Raich DW, et al. Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. *Arch Int Med* 1999;159:2524–2528.[PubMed]
48. ESPRIT Study Group, Halkes PH, van Gijn J, et al. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006;367:1665–1673.
49. De Schryver ELLM, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. In: *The Cochrane Library*, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 2005.[PubMed]
50. Chan FKL, Ching JYL, Hung LCT, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005;352:238–244.[PubMed]
51. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.[PubMed]
52. Steinhubl SR, Berger PB, Mann JT, et al, for the CREDO Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention. A randomized controlled trial. *JAMA* 2002;288:2411–2420.[PubMed]
53. Sabatine MS, Cannon CP, Gibson M, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179–1189.[PubMed]
54. COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607–1621.[PubMed]
55. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial. *Circulation* 2005;111:2233–2240.[PubMed]
56. Wright JM, Lee CH, Chambers GK. Systematic review of antihypertensive therapies: does the evidence assist in choosing a first-line drug? *Can Med Assoc J* 1999;161:25–32. Search date 1997.
57. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003;362:1527–1535. Search date 2003.[PubMed]
58. Taylor DW, Barnett HJM, Haynes RB, et al, for the ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet* 1999;353:2179–2184.[PubMed]
59. Fisher M, Knappertz V. The dose of aspirin for the prevention of cardiovascular and cerebrovascular events. *Curr Med Res Opin* 2006;22:1239–1248.[PubMed]
60. The Dutch TIA Study Group. A comparison of two doses of aspirin (30 mg vs 283 mg a day) in patients after a transient ischaemic attack or minor ischaemic stroke. *N Engl J Med* 1991;325:1261–1266.[PubMed]
61. Farrell B, Godwin J, Richards S, et al. The United Kingdom Transient Ischaemic Attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry* 1991;54:1044–1054.[PubMed]
62. Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications. Systematic review of epidemiologic studies. *Br J Clin Pharmacol* 2001;52:563–571. Search date 2001.
63. Sandercock P, Mielke O, Liu M, et al. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. In: *The Cochrane Library*, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002.
64. Algra A, De Schryver ELLM, van Gijn J, et al. Oral anticoagulants versus antiplatelet therapy for preventing further vascular events after transient ischaemic attack or minor stroke of presumed arterial origin. In: *The Cochrane Library*, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004.
65. ESPRIT Study Group, Halkes PH, van Gijn J, et al. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurol* 2007;6:115–124.
66. Mohr JP, Thompson JLP, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345:1444–1451.[PubMed]
67. Bazzano LA, Reynolds K, Holder KN, et al. Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. *JAMA* 2006;296:2720–2726.[PubMed]
68. Wang X, Qin X, Demirtas H, et al. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. *Lancet* 2007;369:1876–1882.[PubMed]
69. Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *JAMA* 2008;299:2027–2036.[PubMed]
70. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 2004;291:565–575.[PubMed]
71. Rothwell PM, Gutnikov SA, Eliasziw M, et al, for the Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;361:107–116.[PubMed]
72. Chaturvedi S, Bruno A, Feasby T, et al. Carotid endarterectomy—an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005;65:794–801.[PubMed]
73. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European carotid surgery trial (ECST). *Lancet* 1998;351:1379–1387.[PubMed]
74. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445–453.[PubMed]
75. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1998;339:1415–1425.[PubMed]
76. Mayberg MR, Wilson E, Yatsu F, et al, for the Veterans Affairs Cooperative Studies Program 309 Trialist Group. Carotid endarterectomy and prevention of cerebral ischaemia in symptomatic carotid stenosis. *JAMA* 1991;266:3289–3294.[PubMed]

77. Rothwell P, Slattery J, Warlow C. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review. *BMJ* 1997;315:1571–1577. Search date 1996. [PubMed]
78. Bond R, Rerkasem K, Rothwell PM. A systematic review of the risks of carotid endarterectomy in relation to the clinical indication and the timing of surgery. *Stroke* 2003;34:2290–3301. Search date 2000. [PubMed]
79. Bond R, Narayan S, Rothwell PM, et al. Clinical and radiological risk factors for operative stroke and death in the European Carotid Surgery Trial. *Eur J Vasc Endovasc Surg* 2002;23:108–116. [PubMed]
80. Bond R, Rerkasem K, Cuffe R, et al. A systematic review of the associations between age and sex and the operative risks of carotid endarterectomy. *Cerebrovasc Dis* 2005;20:69–77. [PubMed]
81. Rothwell PM, Gibson RJ, Slattery J, et al. Equivalence of measurements of carotid stenosis: a comparison of three methods on 1001 angiograms. *Stroke* 1994;25:2435–2439. [PubMed]
82. Cina CS, Devereaux PJ. Coronary-artery revascularization before elective major vascular surgery. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpoint G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG. *N Engl J Med*. 2004;351:2795–804. *Vascular Med* 2006;11:61–63. [PubMed]
83. Goldstein LB, Hasselblad V, Matchar DB, et al. Comparison and meta-analysis of randomised trials of endarterectomy for symptomatic carotid artery stenosis. *Neurology* 1995;45:1965–1970. [PubMed]
84. Naylor AR, Mehta Z, Rothwell PM, et al. Carotid artery disease and stroke during coronary artery bypass surgery: a critical review of the literature. *Eur J Vasc Endovasc Surg* 2002;23:283–294. Search date 2000. [PubMed]
85. Naylor AR, Cuffe RL, Rothwell PM, et al. A systematic review of outcomes following staged and synchronous carotid endarterectomy and coronary artery bypass. *Eur J Vasc Endovasc Surg* 2003;25:380–389. Search date 2002. [PubMed]
86. Hill MD, Shrive FM, Kennedy J, et al. Simultaneous carotid endarterectomy and coronary artery bypass surgery in Canada. *Neurology* 2005;64:1435–1437. [PubMed]
87. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;363:915–924. [PubMed]
88. Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & sons, Ltd. Search date 2004.
89. Whitty C, Sudlow C, Warlow C. Investigating individual subjects and screening populations for asymptomatic carotid stenosis can be harmful. *J Neurol Neurosurg Psychiatry* 1998;64:619–623. [PubMed]
90. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic stenosis: Asymptomatic Carotid Surgery Trial. *Stroke* 2004;35:2425–2427. [PubMed]
91. Rothwell PM. ACST: which subgroups will benefit most from carotid endarterectomy? *Lancet* 2004;364:1122–1123. [PubMed]
92. Cao PG, De Rango P, Zannetti S, et al. Everson versus conventional carotid endarterectomy for preventing stroke. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002.
93. Markovic DM, Davidovic LB, Cvetkovic DD, et al. Single-center prospective, randomized analysis of conventional and eversion carotid endarterectomy. *J Cardiovasc Surg* 2008;49:619–625. [PubMed]
94. Coward LJ, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 2003. [PubMed]
95. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;357:1729–1737. [PubMed]
96. McCabe DJH, Pereira AC, Clifton A, et al. Restenosis after carotid angioplasty, stenting, or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). *Stroke* 2005;36:281–286. [PubMed]
97. Naylor AR, Bolia A, Abbott RJ, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg* 1998;28:326–334. [PubMed]
98. Gurm HS, Nallamothu BK, Yadav J, et al. Safety of carotid artery stenting for symptomatic carotid artery disease: a meta-analysis. *Eur Heart J* 2008;29:113–119. [PubMed]
99. Jeng JS, Liu HM, Tu YK, et al. Carotid angioplasty with or without stenting versus carotid endarterectomy for carotid artery stenosis: a meta-analysis. *J Neurol Sci* 2008;270:40–47. [PubMed]
100. Gurm HSY. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;358:1572–1579. [PubMed]
101. Groschel K, Riecker A, Schulz JB, et al. Systematic review of early recurrent stenosis after carotid angioplasty and stenting. *Stroke* 2005;36:367–373. [PubMed]
102. Alberts MJ, for the Publications Committee of the WALLSTENT. Results of a multicentre prospective randomised trial of carotid artery stenting vs. carotid endarterectomy. *Stroke* 2001;32:325.
103. Brooks WH, McClure RR, Jones MR, et al. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol* 2001;38:1589–1595. [PubMed]
104. Reimers B, Corvaja N, Moshiri S, et al. Cerebral protection with filter devices during carotid artery stenting. *Circulation* 2001;104:12–15. [PubMed]
105. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet* 1993;342:1255–1262. [PubMed]
106. Hart R, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501. Search date 1999. [PubMed]
107. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation: a multicenter, prospective randomised trial. Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. *Stroke* 2000;31:817–821. [PubMed]
108. Morocutti C, Amabile G, Fattapposta F, et al, for the SIFA Investigators. Indobufen versus warfarin in the secondary prevention of major vascular events in non-rheumatic atrial fibrillation. *Stroke* 1997;28:1015–1021. [PubMed]
109. ACTIVE Writing Group on behalf of the ACTIVE Investigators, Connolly S, Pogue J, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903–1912. [PubMed]
110. Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003;362:1691–1698. [PubMed]
111. Albers GW, Diener HC, Frison L, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 2005;293:690–698. [PubMed]
112. Boos CJ, Lip GY. Ximelagatran: an eulogy. *Thrombosis Res* 2006;118:301–304. [PubMed]
113. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. *Arch Intern Med* 1994;154:1449–1457. [PubMed]
114. Saxena R, Koudstaal P. Anticoagulants for preventing stroke in patients with non-rheumatic atrial fibrillation and a history of stroke or transient ischemic attacks. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 2003.
115. Saxena R, Koudstaal P. Anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-rheumatic atrial fibrillation and a history of stroke or transient ischemic attacks. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons Ltd. Search date 2003.
116. Aguilar M, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004.
117. Segal JB, McNamara RL, Miller MR, et al. Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 1999.
118. National Collaborating Centre for Chronic Conditions. Atrial fibrillation: national clinical guideline for management in primary and secondary care. London: Royal College of Physicians, 2006.
119. Chen ZM, Sandercock P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40,000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. On behalf of the CAST and IST collaborative groups. *Stroke* 2000;31:1240–1249. [PubMed]
120. Lip GYH, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *Thrombosis Res* 2006;118:321–333. [PubMed]
121. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: stroke prevention in atrial fibrillation III randomised clinical trial. *Lancet* 1996;348:633–638. [PubMed]
122. Perret-Guillaume C, Wahl DG. Low-dose warfarin in atrial fibrillation leads to more thromboembolic events without reducing major bleeding when compared to adjusted-dose – a meta-analysis. *Thromb Haemost* 2004;91:394–402. Search date 2002. [PubMed]
123. Van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation. An individual patient meta-analysis. *JAMA* 2002;288:2441–2448. [PubMed]
124. Lechat P, Lardoux H, Mallet A, et al. Anticoagulant (fluidione) aspirin combination in patients with high risk atrial fibrillation. A randomised trial (Fluidione, fibrillation Auriculaire, Aspirin et Contraste Spontane; FFAACS). *Cerebrovasc Dis* 2001;12:245–252. [PubMed]
125. Perez-Gomez F, Alegria E, Berjon J, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol* 2004;44:1557–1566. [PubMed]
126. Hart R, Sherman D, Easton D, et al. Prevention of stroke in patients with non-valvular atrial fibrillation. *Neurology* 1998;51:674–681. [PubMed]
127. Taylor F, Cohen H, Ebrahim S. Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. *BMJ* 2001;322:321–326. Search date 1999. [PubMed]
128. Lip GYH, Boos CJ. Antithrombotic treatment in atrial fibrillation. *Heart* 2006;92:155–161. [PubMed]
129. Ezekowitz M, Levine J. Preventing stroke in patients with atrial fibrillation. *JAMA* 1999;281:1830–1835. [PubMed]
130. Feinberg W. Anticoagulation for prevention of stroke. *Neurology* 1998;51(suppl 3):20–22.
131. Albers G. Choice of antithrombotic therapy for stroke prevention in atrial fibrillation. Warfarin, aspirin, or both? *Arch Intern Med* 1998;158:1487–1491. [PubMed]
132. Nademanee K, Kosar E. Long-term antithrombotic treatment for atrial fibrillation. *Am J Cardiol* 1998;82:37N–42N.
133. Green CJ, Hadorn DC, Bassett K, et al. Anticoagulation in chronic non-valvular atrial fibrillation: a critical appraisal and meta-analysis. *Can J Cardiol* 1997;13:811–815. [PubMed]
134. Blakely J. Anticoagulation in chronic non-valvular atrial fibrillation: appraisal of two meta-analyses. *Can J Cardiol* 1998;14:945–948. [PubMed]
135. The European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with non-rheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med* 1995;333:5–10. [PubMed]
136. Hylek EM, Skates SJ, Sheehan MA, et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with non-rheumatic atrial fibrillation. *N Engl J Med* 1996;335:540–546. [PubMed]
137. Evans A, Kalra L. Are the results of randomized controlled trials on anticoagulation in patients with atrial fibrillation generalizable to clinical practice? *Arch Intern Med* 2001;161:1443–1447. Search date not reported. [PubMed]

138. Aguilar MI, Hart RG. Antiplatelet therapy for preventing stroke in patients with nonvalvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Stroke* 2006;37:274–275.
139. Stroke Prevention in Atrial Fibrillation Investigators. A differential effect of aspirin in prevention of stroke on atrial fibrillation. *J Stroke Cerebrovasc Dis* 1993;3:181–188.
140. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. [erratum appears in *BMJ* 2002;324:141.] *BMJ* 2002;324:71–86. [PubMed]
141. Edvardsson N, Juul-Moller S, Ombus R, et al. Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation. *J Intern Med* 2003;254:95–101. [PubMed]
142. Aguilar M, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004. [PubMed]
143. Sato H, Ishikawa K, Kitabatake A, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. *Stroke* 200;37:447–451. [PubMed]
144. Petersen P, Boysen G, Godtfredsen J, et al. Placebo controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASK study. *Lancet* 1989;1:175–179. [PubMed]
145. Singer DE, Hughes RA, Gress DR, et al. The effect of aspirin on the risk of stroke in patients with nonrheumatic atrial fibrillation: the BAATAF Study. *Am Heart J* 1992;124:1567–1573. [PubMed]
146. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991;84:527–539. [PubMed]

**Gregory YH Lip**

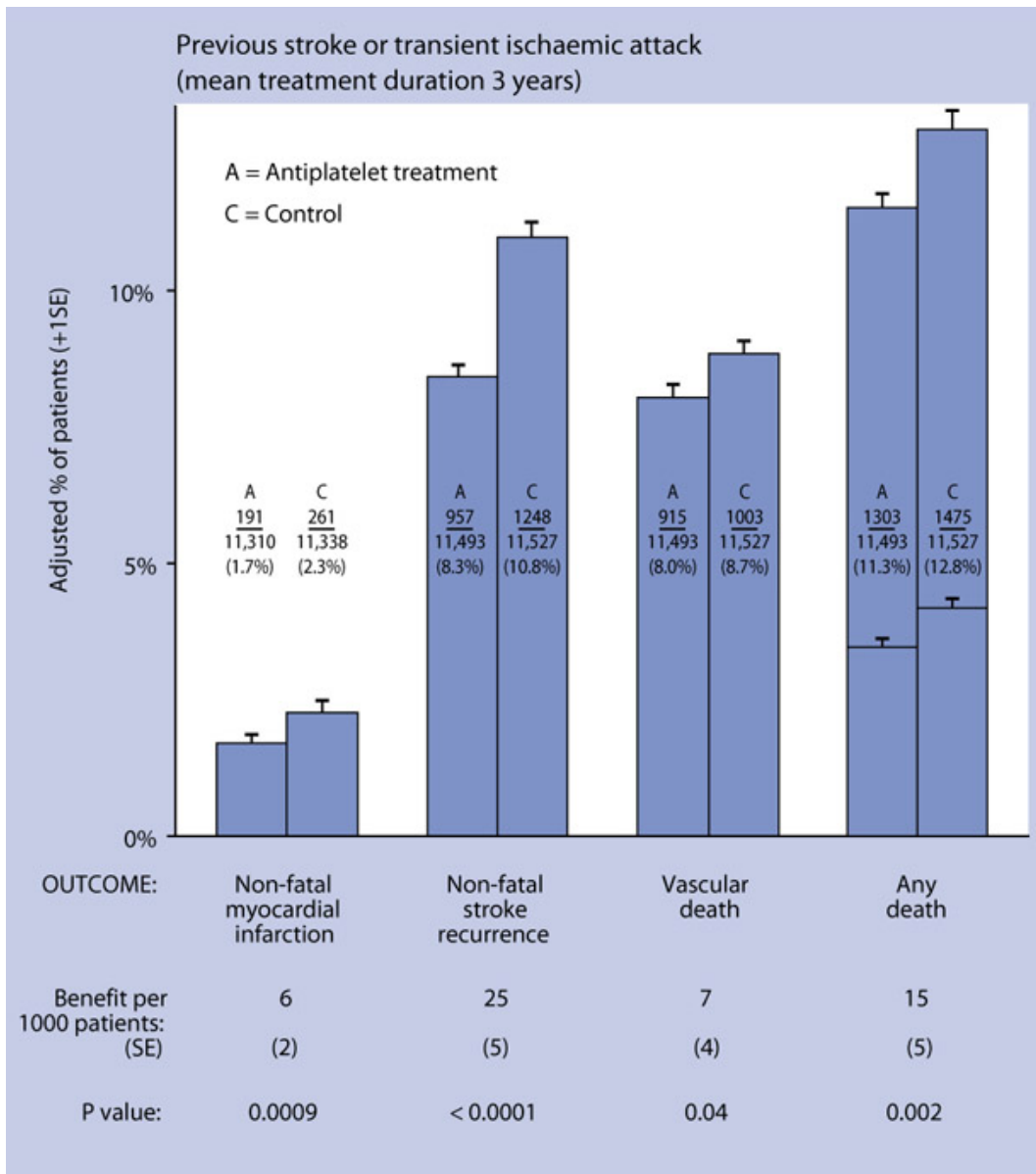
Professor of Cardiovascular Medicine, University of Birmingham, Visiting Professor of Haemostasis Thrombosis & Vascular Sciences, University of Aston in Birmingham  
 Centre for Cardiovascular Sciences  
 City Hospital  
 Birmingham  
 UK

**Lalit Kalra**

Professor of Stroke Medicine  
 London School of Medicine  
 King's College  
 London  
 UK

Competing interests: GL is clinical advisor to Guideline Development Group writing National Institute for Health and Clinical Excellence (NICE) guidelines on atrial fibrillation management. He has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for the management of atrial fibrillation and thrombosis. LK declares that he has no competing interests.

The following previous contributors of this review would also like to be acknowledged: Cathie Sudlow, Peter Rothwell, Colin Baigent, Gord Gubitzi, Peter Sandercock, and Bethan Freestone.



**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.

**Disclaimer**

The information contained in this publication is intended for medical professionals. Categories presented in Clinical Evidence indicate a judgement about the strength of the evidence available to our contributors prior to publication and the relevant importance of benefit and harms. We rely on our contributors to confirm the accuracy of the information presented and to adhere to describe accepted practices. Readers should be aware that professionals in the field may have different opinions. Because of this and regular advances in medical research we strongly recommend that readers' independently verify specified treatments and drugs including manufacturers' guidance. Also, the categories do not indicate whether a particular treatment is generally appropriate or whether it is suitable for a particular individual. Ultimately it is the readers' responsibility to make their own professional judgements, so to appropriately advise and treat their patients. To the fullest extent permitted by law, BMJ Publishing Group Limited and its editors are not responsible for any losses, injury or damage caused to any person or property (including under contract, by negligence, products liability or otherwise) whether they be direct or indirect, special, incidental or consequential, resulting from the application of the information in this publication.



**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) <sup>[140]</sup> <sup>[11]</sup>	CV events	Antiplatelet treatment v placebo/no antiplatelet treatment	4	0	0	0	0	High	
7 (15,527) <sup>[14]</sup>	CV events	Any treatment to reduce blood pressure v placebo/no treatment	4	0	0	0	0	High	
7 (15,527) <sup>[14]</sup>	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) <sup>[14]</sup>	CV events	ACE inhibitors v placebo	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (6216) <sup>[14]</sup>	CV events	Diuretics v placebo/no treatment	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (3544) <sup>[14]</sup>	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) <sup>[14]</sup>	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) <sup>[16]</sup>	CV events	Angiotensin receptor blockers v placebo	4	0	0	-1	0	Moderate	Directness point deducted for composite outcome
1 (20,332) <sup>[16]</sup>	Mortality	Angiotensin receptor blockers versus placebo	4	0	0	-1	0	Moderate	Directness point deducted for composite outcome
47 (at least 121,285) <sup>[26]</sup> <sup>[29]</sup> <sup>[27]</sup> <sup>[28]</sup>	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) <sup>[29]</sup> <sup>[27]</sup>	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) <sup>[4]</sup> <sup>[31]</sup> <sup>[32]</sup>	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) <sup>[30]</sup>	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) <sup>[7]</sup> <sup>[38]</sup> <sup>[39]</sup>	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) <sup>[40]</sup>	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) <sup>[41]</sup>	CV events	Clopidogrel plus aspirin v clopidogrel alone	4	0	0	0	0	High	
6 (7648) <sup>[42]</sup>	CV events	Dipyridamole plus aspirin v aspirin alone	4	0	0	-1	0	Moderate	Directness point deducted for composite outcome
1 (20,332) <sup>[43]</sup>	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) <sup>[140] [44] [45]</sup>	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) <sup>[56] [57]</sup>	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) <sup>[56]</sup>	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) <sup>[140] [58]</sup>	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) <sup>[63]</sup>	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) <sup>[63]</sup>	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 <sup>[63]</sup>	Adverse effects	Anticoagulants v placebo/no treatment	4	0	0	0	+1	High	Effect-size point added for RR greater than 2	
4 (2760) <sup>[64] [65]</sup>	CV events	Anticoagulation v antiplatelet treatment	4	0	0	-1	0	Moderate	Directness point deducted for composite outcome	
1 (1068) <sup>[65]</sup>	Mortality	Anticoagulation v antiplatelet treatment	4	0	0	-1	0	Moderate	Directness point deducted for composite outcome	
14 (at least 22,400) <sup>[67] [68] [69]</sup>	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) <sup>[67] [69]</sup>	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) <sup>[70]</sup>	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) <sup>[71] [72]</sup>	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) <sup>[71]</sup>	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) <sup>[71]</sup> <sup>[72]</sup>	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) <sup>[71]</sup> <sup>[72]</sup>	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) <sup>[71]</sup> <sup>[73]</sup> <sup>[74]</sup> <sup>[75]</sup> <sup>[76]</sup>	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) <sup>[88]</sup>	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) <sup>[92]</sup> <sup>[93]</sup>	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) <sup>[93]</sup>	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) <sup>[92]</sup> <sup>[93]</sup>	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) <sup>[95]</sup> <sup>[94]</sup>	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) <sup>[95]</sup> <sup>[94]</sup>	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) <sup>[98]</sup> <sup>[99]</sup> <sup>[100]</sup>	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) <sup>[98]</sup> <sup>[99]</sup> <sup>[100]</sup>	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) <sup>[105]</sup>	CV events	Adjusted-dose warfarin v placebo	4	0	0	0	0	High		
1 (115) <sup>[107]</sup>	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) <sup>[106]</sup> <sup>[109]</sup>	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) <sup>[110]</sup> <sup>[111]</sup>	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) <sup>[117]</sup>	CV events	Aspirin v placebo	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (782) <sup>[117]</sup>	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) <sup>[106]</sup>	CV events	Adjusted-dose warfarin v placebo	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (1044) <sup>[121]</sup>	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) <sup>[120]</sup> <sup>[122]</sup>	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) <sup>[106]</sup> <sup>[120]</sup> <sup>[123]</sup>	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) <sup>[109]</sup>	CV events	Adjusted-dose warfarin v other antiplatelet treatments/combinations	4	0	0	0	0	High	
3 (1266) <sup>[124]</sup> <sup>[125]</sup>	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 <sup>[112]</sup>	CV events	Adjusted-dose warfarin v other anticoagulants	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 SR <sup>[112]</sup>	Mortality	Adjusted-dose warfarin v other anticoagulants	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (1965) <sup>[138]</sup>	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) <sup>[138]</sup>	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) <sup>[113]</sup>	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) <sup>[141]</sup>	CV events	Minidose warfarin plus aspirin v no anti-coagulation	4	0	0	-1	0	Moderate	Directness point deducted for inclusion of other risk groups
At least 3 RCTs (at least 1965 people) <sup>[142] [106] [143]</sup>	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