National Clinical Guideline Centre

Atrial Fibrillation

Management of atrial fibrillation

Update guideline

Appendices A - R

June 2014

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians

The Royal College of Surgeons of England

RCGP Royal College of General Practitioners

Royal College of Nursing

NICE accredited

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Contents

This guideline has been partially updated. Please refer to the Full guideline to check which sections have been updated.

Appendices

Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Atrial fibrillation: the management of atrial fibrillation

1.1 Short title

Atrial fibrillation

2 The remit

This is a partial update of 'Atrial fibrillation' (NICE clinical guideline 36). See section 4.3.1 for details of which sections will be updated. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

This update is being undertaken as part of the guideline review cycle.

3 Clinical need for the guideline

3.1 Epidemiology

a) Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia; it affects about 1.3% of the population in England and Wales. Men are more commonly affected than women and the prevalence of AF increases with age.

b) Early recognition of AF can be difficult. The sometimes 'silent' nature of the arrhythmia means that AF may remain undiagnosed for a long time, and about one third of people with AF are not aware of the rhythm disturbance. Many people with AF may never present to hospital, which may cause an underestimation of the prevalence of AF.

c) AF can lead to complications such as heart failure and stroke. The risk of stroke in people with AF is five times higher than in a person with a normal heart rhythm.

d) People with AF have an increased rate of hospitalisations compared with people without AF; AF accounts directly for about 130,000 finished consultant episodes per year in England.

e) AF is associated with an increased risk of mortality. The mortality rate for people with AF is double that for people without AF, independent of other known predictors of mortality.

f) Several conditions are associated with an increased risk of developing AF. These include hypertension, valvular heart diseases, diabetes mellitus, heart failure and chronic or acute alcohol use.

3.2 Current practice

a) The aim of treatment for AF is to prevent complications, in particular stroke, and to alleviate symptoms.

b) AF is confirmed by an electrocardiogram (ECG), and an echocardiogram may also be performed.

c) Drug treatments for AF include anticoagulants to reduce the risk of stroke, and antiarrhythmics to restore or maintain the normal heart rhythm or to slow the heart rate in patients who remain in AF.

d) Non-pharmacological management of AF includes:

- electrical cardioversion, which may be used to 'shock' the heart back to its normal rhythm
- catheter or surgical ablation to create lesions to stop the abnormal electrical impulses that cause AF.

e) People with AF receive anticoagulation prophylaxis to reduce the risk of clot formation, because of their increased risk of stroke. Until

recently this has been with traditional anticoagulants such as warfarin or heparin. However, newer antithrombotic agents are now being used as alternatives to warfarin for treating people with non-valvular AF.

f) Current good practice in the care of people with AF includes the regular review of stroke and bleeding risk, together with assessment of the efficacy of anticoagulant therapy and the adequacy of symptom control.

g) An update of the guideline is needed because there is:

- new evidence available for several clinical areas, including stroke and bleeding risk stratification, the role of new antithrombotic agents and ablation strategies
- variation in practice as to when it is appropriate to offer cardioversion, and whether electrical or pharmacological cardioversion should be used, and which first-line treatments should be used for rate control in AF.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 years or older) with AF, including:

- new-onset or acute AF

- chronic AF, including paroxysmal (recurrent), persistent and permanent
- post-operative AF
- atrial flutter

b) Specific consideration will be given to the needs of:

- older people
- people with left ventricular dysfunction
- people with reversible causes of AF.

4.1.2 Groups that will not be covered

a) People under 18 years.

b) People with congenital heart disease precipitating AF.

4.2 Healthcare setting

a) All settings where NHS healthcare is provided or commissioned.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

Areas that were not in the original guideline that will be included in the update are denoted by an asterisk (*).

a) Risk stratification for:

- stroke or thromboembolic events
- bleeding.

b) Prevention of stroke using:

- antithrombotic therapy
- left atrial appendage occlusion*.

c) Treatment of AF with:

- rhythm-control strategies using:
  - pharmacological management
  - cardioversion (electrical and pharmacological)
  - atrial ablation, including criteria for referral, and catheter and surgical ablation strategies (as stand-alone or concomitant treatment) that are routinely use in clinical practice (this guideline will cross-refer to the relevant NICE interventional procedures guidance)*.
- Rate-control strategies using:
  - pharmacological management
  - 'ablate and pace' strategies*.

d) Referral of people with AF to specialist care.

e) Review and monitoring of*:

- symptoms of AF
- rhythm control and management
- indications for anticoagulation and bleeding risk
- quality of control of anticoagulation, including time in therapeutic range.

f) Patient information and support specific to AF*.

Note that guideline recommendations about use of drugs will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

4.3.2 Clinical issues that will not be covered

Areas from the original guideline that will not be updated

a) Identification and diagnosis of AF (the 2006 recommendations will be incorporated into the updated guideline).

b) Self-monitoring or self-management of anticoagulation (this guideline will cross-refer to Venous thromboembolic disease: the management of venous thromboembolic disease and the role of thrombophilia testing [NICE clinical guideline 144]).

Areas not covered by the original guideline or the update

a) Treatment of comorbidities associated with AF.

4.4 Main outcomes

a) Health-related quality of life.

b) Mortality.

c) Stroke or thromboembolic complications.

d) Major bleeding.

e) Hospitalisation with a primary diagnosis of AF.

f) Patients developing heart failure.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in July 2012.

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

This guideline will update and replace the following NICE guidance:

- Atrial fibrillation. NICE clinical guideline 36 (2006).

5.1.2 Other related NICE guidance

- Venous thromboembolic disease. NICE clinical guideline 144 (2012).
- Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. NICE technology appraisal guidance 256 (2012).
- Percutaneous balloon cryoblation for pulmonary vein isolation in atrial fibrillation. NICE interventional procedure guidance 427 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Dabigatran etexilate for the prevention of stroke and systemic embolism atrial fibrillation. NICE technology appraisal guidance 249 (2012).
- Hypertension. NICE clinical guideline 127 (2011).
- Thoracoscopic exclusion of the left atrial appendage in atrial fibrillation (with or without other cardiac surgery) for the prevention of thromboembolism. NICE interventional procedure guidance 400 (2011).
- Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation. NICE interventional procedure guidance 399 (2011).
- Chronic heart failure. NICE clinical guideline 108 (2010)

- Alcohol-use disorders. NICE clinical guideline 100 (2010).
- Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. NICE interventional procedure guidance 349 (2010).
- Dronedarone for the treatment of non-permanent atrial fibrillation. NICE technology appraisal guidance 197 (2010).
- Percutaneous (non-thoracscopic) epicardial catheter radiofrequency ablation for atrial fibrillation. NICE interventional procedure guidance 294 (2009).
- Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation. NICE interventional procedure guidance 286 (2009).
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. NICE technology appraisal guidance 170 (2009).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Type 2 diabetes - newer agents. Nice clinical guideline 87 (2009).
- Type 2 diabetes. NICE clinical guideline 66 (2008).
- Stroke. NICE clinical guideline 68 (2008).
- High intensity focused ultrasound ablation of atrial tissue for atrial fibrillation as an associated procedure with other cardiac surgery. NICE interventional procedure guidance 184 (2006).
- Percutaneous radiofrequency catheter ablation for atrial fibrillation. NICE interventional procedure guidance 168 (2006).
- Cryoablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 123 (2005).
- Microwave ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 122 (2005).
- Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 121 (2005).
- Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. NICE technology appraisal guidance 52 (2002).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- WatchBP Home A for diagnosing and monitoring hypertension and detecting atrial fibrillation. NICE medical technologies guidance. Publication expected August 2012.
- MI: secondary prevention (update). NICE technology appraisal guidance. Publication expected February 2013.
- Stroke and systemic embolism (prevention, non-valvular atrial fibrillation) - apixaban. NICE technology appraisal guidance. Publication expected April 2013.
- Physical activity advice in primary care. NICE public health guidance. Publication expected May 2013.
- Stroke rehabilitation. NICE clinical guideline. Publication expected June 2013.
- Myocardial infarction with ST-segment-elevation. NICE clinical guideline. Publication expected July 2013.
- Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120). NICE technology appraisal guidance. Publication expected September 2013.
- Type 1 Diabetes (update). NICE clinical guideline. Publication expected July 2014.
- Type 2 diabetes. NICE clinical guideline. Publication date to be confirmed.
- Venous thromboembolism (prevention) - rivaroxaban. NICE technology appraisal guidance. Publication date to be confirmed.
- Acute heart failure. NICE clinical guideline. Publication date to be confirmed.
- Atrial fibrillation - idraparinux sodium. NICE technology appraisal guidance. Appraisal suspended.

- Vernakalant for the treatment of rapid conversion of recent onset atrial fibrillation = 7 days. NICE technology appraisal guidance. Appraisal suspended.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'.

Information on the progress of the guideline will also be available from the NICE website.

Appendix B: Declarations of interest

B.1 Introduction

All members of the GDG, expert co-optees and all members of the NCGC staff were required to make formal declarations of interest at the outset of each meeting, and these were updated at every subsequent meeting throughout the development process.

B.2 Campbell Cowan

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Personal pecuniary interest: I participated in a meeting organised by Boehringer-Ingelheim in January 2012 to present the GRASP-AF data. I declined an honorarium for my participation, but my standard class rail fare to attend the meeting was reimbursed by Boehringer-Ingleheim. Personal family interest: None. Non-personal pecuniary interest: Sponsorship of departmental and MDT meetings by various pharmaceutical companies to provide hospitality. I have no direct relations in the organisation of these meetings. A research fellow in the electrophysiology Department in Leeds General Infirmary is partially funded from a research project undertaken in conjunction with St Jude Medical. The fellow does not work directly with me and I do not have managerial responsibility for electrophysiology services in the infirmary. Personal non-pecuniary interest: I am the national clinical lead for Atrial Fibrillation (AF) for NHS Improvement. Our work has involved extensive campaigning to improve the uptake of anti-coagulation in patients with AF in accordance with NICE guidelines. I am on the Medical Advisory Committees of two patient organisations, Arrhythmia Alliance and Atrial Fibrillation Association.	None.
Second GDG Meeting 12 September 2012	No change.	None.
Third GDG meeting 24 October 2012	No change.	None.
Fourth GDG meeting 5 December 2012	No change.	None.
Fifth GDG meeting 20 February 2013	Personal non-pecuniary interest; published the following paper in Heart: The use of anticoagulants in the management of atrial fibrillation among general practices in England.[242]	None.
Sixth GDG meeting 18 April 2013	No change.	None.
Seventh GDG meeting 6 June 2013	No change.	None.

GDG meeting	Declaration of Interests	Action taken
Eighth GDG meeting 18 July 2013	No change.	None.
Ninth GDG meeting 10 September 2013	No change.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	No change.	None.
Twelfth GDG meeting 11 March 2014	Personal non-pecuniary interest; speaker at the society of cardiothoracic surgeons annual meeting in Edinburgh (hotel room and rail travel paid for)	None.

B.3 John Campbell

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Did not attend.	None.
Second GDG Meeting 12 September 2012	Personal pecuniary interest: honoraria from BMS prior to 2007 for fees from education. I received funding for travel and conference fees from Sanofi Aventis and Boehringer-Ingelheim, but not within the last 12 months. I received education sponsorship from British Heart Foundation for an induction course in August 2012.	None.
Third GDG meeting 24 October 2012	No change.	None.
Fourth GDG meeting 5 December 2012	Personal non-pecuniary interest; attended educational session that was supported by Boehringer-Ingelheim. No financial support requested.	None.
Fifth GDG meeting 20 February 2013	Personal non-pecuniary interest; support to attend educational half day from Lilly. Hospitality from Lunchtime education sessions from Lilly, Pfizer and Boehringer-Ingelheim.	None.
Sixth GDG meeting 18 April 2013	No change.	None.
Seventh GDG meeting 6 June 2013	Personal non-pecuniary interest; attended regional update meeting organised by Arrhythmia Alliance charity that were sponsored by a number of companies including Medtronic, Pfizer and Boehringer-Ingelheim.	None.
Eighth GDG meeting 18 July 2013	No change.	None.
Ninth GDG meeting 10 September 2013	No change.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting	No change.	None.

GDG meeting	Declaration of Interests	Action taken
23 October 2013		
Twelfth GDG meeting 11 March 2014	No change.	None.

B.4 V-Lin Cheong

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Did not attend.	None.
Second GDG Meeting 12 September 2012	Nothing to declare.	None.
Third GDG meeting 24 October 2012	Did not attend.	None.
Fourth GDG meeting 5 December 2012	No change.	None.
Fifth GDG meeting 20 February 2013	Did not attend.	None.
Sixth GDG meeting 18 April 2013	No change.	None.
Seventh GDG meeting 6 June 2013	Did not attend.	None.
Eighth GDG meeting 18 July 2013	No change.	None.
Ninth GDG meeting 10 September 2013	No change.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	Did not attend	None.
Twelfth GDG meeting 11 March 2014	Personal pecuniary interest: received honoraria from Takeda UK Ltd for consulting on a consensus study on pharmaceutical rebate scheme	None

B.5 George Chung

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Nothing to declare.	None.
Second GDG Meeting 12 September 2012	No change.	None.

GDG meeting	Declaration of Interests	Action taken
Third GDG meeting 24 October 2012	Did not attend.	None.
Fourth GDG meeting 5 December 2012	Did not attend.	None.
Fifth GDG meeting 20 February 2013	No change.	None.
Sixth GDG meeting 18 April 2013	No change.	None.
Seventh GDG meeting 6 June 2013	No change.	None.
Eighth GDG meeting 18 July 2013	Did not attend.	None.
Ninth GDG meeting 10 September 2013	No change.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	Did not attend.	None.
Twelfth GDG meeting 11 March 2014	Did not attend.	None.

B.6 Matthew Fay

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Non-personal pecuniary interest: Have received honoraria from Abbott, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Pfizer, and Sanofi-Aventis within the last 12 months. These payments are not personally acquired but are paid to the Westcliffe Medical Practice partnership of which I am a partner. Attended following meetings: 1st July 2011 Bradford 7th July 2011 Hallam Stroke Meeting 7th July 2011 Education4health 7th July 2011 APPG on Anticoagulation 12th July 2011 Birmingham (AF course) 29th August to 2nd September European Cardiac Society funded by Bayer 8th September 2011 Bristol (Avon, Gloucestershire, Wiltshire CVD network (2 presentation) 9th September 2011 Bristol 16th September NHS-Improvement London 20th September 2011 Huddersfield 22nd September 2011 Uxbridge (BMS) 29th September 2011 Bradford 1st October 2011 Leeds 2nd October 2011 Birmingham (Heart Rhythm Congress	None.

GDG meeting	Declaration of Interests	Action taken
	Patient Day-STARS) 2nd October 2011 Birmingham (Heart Rhythm Congress Patient Day-AFA) 3rd October 2011 Birmingham (NHS-I at HRC) 3rd October 2011 Birmingham (Sanofi Aventis at HRC) 3rd October 2011 Birmingham (STARS scientific at HRC) 10th October 2011 Bolton for Greater Manchester and Cheshire CVN 11th October 2011 Windermere (DAWN 4S) 13th October 2011 Keighley 3rd November 2011 Telford (CVD Network) 9th November 2011 SPAF Academy Faculty Meeting (SPAF Academy is funded by BI) 16th November 2011 Uxbridge (BMS) 26th November 2011 Gerard's Cross (Daiichi Sankyo) 29th November 2011 Glasgow (NHS-I at the National Stroke Forum) 30th November 2011 Glasgow (BI symposium at the National Stroke Forum) 7th December 2011 Shipley (this was a local thing but presented the Einstein paper re Rivaroxaban in DVT) 9th December 2011 Leeds (Hepatology network) 15th December 2011 Ad Board Pfizer 20th December 2011 Ad Board Abbott 17th January 2012 Shipley 18th January 2012 BI Ad Board 20th January 2012 Birmingham (Bayer) 23rd-25th January 2012 Minneapolis (Medtronic Advisory Event) 2nd February 2012 Accrington CSNLC network 9th February 2012 York (RCGP) 9th February 2012 York (BMS/Pfizer) 15th March 2012 London SPAF Academy (2 presentation and launch of the Stop Start Campaign) 23rd March 2012 Ad Board with Pfizer 30th March 2012 Ad Board with BI 5th April 2012 London NHS-I 19th April 2012 Shipley 20th April 2012 Birmingham (AF course) 24th April 2012 London (BMJ Masterclass) 26th April 2012 Harrogate (Dermatology Specialist Group, this was about primary prevention but I do not know who sponsored the overall conference) 4th May 2012 Birmingham (Roche consensus meeting) 17th May 2012 Birmingham (Anticoagulation in Practice) 22nd May 2012 London (APPG on CVD Outcomes at the invitation of National Stroke Association) 31st May 2012 London DoH CVD Outcomes Strategy meeting 14th June 2012 Wakefield 26th June 2012 London (Hallam AF Meeting) 28th June 2012 London (The Commissioning Show at the invitation of Roche) 10th July 2012 Colchester (East of England Cardiovascular Network) 11th July 2012 Bradford (Medicine Management Group)	

GDG meeting	Declaration of Interests	Action taken
Second GDG meeting 12 September 2012	No change.	None.
Third GDG meeting 24 October 2012	Personal pecuniary interest; was taken for a meal with Sanofi-Aventis. Non-personal pecuniary interest; series of workshops on 'stop start campaign' which is part of stroke prevention in atrial fibrillation (SPAF) Academy, which is funded through Boehringer-Ingelheim and paid to the practice. Personal pecuniary interest; involvement with the development of a national patient decision aid with the BMJ. I continue to work with the AF Association for which I am not paid.	None.
Fourth GDG meeting 5 December 2012	Non-personal pecuniary interest; Presentation on anticoagulation in atrial fibrillation on 17 November 2012 that was funded by Bayer and Westcliffe Medical Practice was funded for the time. Presentation to closed Pfizer meeting on 21st November that was funded by Pfizer and Westcliffe Medical Practice was funded for the time. Personal non-pecuniary interest; Attended ACSMA (improving access to anticoagulation self-monitoring) meeting. Attended PCCJ (Primary Care Cardiology Journal) meeting (largely funded by industry but not funded personally). Attended GRASP-AF launch at House of Commons on 24th October 2012.	None.
Fifth GDG meeting 20 February 2013	Was not present at this item but made the following declaration later by email. Personal non-pecuniary interest; I am involved in the NICE Implementation Collaborative for Novel Anticoagulants. I have presented at a meeting sponsored by Bayer on 'What the guidelines say and how well are we doing'. I attended a parliamentary reception at the invitation of ASCMA.	None.
Sixth GDG meeting 18 April 2013	Non-personal pecuniary interest; I have presented at the SPAF Academy national meeting, the SPAF Academy is supported by Boehringer-Ingelheim and my role has been previously declared 21st March 2013. I have presented at the BMJ Masterclass regarding AF and stroke, the practice was reimbursed for my time (16th April 2013). I have presented to an in-house Pfizer training event, the practice was reimbursed for my time (16th April 2013). Personal non-pecuniary interest; I have lead the development of a thrombosis pathway in my role as a GP Executive of Bradford Districts CCG which utilises Rivaroxaban as an oral anticoagulant. This pathway is an implementation in full of NICE Guideline 144 regarding the diagnosis and treatment of DVT. I have met with MyDiagnostix and Prof Mant about the possibility of an AF screening study, this in the very early stages.	None.
Seventh GDG meeting 6 June 2013	Non-personal pecuniary interest; Presentation at NIMAST (Northern Ireland) stroke group on AF (Logistics funded by NIMAST). AF presentation at Hallam AF conference supported by MA healthcare (logistics funded by MA Health care). NICE Commissioning Guideline on anticoagulation (logistics funded by National Anticoagulation Training Centre).	None.

GDG meeting	Declaration of Interests	Action taken
Eighth GDG meeting 18 July 2013	Non-personal pecuniary interest; meeting in Southampton (Neqas) and London (Impact – Bayer) with logistics and honaria paid by Bayer. Presentation at the commissioning show on AF supported by Inrstar and Roche. Personal non-pecuniary interest; appointed to the NICE Quality Standards Committee as GP representative working with Oberoi consulting with and LUSD project. They are also discussion an AF project.	None.
Ninth GDG meeting 10 September 2013	MF declared a non-personal pecuniary interest: undertook an AF clinic with Apodi for which Westcliffe Medical Partnership was paid for his time (July). Personal non-pecuniary interest: appointed as a medical advisor to Anticoagulation Europe (August). Been supporting the National Stroke Association Aphasia campaign, with piece written for the GP newspapers. Written a piece for Pulse Magazine on HAS-BLED for which I was not paid.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	Did not attend.	None.
Twelfth GDG meeting 11 March 2014	Non-personal pecuniary interest: GP practice received an honorarium from Bayer for speaking at a meeting (February). Personal non-pecuniary interest: appointed clinical lead for NICE implementation collaborative for Yorkshire and Humber around AF and stroke.	None.

B.7 David Fitzmaurice

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Personal pecuniary interest: I have received honoraria from various companies which may have an interest in this report, including Roche diagnostics, Leo Laboratories, Boehringer-Ingelheim and Pfizer. 26-28 August 2011 attendance at European Society of Cardiology, funded by Boehringer-Ingelheim. 7 September 2011 GP meeting, honorarium from Boehringer-Ingelheim. 8 September 2011 two GP meetings, honoraria from Boehringer-Ingelheim. 15 September 2011 GP meeting, honorarium from Boehringer-Ingelheim. 5 December 2011 B-I advisory board regarding Dabigatran. 19 March 2012 Advisory board for Pfizer regarding Apixaban. 28 May 2012 Advisory board for Pfizer regarding Apixaban. Non-personal pecuniary interest: The Department of Primary Care, University of Birmingham, have received educational grants from B-I and Roche Diagnostics UK over the last 12 months. Personal non-pecuniary interest: Medical advisor to Anticoagulation Europe (ACE). Chair of Anticoagulation in	None.

GDG meeting	Declaration of Interests	Action taken
	Practice (AiP)	
Second GDG Meeting 12 September 2012	Did not attend.	None.
Third GDG meeting 24 October 2012	Personal pecuniary interest; Attendance at ESC from 25-28 August 2012 that was funded by Boehringer-Ingelheim. Presentation at symposium on 15th September 2012 that was funded by Bayer and travel and accommodation paid. Attendance at SAPC/RCOP meeting at Glasgow on 2-5 October 2012. Attendance at Garfield TSC – London on 11-12 October. Attendance at NIHR HTA Commissioning board – London 16-17 October.	None.
Fourth GDG meeting 5 December 2012	Personal non-pecuniary interest; attended GRASP-AF launch at House of Commons on 24th October 2012. Spoke at PCCJ (Primary Care Cardiovascular Journal) conference on 16 October 2012.	None.
Fifth GDG meeting 20 February 2013	No change.	None.
Sixth GDG meeting 18 April 2013	No change.	None.
Seventh GDG meeting 6 June 2013	No change.	Declare and withdrew from discussion and drafting of recommendations relating to antithrombotic therapy.
Eighth GDG meeting 18 July 2013	No change.	None.
Ninth GDG meeting 10 September 2013	No change. Previous personal pecuniary interests have expired.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	Non-personal pecuniary interest; chairman at four educational meetings on AF organised by Omnia-Med. I received a fee for this which was passed onto the university minus expenses (12, 18, 25 and 26 September 2013).	None.
Twelfth GDG meeting 11 March 2014	Did not attend.	None.

B.8 Stephen Hunter (co-opted expert)

GDG meeting	Declaration of Interests	Action taken
Third GDG meeting 24 October 2012	Personal pecuniary interest; I provide consultancy work to Atricure and I am a proctor for their training programme. Atricure make ablation devises for the treatment of atrial fibrillation and a devise for closing the left atrial appendage. I provide educational/consultancy (proctoring) to St Jude Medical and Edwards Lifesciences. Personal family interest; None. Non-personal pecuniary interest; None Personal non-pecuniary interest; I have a clinical interest in the surgical treatment of atrial fibrillation and consequently I have an international reputation. I am frequently invited to international meetings to talk on this subject.	None. As a co-opted expert SH did not take part in formulation of the recommendations.

B.9 Gregory Lip

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Personal pecuniary interest: I have served as a consultant : Sept 2011 – Boehringer-Ingelheim satellite, Venice Arrhythmia. Oct 2011 – Bayer satellite, Eurothrombosis meeting. Jan 2012 – Boehringer-Ingelheim CME meeting, Belfast. March 2012 – Chaired advisory board for BMS/Pfizer. March 2012 – Chaired advisory board for Daiichi-Sankyo. April 2012 – Boehringer-Ingelheim satellite at World Congress of Cardiology, Dubai. May 2012 – Advisory board for Roche May 2012 – Boehringer-Ingelheim lecture, British Cardiac Society. June 2012 – Chaired advisory board for BMS/Pfizer. July 2012 – Advisory board for Roche. July 2012 – Boehringer-Ingelheim symposium at South Africa Heart meeting. I have lectured in CPD/CME-accredited educational symposia for Bayer, BMS/Pfizer Boehringer-Ingelheim and Sanofi Aventis (Sanofi Aventis was over 12 months ago). Lectures were mostly on AF management, AF in general or stroke prevention were only given in CME/CPD accredited programmes and used own slides. Non-personal pecuniary interest: My department has received unrestricted non-promotional educational grants for research from Bayer and Boehringer-Ingelheim.	None.
Second GDG Meeting 12 September 2012	Did not attend.	None.
Third GDG meeting 24 October 2012	Did not attend.	None.
Fourth GDG	Personal pecuniary interest;	None.

GDG meeting	Declaration of Interests	Action taken
meeting 5 December 2012	• Boehringer-Ingelheim satellite symposium at ESC meeting (August 2012), • chaired advisory board for Daiichi-Sankyo at ESC Munich (August 2012), • Boehringer-Ingelheim satellite symposium at Asia-Pacific Heart Rhythm Society, Taipei (September 2012) • Chaired advisory board for Daiichi-Sankyo (November 2012).	
Fifth GDG meeting 20 February 2013	No change.	None.
Sixth GDG meeting 18 April 2013	No change.	None.
Seventh GDG meeting 6 June 2013	No change.	Declared and withdrew from discussion and drafting of recommendations relating to antithrombotic therapy.
Eighth GDG meeting 18 July 2013	No change.	Declared and withdrew from discussion and drafting of recommendations relating to bleeding risk scores.
Ninth GDG meeting 10 September 2013	No change.	Declared and withdrew from discussion and drafting of recommendations relating to stroke risk scores.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	No change.	Declared and withdrew from discussion and drafting of recommendations relating to antithrombotic therapy and stroke risk tools.
Twelfth GDG meeting 11 March 2014	No change.	None.

B.10 Clifford Mann

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Nothing to declare.	None.
Second GDG	No change.	None.

GDG meeting	Declaration of Interests	Action taken
Meeting 12 September 2012		
Third GDG meeting 24 October 2012	No change.	None.
Fourth GDG meeting 5 December 2012	No change.	None.
Sixth GDG meeting 18 April 2013	Non personal pecuniary interest; flight and hotel to Lyon to attend European Trauma conference from Boehringer-Ingelheim in May 2013. Flight and hotel to Turin to given presentation on UK ED 4 hour target from Angelini in April 2013. No fee and reasonable expenses only.	None.
Seventh GDG meeting	Personal non-pecuniary interest; Attended the 14th European Congress of Trauma and Emergency Surgery in Lyon, France. Flight and hotel and conference registration paid for by Boehringer-Ingelheim.	None.
Eighth GDG meeting 18 July 2013	No change.	None.
Ninth GDG meeting 10 September 2013	No change.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	Non-personal pecuniary interest; payment from Boehringer-Ingelheim into departmental charity fund of which I am not a signatory.	None.
Twelfth GDG meeting 11 March 2014	No change.	None.

B.11 Nick Mills

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Nothing to declare.	None.
Second GDG Meeting 12 September 2012	No change.	None.
Third GDG meeting 24 October 2012	No change.	None.
Fourth GDG meeting 5 December 2012	No change.	None.
Fifth GDG meeting 20 February 2013	No change.	None.
Sixth GDG meeting 18 April 2013	Did not attend.	None.

GDG meeting	Declaration of Interests	Action taken
Seventh GDG meeting 6 June 2013	No change.	None.
Eight GDG meeting 18 July 2013	Did not attend.	None.
Ninth GDG meeting 10 September 2013	Did not attend.	None.
Tenth GDG meeting 11 September 2013	Did not attend.	None.
Eleventh GDG meeting 23 October 2013	No change.	None.
Twelfth GDG meeting 11 March 2014	No change.	None.

B.12 Eileen Porter

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Personal non-pecuniary interest: All party parliamentary group on atrial fibrillation – submitted comments.	None.
Second GDG Meeting 12 September 2012	No change.	None.
Third GDG meeting 24 October 2012	No change.	None.
Fourth GDG meeting 5 December 2012	No change.	None.
Fifth GDG meeting 20 February 2013	Did not attend.	None.
Sixth GDG meeting 18 April 2013	Did not attend.	None.
Seventh GDG meeting 6 June 2013	No change.	None.
Eighth GDG meeting 18 July 2013	No change.	None.
Ninth GDG meeting 10 September 2013	No change.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	No change.	None.
Twelfth GDG meeting	No change.	None.

GDG meeting	Declaration of Interests	Action taken
11 March 2014		

B.13 Suzannah Power

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Not present.	None.
Second GDG Meeting 12 September 2012	Personal pecuniary interest; part-time role at Heathen Wood and Wrexham Park Hospitals NHS Foundation Trust in Market Intelligence/Patient Involvement. I sit on the research for Patient Benefit (South West) funding committee (honorary role). Personal family interest; family NHS members – no interests. Non-personal pecuniary interest; none. Personal non-pecuniary interest; I sit on the BHF council as Patient Representative.	None.
Third GDG meeting 24 October 2012	No change.	None.
Fourth GDG meeting 5 December 2012	No change.	None.
Fifth GDG meeting 20 February 2013	No change.	None.
Sixth GDG meeting 18 April 2013	No change.	None.
Seventh GDG meeting 6 June 2013	Not present at meeting.	None.
Eighth GDG meeting 18 July 2013	No change.	None.
Ninth GDG meeting 10 September 2013	No change.	None.
Tenth GDG meeting 11 September 2013	Did not attend	None.
Eleventh GDG meeting 23 October 2013	Did not attend	None.
Twelfth GDG meeting 11 March 2014	Did not attend.	None.

B.14 Peter Rose (co-opted expert)

GDG meeting	Declaration of Interests	Action taken
Tenth GDG meetings 11 September 2013	PR declared a personal pecuniary interest; advisory boards from Boehringer-Ingelheim, Roche, Daiichi, BSM	None. As a co-opted expert PR did not take part in formulation of the recommendations.

B.15 Rebekah Schiff

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Personal non-pecuniary interest: Royal Society of Medicine talk on Top Tips in Atrial Fibrillation – April 2012.	None.
Second GDG Meeting 12 September 2012	No change.	None.
Third GDG meeting 24 October 2012	No change.	None.
Fourth GDG meeting 5 December 2012	No change.	None.
Fifth GDG meeting 20 February 2013	No change.	None.
Sixth GDG meeting 18 April 2013	No change.	None.
Seventh GDG meeting 6 June 2013	No change.	None.
Eighth GDG meeting 18 July 2013	No change.	None.
Ninth GDG meeting 10 September 2013	Did not attend	None.
Tenth GDG meetings 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	No change.	None.
Twelfth GDG meeting 11 March 2014	No change.	None.

B.16 Richard Schilling

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Personal pecuniary interest: by date paid: 17 August 2011 honorarium from Touch Briefings for interview and article European Cardiology Vol. 6, 9 March 2010. 30 August 2011 honorarium from Biosense Webster for Israel trip from 17-19 July. 2 September 2011 honorarium from Hansen for providing experience on Hansen robot (12 July 2011). 23 September 2011 reimbursement of travel expenses for 29 august ESC2011 in Paris form Daiichi-Sankyo. 10 November 2011 honorarium from St Jude Medical for Euro Japan (19-21 September). 17 November 2011 honorarium from APHRS for Japan 19-	None.

GDG meeting	Declaration of Interests	Action taken
	21 September trip. 28 November 2011 honoraria from BMJ for MC304/RS 29 November 2011 expenses for BMJ from 7 November 2011 14 December 2011 expenses from Biosense Webster for Israel trip 17-19 July 2011. 19 December 2011 honoraria from Hansen for lecturing at flexible Robotics Institute 9th November 2012. 20 December 2011 from Medtronic for Heart Rhythm Congress honorarium. 23 December 2011 expenses and honorarium from Daiichi-Sankyo for advisory board meeting. 20 February 2012Remibursement flights to Australia for lecture tour 13-17 August 2012 from Conference Company of Australia (Australian cardiac society). 29 February 2012 honorarium from Pri-Med Educational Programmes LTD for advisory panel 26 January 2012. 5 March 2012 honorarium teaching basic EP course September for European heart Rhythm Alliance. 6 March 2012 honorarium for MCZ16/RS from BMJ. 28 March 2012 reimbursement travel expenses from 24 January 2012 from RCPE. 29 March 2012 honorarium from royal college of GPs for Annual Primary Care conference 4-6 October. 2 April 2012 reimbursement travel expenses for master class on 19 March 2012 for BMJ. 18 May 2012 speaker at 4th practical session AFIB symposium Prague 14 March 2012 from Biosense Webster. 5 July 2012 honorarium plus expenses for EE Smart touch Round table meeting on 16 May 2011 from Biosense Webster. 12 July 2012 speaker at HRS symposium Boston on 10 May 2012 for Non-personal pecuniary interest: My department currently receives the following research support: AF Robotic Navigation – Hansen medical, CABANA – Mayo clinic (grant provided by St Jude Medical, Biosense Webster and NHLBI/NIH), CFE (Research Fellow WU) – Biosense Webster, Cardiology Research coordinator – Medtronic, CASTLE-AF – Biotronik, CRYO vs. RFA – Medtronic, LIAISE – Medtronic, Prediction – Sorin Group, Research Fellow – Boston Scientific, Sponsored nurse – St Jude Medical, NOTICE-HF – Boston Scientific, PARADYM RF – Sorin Group, QUAD – St Jude Medical, PREFER AF – SSS International Clinical Research, Erase VT – Imperial College funded by Hansen medical. Personal non-pecuniary interest: In presentations I consistently state that there is strong evidence for catheter ablation being superior to drugs for controlling symptomatic AF. I also state that there is no evidence to date for prognostic benefit to ablation. I also have publically stated that the evidence for the superiority of newer anticoagulants over warfarin in the western European	

GDG meeting	Declaration of Interests	Action taken
	population is not strong.	
Second GDG Meeting 12 September 2012	Personal pecuniary interest; buffet lunch with Daichii Sankyo on 10 September 2012.	None.
Third GDG meeting 24 October 2012	Personal pecuniary interest; travel and accommodation to teach at EP course from European Society of Cardiology. Personal non-pecuniary interest; filmed video for patient information for atrial fibrillation ablation for Hansen medical.	None.
Fourth GDG meeting 5 December 2012	Did not attend.	None.
Fifth GDG meeting 20 February 2013	Non-personal pecuniary interest; 4000 euros paid for lectures at Rome meeting. Paid to charity form St Jude Medical.	None.
Sixth GDG meeting 18 April 2013	Non personal pecuniary interest; Flights and hotel all within healthcare compliance guidelines to meetings in Denver, Singapore and Italy over next 2 months. Companies are Biosense Webster, St. Jude, Hansen medical and Estech.	None.
Seventh GDG meeting 6 June 2013	Non-personal pecuniary interest; honorarium donated to research charity for teaching in Singapore and Bangkok. Personal non-pecuniary interest; paid for hotel and flights to teach in Singapore and Bangkok St Jude and Hansen Medical. Paid for hotel and flights to teach at the Heart Rhythm society in Denver by Biosense.	
Eighth GDG meeting 18 July 2013	Non-personal pecuniary interest; received payment for travel and substance from Biosense Webster to Athens for European meeting. Remainder donated to charity.	None.
Ninth GDG meeting 10 September 2013	RS declared a personal non-pecuniary interest; economy flight to European cardiac society AGM by Daiichi Sankyo.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	Personal non –pecuniary interest; travel expenses to conference paid by Biosense	None.
Twelfth GDG meeting 11 March 2014	Personal pecuniary interest: travel to Dubai to speak at meeting, which was funded by Gulf EP organisation. Non-personal pecuniary interest: research fellowship funding and charitable donations from Medtronic, Boston Scientific, Hansen, St. Jude Medical Inc., Biosense Webster.	None.

B.17 National Clinical Guideline Centre

GDG meeting	Declaration of Interests	Action taken
First GDG meeting 12 July 2012	Sara Buckner: Personal pecuniary interest: I undertake consultancy work for medical reviewing for Kent, Surrey and Sussex Health Policy Support Unity. In the past year I have undertaken reviews on: - melatonin for sleep regulation in children with behavioural disorders (Nov-Feb 2012) - removal of skin lesions (march 2012) - Insulin Deglundec for Type 1 and 2 Diabetes (March 2012-August 2012). Funded by NHS.	None.
Second GDG meeting 12 September 2012	Maggie Westby: Non-personal pecuniary interest; my time paid for to be a member of the Steering Group on an Medical Research Council project on economic modelling of patient pathways. AF was one of the pathways modelled. Funded by Medical Research Council.	None.
Third GDG meeting 24 October 2012	Clare Jones and Liz Avital: Personal non-pecuniary interest; attendance at the Cardiology update on 10 October 2012 in London.	None.
Fourth GDG meeting 5 December 2012	No change.	None.
Fifth GDG meeting 20 February 2013	No change.	None.
Sixth GDG meeting 18 April 2013	No change.	None.
Seventh GDG meeting 6 June 2013	No change.	None.
Eighth GDG meeting 18 July 2013	No change.	None.
Ninth GDG meeting 10 September 2013	Jill Parnham: Receive commissions from NICE on behalf of NCGC.	None.
Tenth GDG meeting 11 September 2013	No change.	None.
Eleventh GDG meeting 23 October 2013	No change.	None.
Twelfth GDG meeting 11 March 2014	No change.	None.

Appendix C: Review protocols

C.1 Clinical review protocols

C.1.1 Education

REVIEW DEFINITIONS	
Definition of the guideline condition	Abnormal heart beat that is irregular and sometimes fast
Major age category	Adults (18 years and above)
Purpose of review	Purpose of review not an inclusion criterion
Line of therapy	Line of therapy not an inclusion criterion
Minimum duration of study	Not defined
PICO INCLUSION/EXCLUSION CRITERIA	
Study design	Systematic Review
	RCT (including cluster RCTs)
Unit of randomisation	Patient
Crossover study	Permitted
Other inclusions	None
Other exclusions	None
Review population	People with AF
Interventions: generic/class; specific/drug	Education; Decision aids
	Education; CBT
	Education; Education (videos, literature, talking interventions)
	Usual care; Usual care
	Behavioural ; CBT
	Self-monitoring and education
	Decision aids
Comparison types	Intervention 1 vs intervention 2 (different class)
Outcomes	Health related quality of life at longest endpoint (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
	Hospitalisation at longest endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	TTR at longest endpoint (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
	Stroke and thromboembolic events at longest endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	% of INR in therapeutic range at longest endpoint (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
	Anxiety l (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
	Decision conflict l (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
	Knowledge and understanding at longest endpoint(Continuous; MID: Default

	0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
OTHER INCLUSION CRITERIA	
Allocation concealment	Not inclusion criterion
Sample size	Not inclusion criterion
ANALYSIS	
Population stratification	None
Reasons for stratification	None
Other stratifications	None
Sensitivity/other analysis	None
Subgroup analyses if there is heterogeneity	

C.1.2 Referral

REVIEW DEFINITIONS	
Major age category	Adults (18 and over)
Purpose of review	Purpose of review not an inclusion criterion
Line of therapy	Line of therapy not an inclusion criterion
Minimum duration of study	Not defined
PICO INCLUSION/EXCLUSION CRITERIA	
Study design	Systematic Review
	RCT
	Prospective cohort study
Unit of randomisation	Patient
Crossover study	Not permitted
Other inclusions	All people with AF
Other exclusions	None
Review population	All people with atrial fibrillation
Interventions: generic/class; specific/drug	Referral to specialist AF services; Primary
	Referral to specialist AF services; Secondary
	Referral to specialist AF services; Tertiary
	Referral to specialist AF services; Unknown
	Referral to specialist AF services; Specialist service
	Referral to specialist AF services; Nurse led care
	Routine management; Routine management - primary
	Routine management; Routine management - secondary
	Routine management; Routine management
Comparison types	Intervention vs usual care
	Intervention 1 vs intervention 2 (different class)
	Adherence to guidelines at latest follow-up (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Number of patients referred to anticoagulation clinic at latest follow-up (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Disease awareness at longest follow-up (Dichotomous; MID: Default 1.25 or

	0.75; Available case analysis, reasons: ACA is the NCGC default)
	Mortality at longest follow-up (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Stroke or thromboembolic complications at longest follow-up (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Health related quality of life at longest follow-up (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Rehospitalisation at longest follow-up (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
OTHER INCLUSION CRITERIA	
Allocation concealment	Not inclusion criterion
Sample size	Not inclusion criterion
ANALYSIS	
Population stratification	People with AF
	People with heart failure and AF
Other stratifications	None
Sensitivity/other analysis	None
Subgroup analyses if there is heterogeneity	

C.1.3 Stroke risk tools

REVIEW DEFINITIONS	
Definition of the guideline condition	Abnormal heart beat that is irregular and sometimes fast
Major age category	Adults (18 years and above)
Purpose of review	Purpose of review not an inclusion criterion
Line of therapy	Line of therapy not an inclusion criterion
Minimum duration of study	Not defined
PICO INCLUSION/EXCLUSION CRITERIA	
Study design	Cohort studies
Review population	People with AF Note prevalence Low and high risk groups
Interventions: generic/class; specific/drug	$CHADS_2$ ACCP and ACC/AHA/ESC schemes CHA_2DS_2-VASc
Comparison types	None
Outcomes (patient)	Stroke
	Thromboembolic events
	Mortality (stroke or thrombosis)
Outcomes (statistical)	Hazard ratio for high, moderate thresholds (from multivariable analyses – preferable but might not matter if risk scores include all risk factors)
	Sensitivity at particular thresholds
	Specificity at particular thresholds
	AUC (C indices)
	Calibration

	Net reclassification scores
OTHER INCLUSION CRITERIA	
Allocation concealment	Not inclusion criterion
Sample size	Not inclusion criterion
ANALYSIS	
Population stratification	None
Reasons for stratification	None
Other stratifications	None
Sensitivity/other analysis	None
Subgroup analyses if there is heterogeneity	

C.1.4 Anticoagulation

REVIEW DEFINITIONS	
Definition of the guideline condition	Includes paroxysmal, permanent and persistent atrial fibrillation. Detected by pulse and ECG.
Major age category	Adults (18 years or over)
Purpose of review	Purpose of review not an inclusion criterion
Line of therapy	Line of therapy not an inclusion criterion
Minimum duration of study	Not defined
PICO INCLUSION/EXCLUSION CRITERIA	
Study design	Systematic Review
	RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Other inclusions	None
Other exclusions	People with congenital heart disease precipitating AF, acute AF, rheumatic AF, non AF populations
	Haemodynamically unstable patients
Review population	People with paroxysmal, permanent or persistent atrial fibrillation.
Interventions: generic/class; specific/drug	Antiplatelets; Aspirin
	Antiplatelets; Clopidogrel
	Antiplatelets; Dipyridamole
	Antiplatelets; Dipyridamole with aspirin
	Antiplatelets; Prasugrel
	Antiplatelets; Ticagrelor
	Antiplatelets; Tirofiban
	Antiplatelets; Aspirin + Clopidogrel
	Antiplatelets; Aspirin + Prasugrel
	Antiplatelets; Aspirin + Ticagrelor
	Antiplatelets; Aspirin + Tirofiban
	Antiplatelets; Clopidogrel + Dipyridamole
	Antiplatelets; Clopidogrel + Prasugrel

	Antiplatelets; Clopidogrel + Ticagrelor
	Antiplatelets; Clopidogrel + Tirofiban
	Antiplatelets; Dipyridamole + Prasugrel
	Antiplatelets; Dipyridamole + Ticagrelor
	Antiplatelets; Dipyridamole + Tirofiban
	Antiplatelets; Prasugrel + Ticagrelor
	Antiplatelets; Prasugrel + Tirofiban
	Antiplatelets; Ticagrelor + Tirofiban
	Anticoagulants; Warfarin (Vitamin K Antagonists)
	Anticoagulants; Acenocoumarol and phenprocoumon (Vitamin K Antagonists)
	Anticoagulants; Phenindione (Vitamin K Antagonists)
	Anticoagulants; Rivaroxaban (Direct factor Xa inhibitors)
	Anticoagulants; Apixaban (Direct factor Xa inhibitors)
	Anticoagulants; Dabigatran (Direct thrombin inhibitors)
	Anticoagulants; Argatroban (Direct thrombin inhibitors)
	Anticoagulants; Combinations
	Anticoagulants and antiplatelets; Anticoagulants and antiplatelets
	Anticoagulants and dual antiplatelets; Anticoagulants and antiplatelets
	Control; Placebo
	Control; No treatment
	Control; Placebo or no treatment
Comparison types	Intervention 1 vs intervention 2 (different class)
Outcomes	Health related quality of life at latest endpoint (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
	Ischaemic stroke at a test endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	All cause mortality at a test endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Thromboembolic complications at a test endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Hospitalisation at a test endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Haemorrhagic stroke at a test endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Major bleeding at 30 days (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
OTHER INCLUSION CRITERIA	
Allocation concealment	Not inclusion criterion
Sample size	Not inclusion criterion
ANALYSIS	
Population stratification	None
Reasons for stratification	None
Other stratifications	None
Sensitivity/other analysis	Age over 80
	Risk stratification for stroke (high and low risk)
Subgroup analyses if there	Time in therapeutic range (INR)

is heterogeneity	Age of study (2000 and later; Before 2000); Improvements in trials with age

C.1.5 Bleeding risk

REVIEW DEFINITIONS	
Definition of the guideline condition	Includes paroxysmal, permanent and persistent atrial fibrillation. Detected by pulse and ECG.
Major age category	Adults (18 years or over)
Purpose of review	Purpose of review not an inclusion criterion
Line of therapy	Line of therapy not an inclusion criterion
Minimum duration of study	Not defined
PICO INCLUSION/EXCLUSION CRITERIA	
Study design	Cohort studies
Unit of randomisation	Patient
Crossover study	Permitted
Interventions: Risks tools (must be validated – in different	HAS-BLED $CHADS_2$ Atria $HEMMORR_2HAGES$ score
Outcomes (patient)	Final outcome of bleeds Major bleeds (including fatal and intracranial bleeding) Mortality from bleeding Health related quality of life
Outcomes (statistical)	Sensitivity Specificity Hazard ratios Calibration Net reclassification index AUC (C indices)
Study design	Cohort studies

C.1.6 Monitoring

REVIEW DEFINITIONS	
Definition of the guideline condition	Includes paroxysmal, permanent and persistent atrial fibrillation. Detected by pulse and ECG.
Major age category	Adults (18 years or over)
Purpose of review	Purpose of review not an inclusion criterion
Line of therapy	Line of therapy not an inclusion criterion
Minimum duration of study	Not defined
PICO INCLUSION/EXCLUSION CRITERIA	
Study design	RCTs Systematic reviews Prospective cohort study
Unit of randomisation	Patient
Crossover study	Permitted
Interventions:	Monitoring of (time point):

	a)Symptoms b) Rhythm/ rate control assessment and management c) Indications for and monitoring (regular review of therapeutic range) of anticoagulation
Comparison types	No regular monitoring or monitoring of any time point
Outcomes (patient)	Critical outcomes: Mortality Stroke or thromboembolic complications Health related quality of life Time in therapeutic range (INR) - for monitoring of anticoagulation question Secondary outcomes: Persistence of AF Adherence to national/ international guidelines Major bleeding Rehospitalisation with a primary diagnosis of AF Patients developing heart failure Patient adherence to guidelines
Notes	A meta-analysis will be conducted on RCTs with appropriate outcome data. Sub-group analysis by type of treatment.

C.1.7 Left atrial appendage occlusion

REVIEW DEFINITIONS	
Definition of the guideline condition	Abnormal heart beat that is irregular and sometimes fast
Major age category	Adults (18 years and above)
Purpose of review	Purpose of review not an inclusion criterion
Line of therapy	Line of therapy not an inclusion criterion
Minimum duration of study	Not defined
Comments	Prevention of stroke in people with AF
PICO INCLUSION/EXCLUSION CRITERIA	
Study design	Systematic Review
	RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Other inclusions	None
Other exclusions	Acute AF
Review population	People with AF and indication for anticoagulation
Interventions: generic/class; specific/drug	No treatment
	Placebo; Placebo when warfarin is contraindicated
	Left atrial appendage occlusion
	Antiplatelets; Aspirin
	Antiplatelets; Clopidogrel
	Antiplatelets; Dipyridamole
	Antiplatelets; Dipyridamole with aspirin

	Antiplatelets; Prasugrel
	Antiplatelets; Ticagrelor
	Antiplatelets; Tirofiban
	Antiplatelets; Combinations of above (dual)
	Anticoagulants; Warfarin
	Anticoagulants; Acenocoumarol
	Anticoagulants; Pheniodione
	Anticoagulants; Rivaroxaban
	Anticoagulants; Apixaban
	Anticoagulants; Dabigatran
	Anticoagulants; Argatroban
Comparison types	Intervention vs placebo
	Intervention 1 vs intervention 2 (different class)
Outcomes	Health related quality of life at longest endpoint (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
	Mortality - latest endpoint at Longest endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Ischaemic stroke at longest endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Haemorrhagic stroke at longest endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Major bleeding at Longest endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Hospitalisation at longest endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Procedural complications at longest endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Thromboembolic complications at longest endpoint (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
OTHER INCLUSION CRITERIA	
Allocation concealment	Not inclusion criterion
Sample size	Not inclusion criterion
ANALYSIS	
Population stratification	People who can take anticoagulants
	People who cannot take anticoagulants
Reasons for stratification	People who can't take anticoagulants will be compared to placebo whereas those that can will be compared to anticoagulants.
Other stratifications	None
Sensitivity/other analysis	None
Subgroup analyses if there is heterogeneity	

C.1.8 Rate versus rhythm control strategies

REVIEW DEFINITIONS	
Definition of the guideline condition	Includes paroxysmal, permanent and persistent atrial fibrillation. Detected by pulse and ECG.
Major age category	Adults (18 years or over)
Purpose of review	Purpose of review not an inclusion criterion
Line of therapy	Line of therapy not an inclusion criterion
Minimum duration of study	Not defined
PICO INCLUSION/EXCLUSION CRITERIA	
Study design	Systematic Review
	RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Other inclusions	None
Other exclusions	People with congenital heart disease precipitating AF
	Haemodynamically unstable patients
Review population	People with paroxysmal, permanent or persistent atrial fibrillation.
Interventions: generic/class; specific/drug	Rhythm control strategy:
	Cardioversion (electrical or pharmacological) and
	On-going drug treatment with: Flecainide Propafenone Amiodarone Sotalol Beta-blockers Dronedarone (for comparative purposes only) Calcium channel blockers (should not be used) Digoxin (off label) Vernakalent (for comparative purposes only) Magnesium Alone or in combination
	Insert pacemaker
Comparison	Rate control strategy (see rate protocol for list of drugs)
	Ablate and pace
Outcomes	Critical outcomes: Mortality Health related quality of life Stroke or thromboembolic complications
	Secondary outcomes: Major bleeding – all Re-hospitalisation with a primary diagnosis of AF Patients developing heart failure Restoration of sinus rhythm Recurrence of AF
OTHER INCLUSION CRITERIA	

Allocation concealment	Not inclusion criterion
Sample size	Not inclusion criterion
ANALYSIS	
Population stratification	Heart failure (impaired LV function) Reversible causes (see list in antiarrhythmic protocols)
Reasons for stratification	None
Sensitivity/other analysis	None
Subgroup analyses if there is heterogeneity	None

C.1.9 Rate control strategies

REVIEW DEFINITIONS	
Definition of the guideline condition	
Major age category	Adults (18 and over)
Purpose of review	Purpose of review not an inclusion criterion
Line of therapy	Line of therapy not an inclusion criterion
Minimum duration of study	Not defined
PICO INCLUSION/EXCLUSION CRITERIA	
Study design	Systematic Review
	RCT
Unit of randomisation	Patient
Crossover study	Not stated
Other inclusions	All people with AF
Other exclusions	Population – atrial flutter only
Review population	All people with atrial fibrillation
Interventions: generic/class; specific/drug	Rate control drugs
	Rate control drugs; Calcium limiting antagonists
	Rate control drugs; Beta blockers
	Rate control drugs; Digoxin
	Rate control drugs; Combined rate drugs
	Rate control drugs; Amiodarone
	Rate control drugs; No treatment
	Rate control drugs; Placebo
	Placebo; Placebo
	Placebo; No treatment
Comparison types	Intervention vs placebo
	Intervention 1 vs intervention 2 (different class)
	Mortality (long-term) at latest follow-up (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Rate control - heart rate (time or amount of people) at latest follow-up (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)

	Health relate quality of life (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
	stroke or thromboembolic complications at latest follow-up (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Left ventricular function - number of people/ejection fraction as % at latest follow-up (Continuous; MID: Default 0.5 SD; Available case analysis, reasons: ACA is the NCGC default)
	Time to response at time reported (Time to event; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
	Rate of discontinuation of drug due to side effects at time reported (Dichotomous; MID: Default 1.25 or 0.75; Available case analysis, reasons: ACA is the NCGC default)
OTHER INCLUSION CRITERIA	
Allocation concealment	Not inclusion criterion
Sample size	Not inclusion criterion
ANALYSIS	
Population stratification	People with AF
	People with heart failure and AF
	Paroxysmal AF
	Persistent/permanent AF
	Unstable with acute AF
Reasons for stratification	Heart failure is considered separately as population are more severely ill.
Other stratifications	None
Sensitivity/other analysis	None
Subgroup analyses if there is heterogeneity	None
Search	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.

C.1.10 Rhythm control strategies – restoration of sinus rhythm

Review question	**Review Protocol – What is the most clinical and cost effective means of (excluding ablation) restoring sinus rhythm (a) pharmacological cardioversion, (b) electrical cardioversion or (c) electrical cardioversion combined with antiarrhythmic drugs?**
Objectives	What is the most clinical and cost effective means of (excluding ablation) restoring sinus rhythm (a) pharmacological cardioversion, (b) electrical cardioversion or (c) electrical cardioversion combined with antiarrhythmic drugs?
Population	People with persistent AF undergoing cardioversion (pharmacological or electrical or electrical with drugs). This definition may differ from studies. Include all AF patients. Sub-groups to report separately: 1. Heart failure (impaired LV function) 2. Unstable with acute 3. reversible causes including: • Thyrotoxicosis • Infection e.g. pneumonia, sepsis

	• Trauma • Myocarditis • myocardial ischaemia/infarction • Pericarditis • Malignant hypertension • Pulmonary embolism • Acute alcohol intoxication • Mitral stenosis • Post cardiac surgery e.g. Aortic valve replacement
Intervention	Flecainide Propafenone Amiodarone Sotalol Beta-blockers (full list in rate question) Dronedarone (for comparative purposes only) Calcium channel blockers (should not be used) Digoxin (off label) Vernakalent (for comparative purposes only) Magnesium Alone or in combination Electrical cardioversion alone or in combination with anti-arrhythmic drug therapy
Comparison	No treatment Any intervention
Outcomes	Critical outcomes: Mortality (30 days and longest endpoint) Health-related quality of life Restoration of sinus rhythm/time to restoration for acute Secondary outcomes: Stroke or thromboembolic events Rehospitalisation with a primary diagnosis of AF Patients developing heart failure Maintenance of sinus rhythm/Recurrence of AF
Search	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied
Review strategy	RCTs Systematic reviews

C.1.11 Rhythm control strategies - maintenance of sinus rhythm

Review question	Review Protocol – What is the most clinical and cost effective antiarrhythmic drug alone or in combination for maintaining sinus rhythm in (a) paroxysmal AF and (b) persistent AF after cardioversion?
Population	People with paroxysmal AF Persistent AF after cardioversion Sub-group analysis: 1. Heart failure (impaired LV function) 2. Treated secondary causes/reversible causes including: • Thyrotoxicosis • Infection e.g. pneumonia, sepsis • Trauma • Myocarditis • myocardial ischaemia/infarction • Pericarditis • Malignant hypertension • Pulmonary embolism • Acute alcohol intoxication • Mitral stenosis • Post cardiac surgery e.g. Aortic valve replacement
Intervention	Flecainide Propafenone Amiodarone Sotalol Beta-blockers (full list in rate protocol) Dronedarone (for comparative purposes only) Calcium channel blockers (should not be used) Digoxin (off label) Disopyramide Alone or in combination
Comparison	No treatment Any intervention listed above
Outcomes	Critical outcomes: Mortality (30 days and longest endpoint) Health-related quality of life Recurrence rate – proportion of time in AF Secondary outcomes: Stroke or thromboembolic complications Rehospitalisation with a primary diagnosis of AF Patients developing heart failure Drug withdrawal due to side effects Time to first relapse
Exclusion	Acute and unstable AF Antiarrhythmic drugs as prevention of AF
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only.
Search	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL.

terms	Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.
The review strategy	RCTs Systematic reviews of RCTs
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Within the above sub-groups, further sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. • Comorbidity MIDS – default

C.1.12 Left atrial catheter ablation versus non-ablation therapies

Review Protocol – What is the clinical and cost-effectiveness of catheter ablation?	
Component	Description
Review question	What is the clinical and cost-effectiveness of catheter ablation compared to non-ablation therapies?
Population	People with paroxysmal, permanent or persistent AF.
Intervention	Catheter ablation; including Percutaneous radiofrequency ablation (interventional procedure)
Comparison	Non ablation therapies: Rhythm control drugs Cardioversion Cardioversion and drug therapy Rate control drugs
Outcomes	**Critical outcomes:** Mortality Heath related quality of life Recurrence of symptomatic AF **Secondary outcomes:** Stroke or thromboembolic complications Hospitalisation (cardiovascular) Patients developing heart failure Necessity for concomitant antiarrhythmic drug therapy
Exclusion	None
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied
The review strategy	RCTs Systematic reviews of RCTs
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Within the above sub-groups, further sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Study date

Review Protocol – What is the clinical and cost-effectiveness of catheter ablation?	
	Sub-group analysis of first and second line treatment Sub-group analysis of types of AF

C.1.13 Left atrial surgical versus catheter ablation

Review Protocol – What is the clinical and cost-effectiveness of surgical ablation compared to catheter ablation?	
Component	Description
Review question	What is the clinical and cost-effectiveness of surgical ablation compared to catheter ablation in people with AF?
Population	People with paroxysmal, permanent or persistent AF.
Intervention	Surgical ablation (with or without surgery); including • Radiofrequency ablation • Microwave ablation • Cryoablation • Ultrasound • MAZE (and modified techniques of MAZE) • Cut and sew • Pulmonary vein isolation (PVI) Video assisted thoroscopy (VATS)
Comparison	Catheter ablation; including Percutaneous radiofrequency ablation (interventional procedure)
Outcomes	**Critical outcomes:** Mortality Heath related quality of life Maintenance of sinus rhythm **Secondary outcomes:** Stroke or thromboembolic complications Rehospitalisation (cardiovascular) Major bleeding including intracranial Necessity for concomitant antiarrhythmic drug therapy Need for a pacemaker
Exclusion	None
Search strategy	The databases to be searched are Medline, Embassy, The Cochrane Library, CINAHL. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied
The review strategy	RCTs Systematic reviews of RCTs
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Within the above sub-groups, further sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Left atrial size

Review Protocol – What is the clinical and cost-effectiveness of surgical ablation compared to catheter ablation?	
	Duration of AF

C.1.14 Left atrial surgical ablation versus non-ablation therapies

Review Protocol – What is the clinical and cost-effectiveness of surgical ablation compared to non-ablation therapies?	
Component	Description
Review question	What is the clinical and cost-effectiveness of surgical ablation compared to non-ablation therapies?
Population	People with paroxysmal, permanent or persistent AF that are having pure ablation (lone ablation) or concomitant ablation (with other surgery). Sub-group analysis – age if reported separately
Intervention	Surgical ablation (with or without surgery); including • Radiofrequency ablation • Microwave ablation • Cryoablation • Ultrasound • MAZE (and modified techniques of MAZE) • Cut and sew • Pulmonary vein isolation (PVI) • Video assisted thoroscopy (VATS)
Comparison	Non ablation therapies: Surgery without ablation Rhythm control drugs Cardioversion Cardioversion and drug therapy Rate control drugs
Outcomes	**Critical outcomes:** Mortality Heath related quality of life Maintenance of sinus rhythm **Secondary outcomes:** Stroke or thromboembolic complications Major bleeding including intracranial Rehospitalisation (cardiovascular) Necessity for concomitant antiarrhythmic drug therapy
Exclusion	Heart transplant patients
Search strategy	The databases to be searched are Medline, Embassy, The Cochrane Library, CINAHL. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied
The review strategy	RCTs Systematic reviews of RCTs

Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Within the above sub-groups, further sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. None reported

C.1.15 Pace and ablate

Review Protocol – What is the clinical and cost-effectiveness of atrioventricular junction ablation and pacing?	
Component	Description
Review question	What is the clinical and cost-effectiveness of atrioventricular junction ablation and pacing compared to usual care in the treatment of AF?
Population	People with AF Sub-groups: age, heart failure and biventricular devices.
Intervention	Atrioventricular junction ablation and pacing (rate control strategy) Biventricular Single ventricular pace maker
Comparison	Usual care (including catheter/surgical ablation) Rate control drugs
Outcomes	Critical outcomes: All cause mortality (30 days and latest endpoint) Heart failure Health -related quality of life Secondary outcomes: Stroke or thromboembolic complications Re-hospitalisation with a primary diagnosis of AF or heart failure Left ventricular function
Exclusion	None
Search strategy	The databases to be searched are Medline, Embase and The Cochrane Library. Studies will be restricted to English language only.
Search terms	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Studies will be restricted to English language only. Systematic review and RCT search filters will be applied.
The review strategy	Randomised controlled trials (RCTs) Systematic review of RCTs
Analysis	A meta-analysis will be conducted on RCTs with appropriate outcome data. Within the above sub-groups, further sub-grouping will occur if there is statistical heterogeneity in meta-analysis results. Age LV function/heart failure

C.1.16 Acute atrial fibrillation

These are included in the rate control and restoration of sinus rhythm protocols (see Appendix C.1.9 and C.1.10).

C.2 Economic review protocol

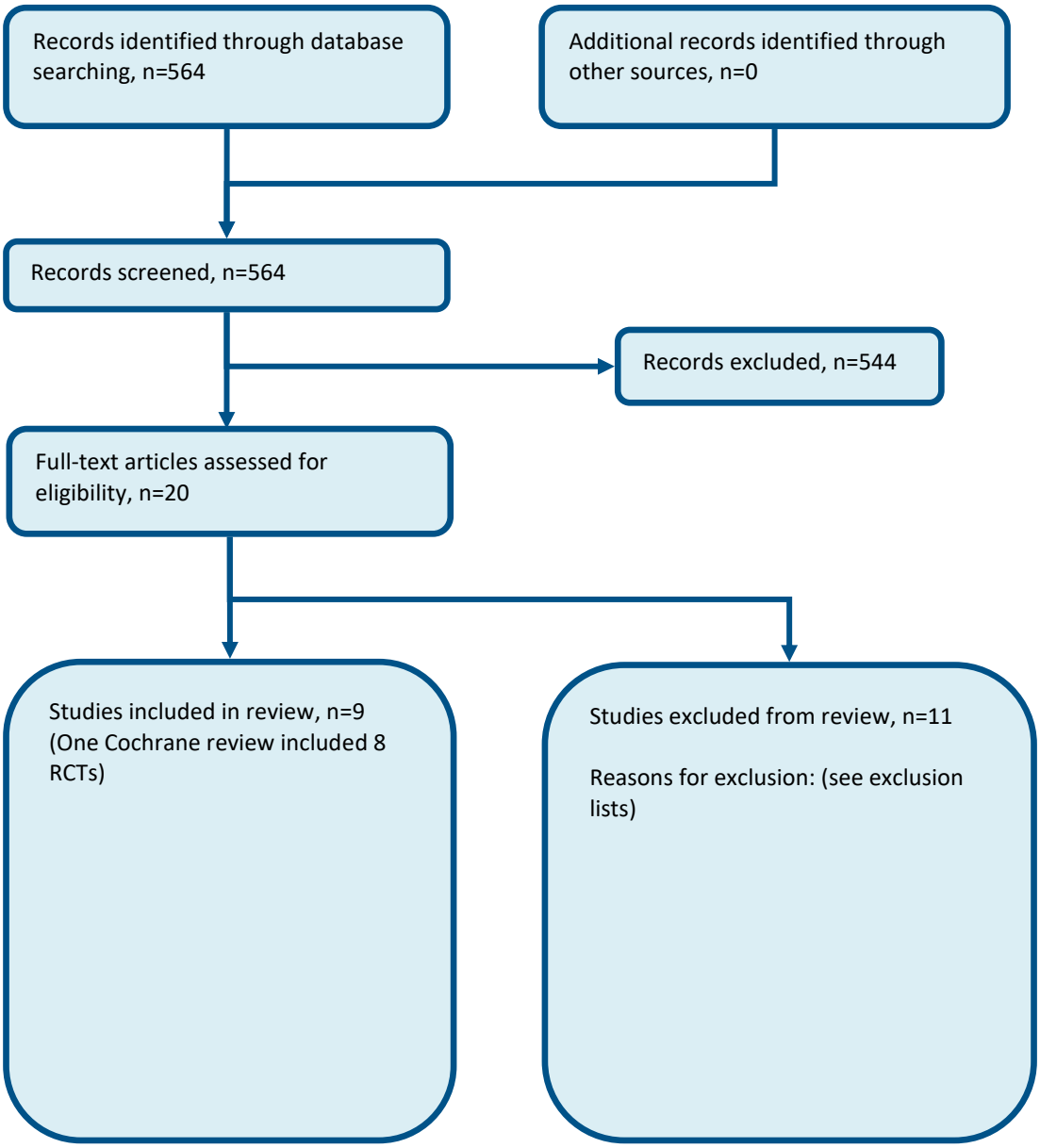
Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to the review questions set out above.
Criteria	• Populations, interventions and comparators must be as specified in the individual review protocols above. • Studies must be of a relevant economic study design (cost–utility analysis, cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations.[a] Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix F [in Full Guideline].
Review strategy	Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[688] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix I. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (for example, USA,

	Switzerland) • non-OECD settings (always 'Not applicable'). *Economic study type:* • cost–utility analysis • other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis) • comparative cost analysis • non-comparative cost analyses including cost-of-illness studies (always 'Not applicable'). *Year of analysis:* • The more recent the study, the more applicable it is. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

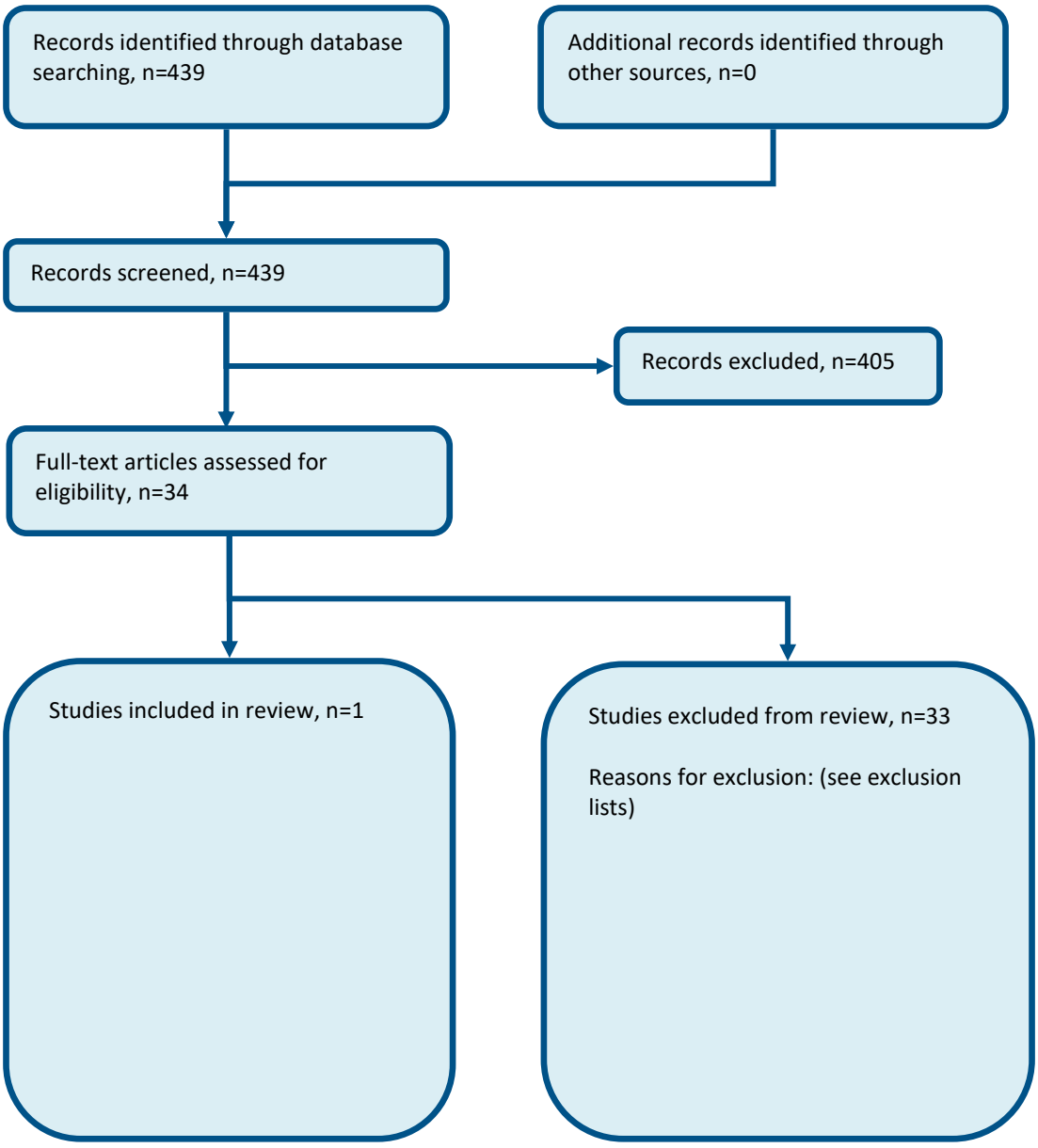
(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

Appendix D: Clinical article selection

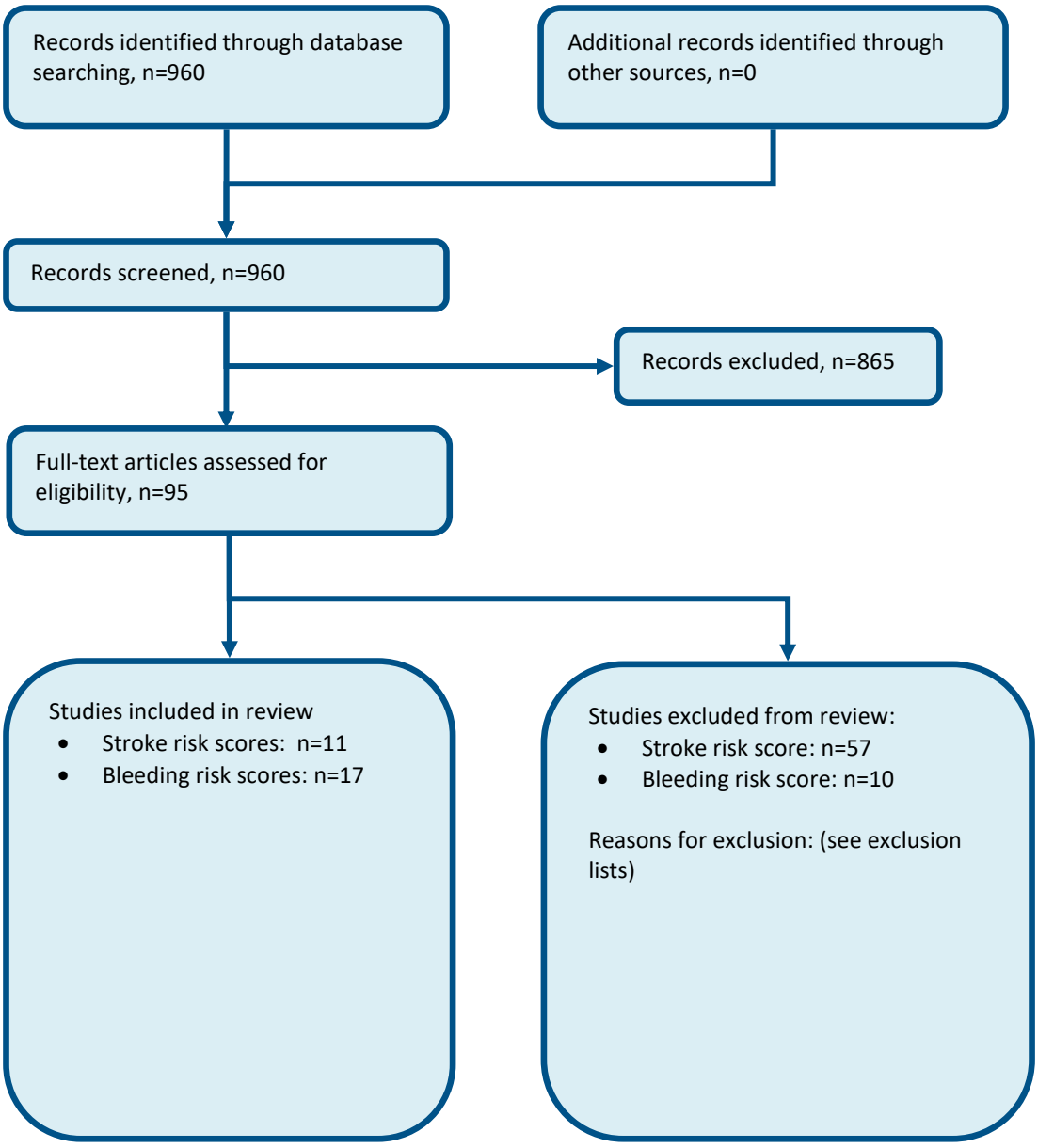
D.1 Education



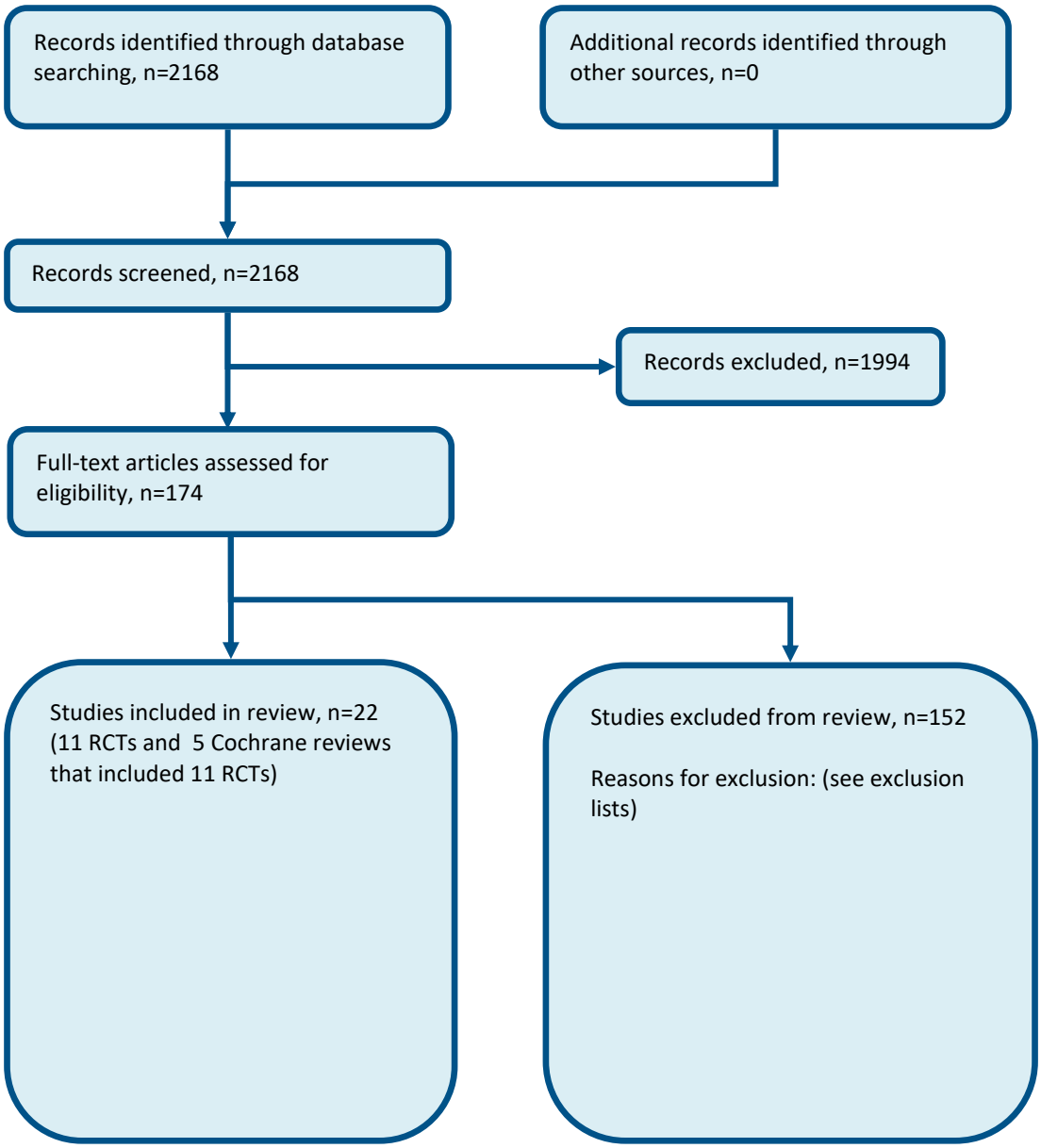
D.2 Referral to specialist care



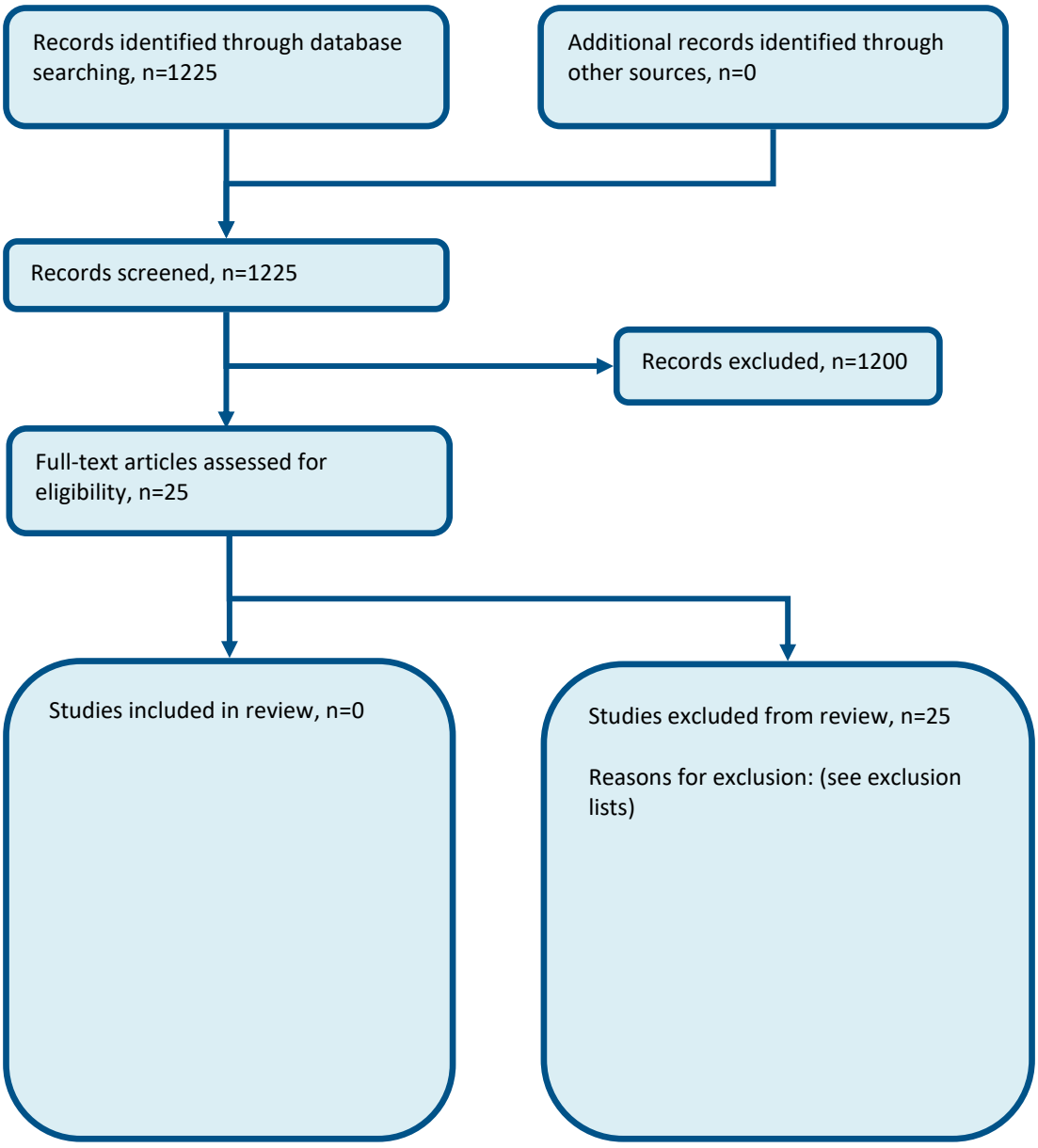
D.3 Stroke and bleeding risk tools



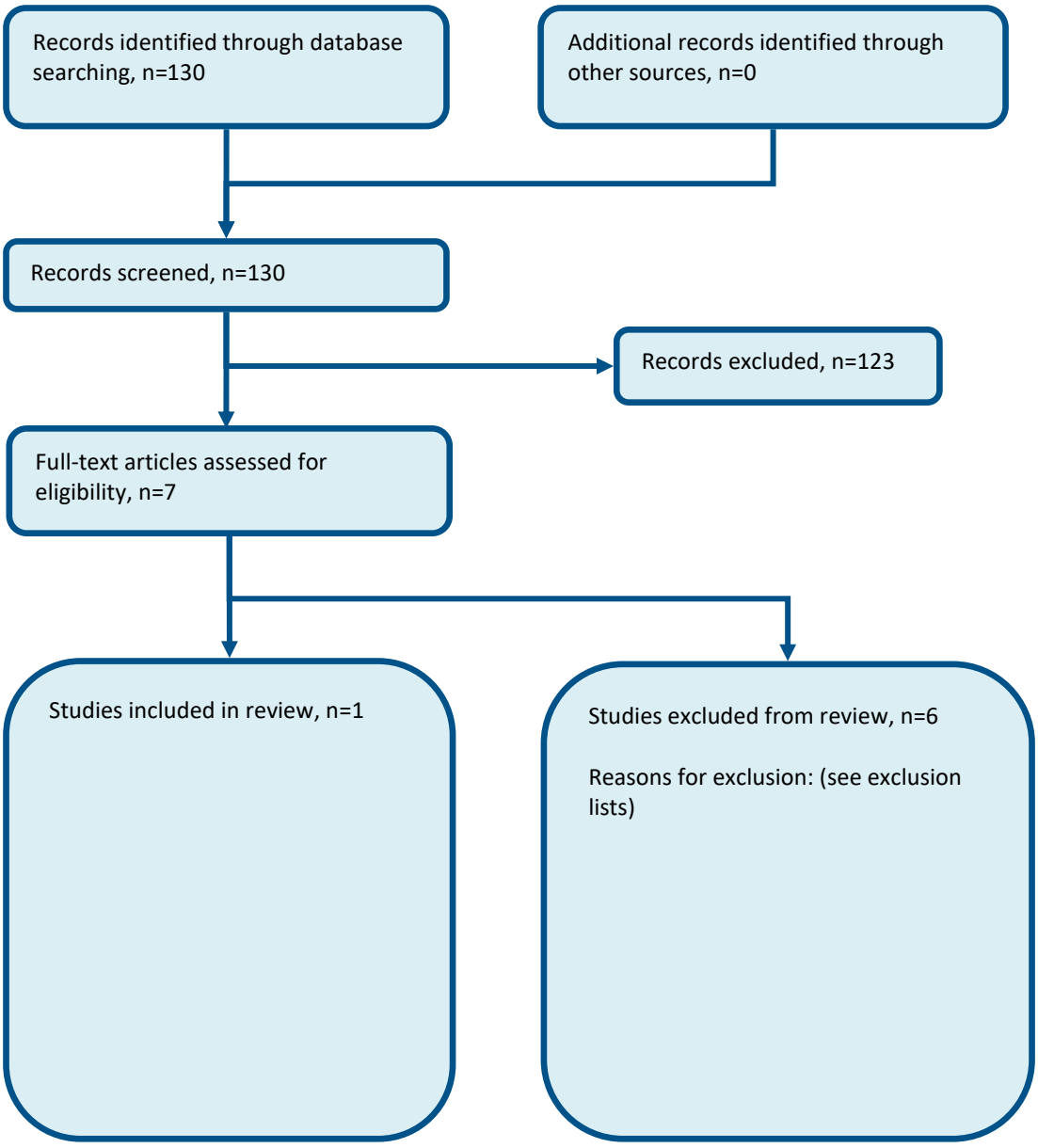
D.4 Anticoagulation



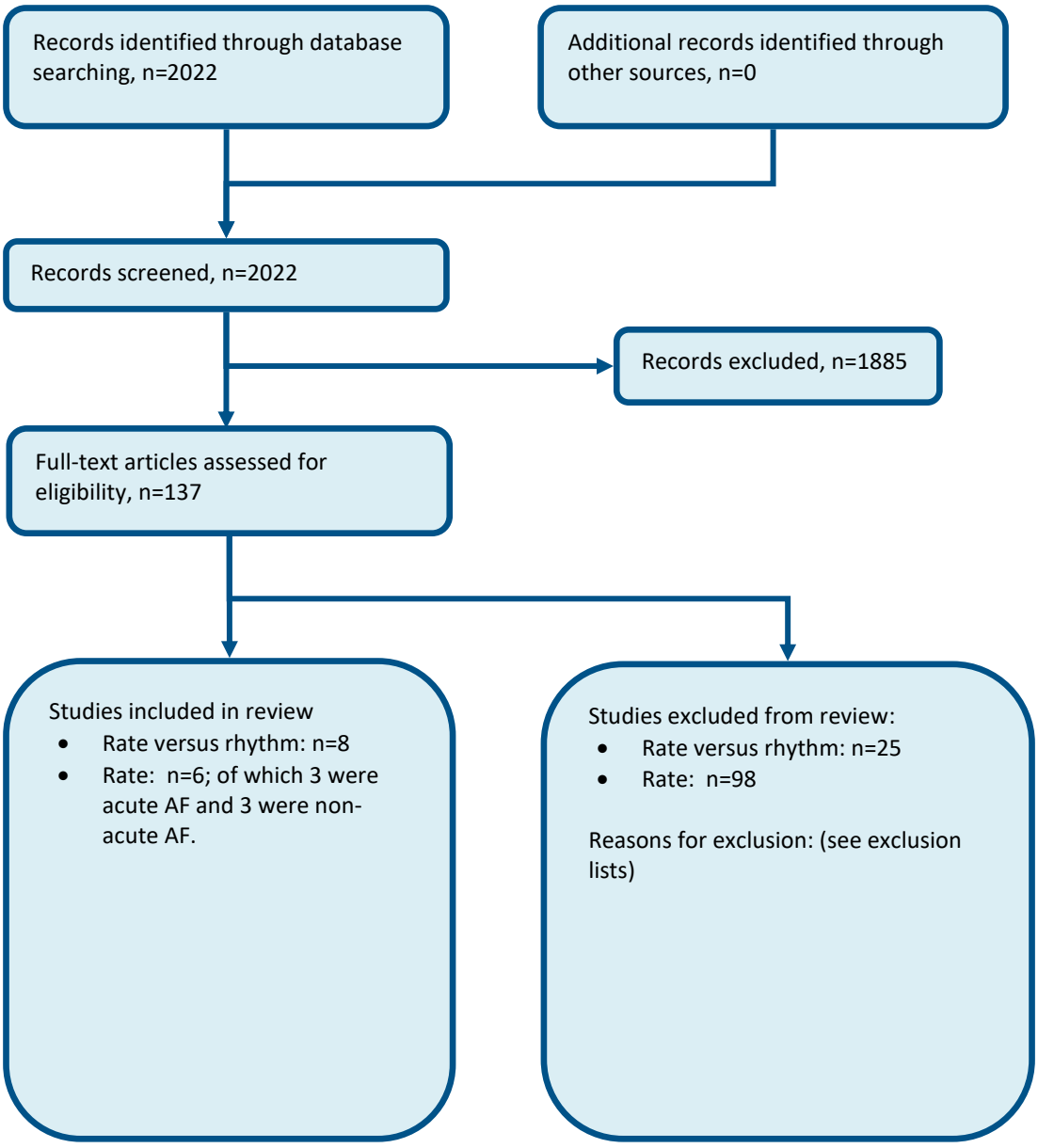
D.5 Monitoring



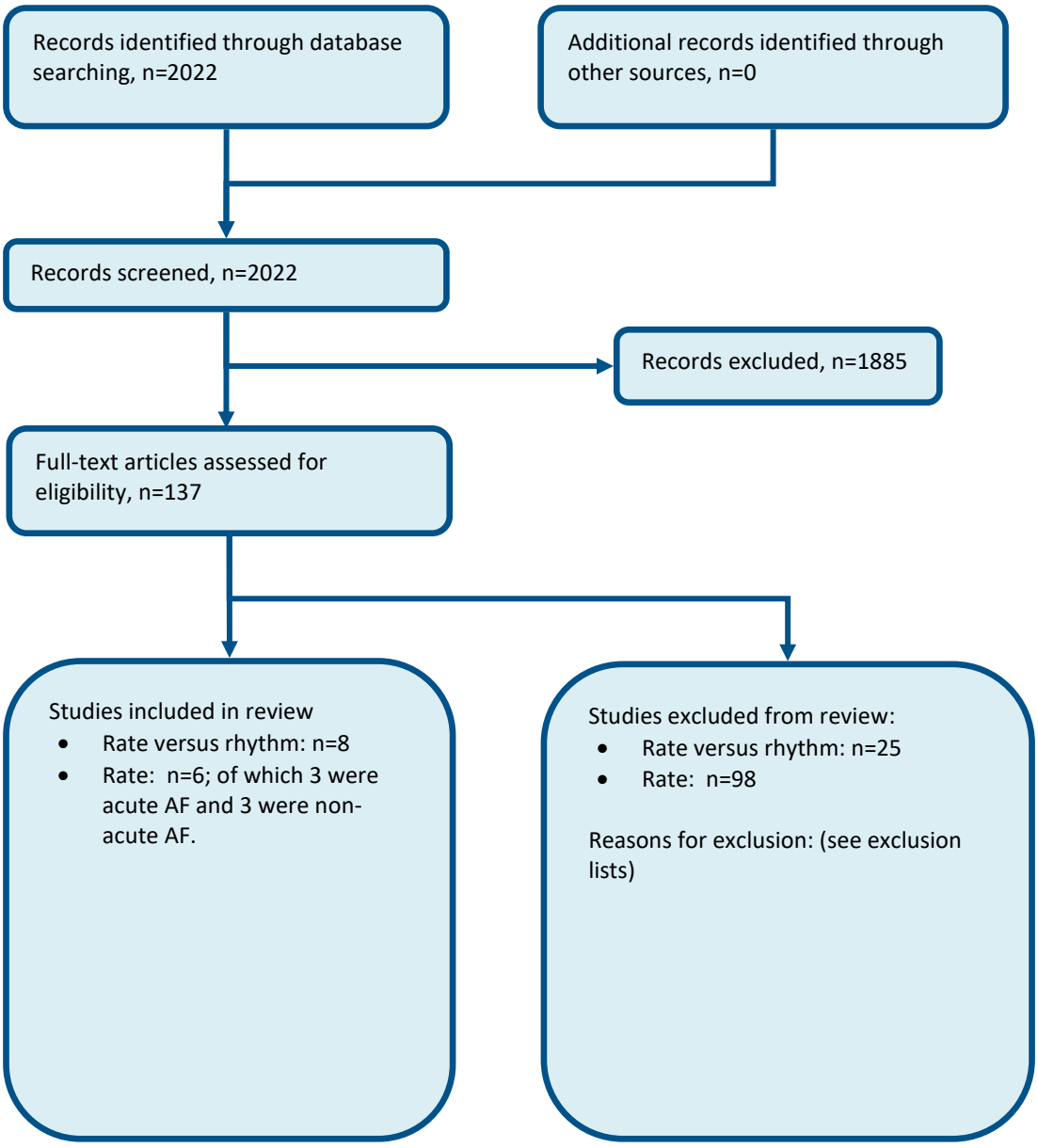
D.6 Left Atrial Appendage Occlusion



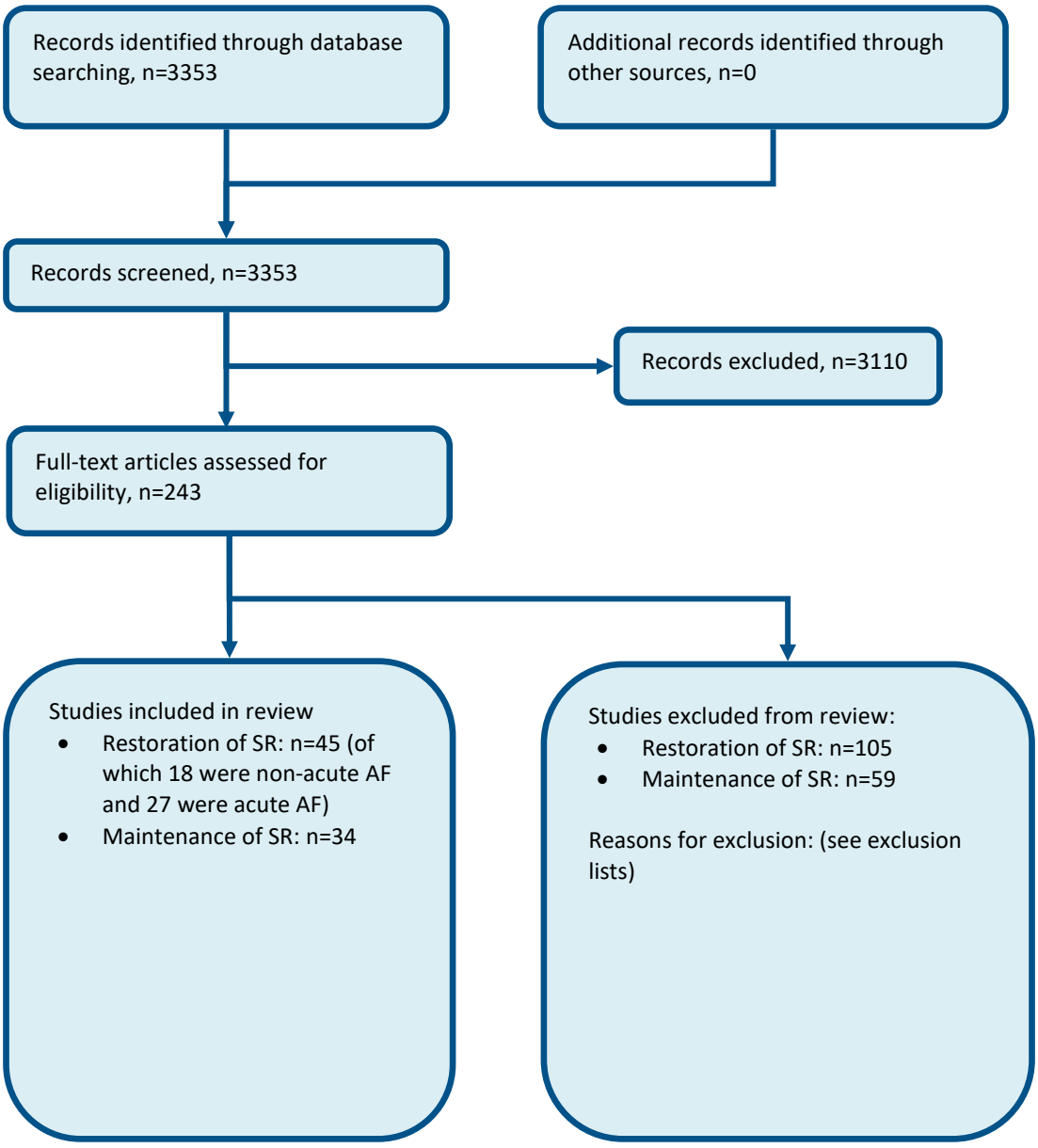
D.7 Rate versus rhythm control strategies



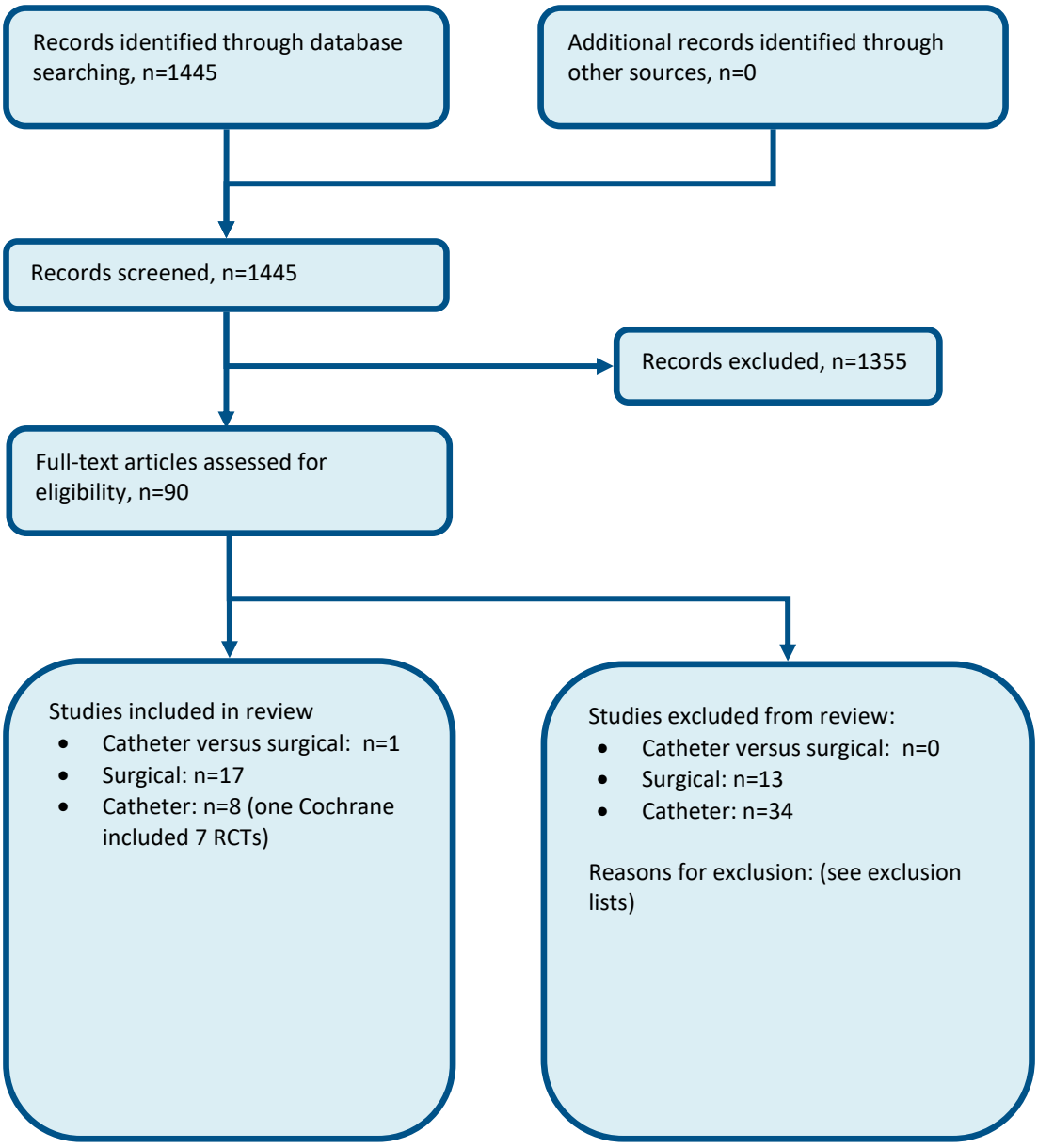
D.8 Rate control strategies



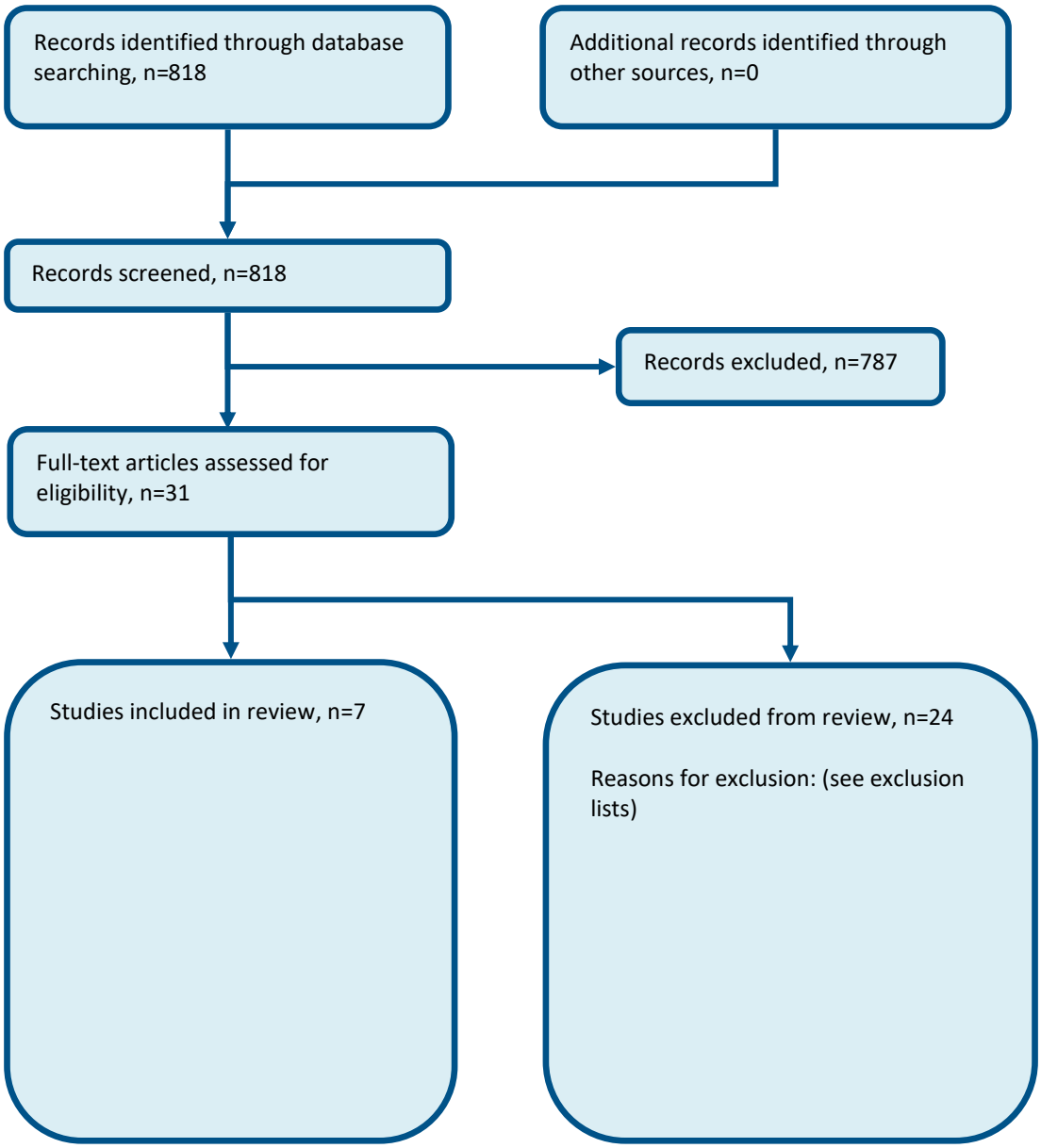
D.9 Rhythm control strategies (restoration and maintenance of sinus rhythm)



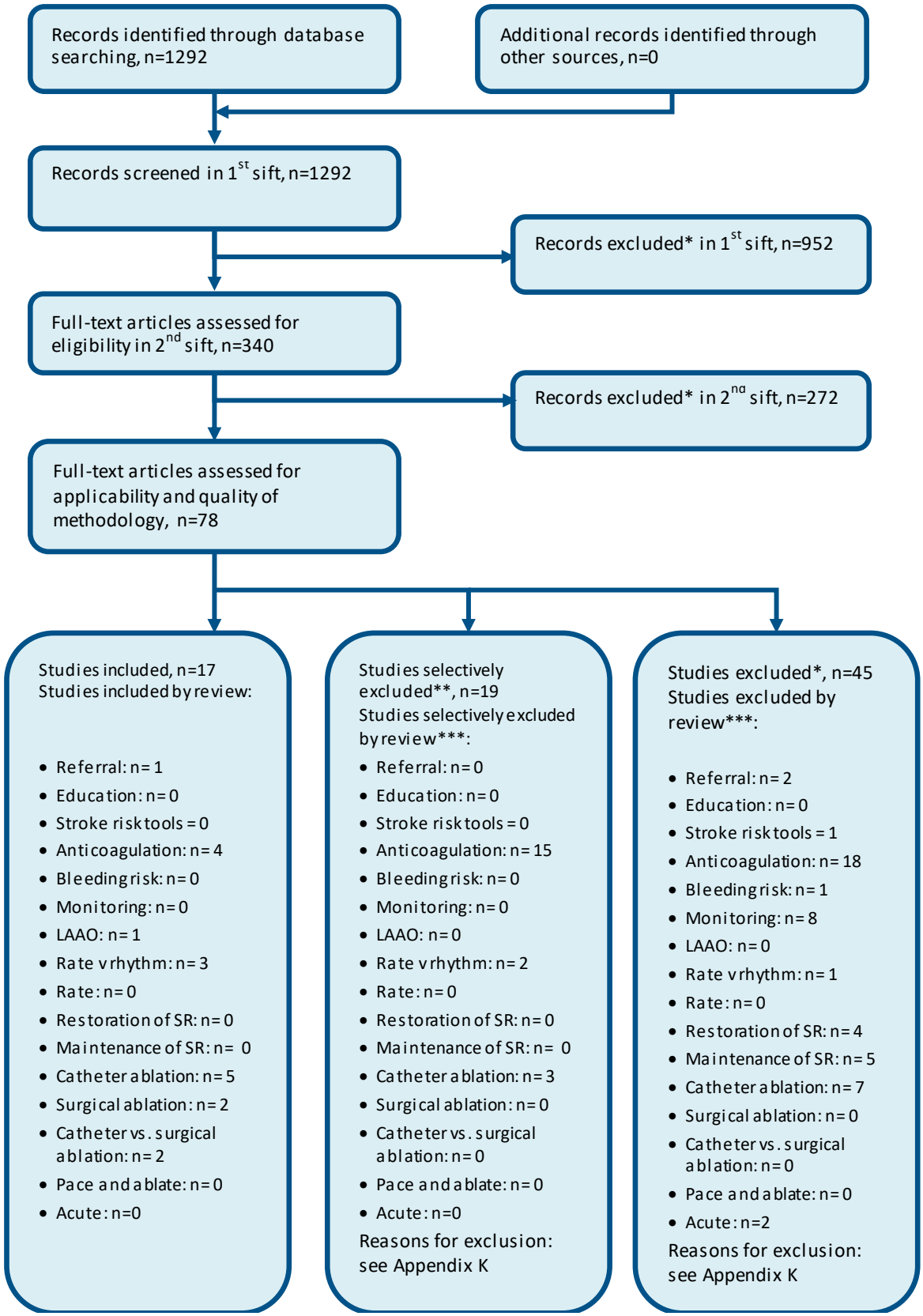
D.10 Left atrial ablation



D.11 Pace and ablate



Appendix E: Economic article selection



* Non-relevant population, intervention, comparison, design or setting; non-English language.

** Studies selectively excluded due to availability of superior evidence.

***Numbers not mutually exclusive, due to 3 studies spanning several review topics.

Appendix F: Literature search strategies

Contents

Search strategies used for the atrial fibrillation guideline are outlined below and were run in accordance with the methodology in the NICE Guidelines Manual 2012.[688] All searches were run up to 3 October 2013 unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text. Where possible searches were limited to retrieve material published in English.

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Additional searches were run in CINAHL (EBSCO), PsycInfo (OVID) and HMIC (OVID) for some questions. Usually, searches were constructed in the following way:

- A PICO format was used for **intervention** searches where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

- A PEO format was used for **prognosis** searches where population (P) terms were combined with exposure (E) terms and sometimes outcomes (O). Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). Searches in NHS EED and HEED were constructed only using population terms. For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy.

F.1 Population search strategies

Medline search terms

1	exp atrial fibrillation/
2	(atrial adj3 fibrillat*).ti,ab.
3	((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab.
4	or/1-3
5	limit 4 to english language
6	letter/
7	editorial/
8	news/
9	exp historical article/
10	anecdotes as topic/
11	comment/
12	case report/
13	(letter or comment*).ti.
14	or/6-13
15	randomized controlled trial/ or random*.ti,ab.
16	14 not 15
17	animals/ not humans/
18	animals, laboratory/
19	exp animal experiment/
20	exp animal model/
21	exp rodentia/
22	(rat or rats or mouse or mice).ti.
23	or/16-22
24	5 not 23

Embase search terms

1	heart atrium fibrillation/
2	(atrial adj3 fibrillat*).ti,ab.
3	((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab.
4	or/1-3
5	limit 4 to english language
6	letter.pt. or letter/
7	note.pt.
8	editorial.pt.

9	case report/ or case study/
10	(letter or comment*).ti.
11	or/6-10
12	randomized controlled trial/ or random*.ti,ab.
13	11 not 12
14	animal/ not human/
15	nonhuman/
16	exp animal experiment/
17	exp experimental animal/
18	animal model/
19	exp rodent/
20	(rat or rats or mouse or mice).ti.
21	or/13-20
22	5 not 21

Cochrane search terms

#1	MeSH descriptor Atrial Fibrillation, this term only
#2	(atrial near/3 fibrillat*):ti,ab
#3	(auricular near/3 fibrillat*):ti,ab
#4	(supraventricular near/3 *arrhythmia*):ti,ab
#5	(#1 OR #2 OR #3 OR #4)

CINAHL search terms

S1	(MH "Arrhythmia, Atrial") OR (MH "Atrial Fibrillation")
S2	(atrial n3 fibrillat*)
S3	((auricular n3 fibrillat*) or (supraventricul* n3 arrhythmi*))
S4	S1 OR S2 OR S3
S5	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S6	S4 NOT S5

PsycInfo search terms

1	"fibrillation (heart)"/
2	(atrial adj3 fibrillat*).ti,ab.
3	((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab.
4	or/1-3
5	limit 4 to english language

HMIC search terms

1	exp arrhythmia/
2	(atrial adj3 fibrillat*).ti,ab.
3	((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab.
4	or/1-3

F.2 Study filter search terms

F.2.1 Systematic review search terms

Medline search terms

1	meta-analysis/
2	meta-analysis as topic/
3	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11	or/1-10

Embase search terms

1	systematic review/
2	meta-analysis/
3	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11	or/1-10

F.2.2 Randomised controlled studies (RCTs) search terms

Medline search terms

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomi#ed.ab.
4	placebo.ab.
5	randomly.ab.
6	Clinical Trials as topic.sh.
7	trial.ti.
8	or/1-7

Embase search terms

1	random*.ti,ab.

2	factorial*.ti,ab.
3	(crossover* or cross over*).ti,ab.
4	((doubl* or singl*) adj blind*).ti,ab.
5	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6	crossover procedure/
7	single blind procedure/
8	randomized controlled trial/
9	double blind procedure/
10	or/1-9

F.2.3 Observational studies search terms

Medline search terms

1	epidemiologic studies/
2	exp case control studies/
3	exp cohort studies/
4	cross-sectional studies/
5	case control.ti,ab.
6	(cohort adj (study or studies or analys*)).ti,ab.
7	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9	or/1-8

Embase search terms

1	clinical study/
2	exp case control study/
3	family study/
4	longitudinal study/
5	retrospective study/
6	prospective study/
7	cross-sectional study/
8	cohort analysis/
9	follow-up/
10	cohort*.ti,ab.
11	9 and 10
12	case control.ti,ab.
13	(cohort adj (study or studies or analys*)).ti,ab.
14	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16	or/1-8,11-15

F.2.4 Prognosis search terms

Medline search terms

1	(prognos* or predict*).ti,ab.
2	exp prognosis/
3	exp "predictive value of tests"/
4	or/1-3

Embase search terms

1	(prognos* or predict*).ti,ab.
2	prognosis/
3	predictive value/
4	or/1-3

F.2.5 Health economic search terms

Medline search terms

1	economics/
2	value of life/
3	exp "costs and cost analysis"/
4	exp economics, hospital/
5	exp economics, medical/
6	economics, nursing/
7	economics, pharmaceutical/
8	exp "fees and charges"/
9	exp budgets/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/1-16

Embase search terms

1	health economics/
2	exp economic evaluation/
3	exp health care cost/
4	exp fee/
5	budget/
6	funding/
7	budget*.ti,ab.
8	cost*.ti.
9	(economic* or pharmaco?economic*).ti.
10	(price* or pricing*).ti,ab.
11	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12	(financ* or fee or fees).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	or/1-13

F.2.6 Quality of life search terms

Medline search terms

1	quality-adjusted life years/
2	sickness impact profile/
3	(quality adj2 (wellbeing or well being)).ti,ab.
4	sickness impact profile.ti,ab.
5	disability adjusted life.ti,ab.
6	(qal* or qtime* or qwb* or daly*).ti,ab.
7	(euroqol* or eq5d* or eq 5*).ti,ab.
8	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
10	(hui or hui1 or hui2 or hui3).ti,ab.
11	(health* year* equivalent* or hye or hyes).ti,ab.
12	discrete choice*.ti,ab.
13	rosser.ti,ab.
14	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
16	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
18	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
19	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
20	or/1-19

Embase search terms

1	quality adjusted life year/
2	"quality of life index"/
3	short form 12/ or short form 20/ or short form 36/ or short form 8/
4	sickness impact profile/
5	(quality adj2 (wellbeing or well being)).ti,ab.
6	sickness impact profile.ti,ab.
7	disability adjusted life.ti,ab.
8	(qal* or qtime* or qwb* or daly*).ti,ab.
9	(euroqol* or eq5d* or eq 5*).ti,ab.
10	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
12	(hui or hui1 or hui2 or hui3).ti,ab.
13	(health* year* equivalent* or hye or hyes).ti,ab.
14	discrete choice*.ti,ab.
15	rosser.ti,ab.
16	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
18	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
20	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
21	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.

22	or/1-21

F.3 Searches by specific questions

F.3.1 Referral

What is the clinical and cost effectiveness of referral to specialist AF services?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	Referral		SRs RCTs Observational (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

Referral search terms

Medline search terms

1	nurse's practice patterns/
2	ambulatory care/
3	"referral and consultation"/
4	specialization/
5	((atrial or fibrillat* or arrhythmi* or af) adj2 (service or clinic*1 or hospital*1 or centre* or center* or specialist* or physician* or doctor* or nurse*or gp)).ti,ab.
6	(specialist* adj2 (service* or clinic*1 or hospital*1 or centre* or center* or physician or doctor* or nurse* or gp)).ti,ab.
7	(nurse* adj2 (led or care or service* or centre* or center* or clinic*1)).ti,ab.
8	or/1-7

Embase search terms

1	*ambulatory care/
2	*nursing care/
3	*patient referral/
4	*medical specialist/
5	((atrial or fibrillat* or arrhythmi* or af) adj2 (service or clinic*1 or hospital*1 or centre* or center* or specialist* or physician* or doctor* or nurse*or GP)).ti,ab.
6	(specialist* adj2 (service* or clinic*1 or hospital*1 or centre* or center* or physician or doctor* or nurse* or GP)).ti,ab.
7	(nurse* adj2 (led or care or service* or centre* or center* or clinic*1)).ti,ab.
8	or/1-7

Cochrane search terms

#1	[mh ^"Nurse's Practice Patterns"]
#2	[mh ^"Ambulatory Care"]
#3	[mh ^"Referral and Consultation"]
#4	[mh ^Specialization]
#5	((atrial or fibrillat* or arrhythmi* or af) near/2 (service or clinic or clinics or hospital or hospitals or centre* or center* or specialist* or physician* or doctor* or nurse*or GP)):ti,ab

#6	(specialist* near/2 (service* or clinic or clinics or hospital or hospitals or centre* or center* or physician or doctor* or nurse* or GP)):ti,ab
#7	(nurse* near/2 (led or care or service* or centre* or center* or clinic or clinics)):ti,ab
#8	{or #1-#7}

CINAHL search terms

S1	(MH "Referral and Consultation+") OR (MH "Ambulatory Care") OR (MH "Ambulatory Care Nursing") OR (MH "Ambulatory Care Facilities") OR (MH "Nurse-Managed Centers") OR (MH "Nurse Specialist Service (Saba CCC)") OR (MH "Clinical Nurse Specialists")
S2	((atrial or fibrillat* or arrhythmi* or af) n2 (service or clinic or clinics or hospital or hospitals or centre* or center* or specialist* or physician* or doctor* or nurse*or GP))
S3	(specialist* n2 (service* or clinic or clinics or hospital or hospitals or centre* or center* or physician or doctor* or nurse* or GP))
S4	(nurse* n2 (led or care or service* or centre* or center* or clinic or clinics))
S5	S1 OR S2 OR S3 OR S4

HMIC search terms

1	ambulatory care/ or ambulatory care services/
2	nurse led services/
3	specialist services/
4	exp referral/
5	((atrial or fibrillat* or arrhythmi* or af) adj2 (service or clinic*1 or hospital*1 or centre* or center* or specialist* or physician* or doctor* or nurse*or GP)).ti,ab.
6	(specialist* adj2 (service* or clinic*1 or hospital*1 or centre* or center* or physician or doctor* or nurse* or GP)).ti,ab.
7	(nurse* adj2 (led or care or service* or centre* or center* or clinic*1)).ti,ab.
8	or/1-7

F.3.2 Education

What educational and behavioural interventions are clinically and cost effective for aiding the management of anticoagulant therapy, rate and rhythm and symptoms in patients with AF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	Education		SRs RCTs (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

Education search terms

Medline search terms

1	health knowledge, attitudes, practice/
2	patient participation/
3	exp information services/
4	patient education as topic/ or patient education handout/
5	"patient acceptance of health care"/ or exp patient satisfaction/
6	communication/
7	exp consumer health information/

8	((educat* or train* or teach*) adj3 (program* or intervention*)).ti,ab.
9	(patient* adj3 (train* or teach* or educat* or inform*)).ti,ab.
10	((patient or patients) adj3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet* or website* or knowledge or app or apps)).ti,ab.
11	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
12	motivation/
13	motivational interview*.ti,ab.
14	contingency management.ti,ab.
15	biofeedback.ti,ab.
16	bio-feedback.ti,ab.
17	goals/
18	(goal* adj3 set*).ti,ab.
19	decision support techniques/
20	decision* aid*.ti,ab.
21	(decision* adj3 support*).ti,ab.
22	exp communications media/
23	exp counseling/
24	exp psychotherapy/
25	social support/
26	(psycholog* or council* or counsel* or psychotherap* or psychosocial).ti,ab.
27	((support* or advice or advise) adj3 (telephone* or internet or program* or group*)).ti,ab.
28	(behavi* adj3 (therap* or manage* or modif* or chang* or intervention*)).ti,ab.
29	(cogniti* adj3 (therap* or intervention*)).ti,ab.
30	cbt.ti,ab.
31	((anxiety* or anxious*) adj3 (manag* or treat* or therap*)).ti,ab.
32	or/1-31

Embase search terms

1	attitude to health/
2	patient participation/
3	*motivation/
4	decision support system/
5	*mass medium/
6	patient attitude/ or *patient preference/ or *patient satisfaction/ or consumer attitude/
7	consumer health information/
8	information service/ or information center/ or publication/ or book/
9	patient information/ or patient education/
10	medical information/
11	health literacy/
12	exp *interpersonal communication/
13	exp *counseling/
14	exp *psychotherapy/
15	*psychosocial care/
16	*social support/
17	((educat* or train* or teach*) adj3 (program* or intervention*)).ti,ab.

18	(patient* adj3 (train* or teach* or educat* or inform*)).ti,ab.
19	((patient or patients) adj3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet* or website* or knowledge or app or apps)).ti,ab.
20	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
21	motivational interview*.ti,ab.
22	contingency management.ti,ab.
23	biofeedback.ti,ab.
24	bio-feedback.ti,ab.
25	(goal* adj3 set*).ti,ab.
26	decision* aid*.ti,ab.
27	(decision* adj3 support*).ti,ab.
28	(psycholog* or council* or counsel* or psychotherap* or psychosocial).ti,ab.
29	((support* or advice or advise) adj3 (telephone* or internet or program* or group*)).ti,ab.
30	(behavi* adj3 (therap* or manage* or modif* or chang* or intervention*)).ti,ab.
31	(cogniti* adj3 (therap* or intervention*)).ti,ab.
32	cbt.ti,ab.
33	((anxiety* or anxious*) adj3 (manag* or treat* or therap*)).ti,ab.
34	or/1-33

Cochrane search terms

#1	[mh ^"Health Knowledge, Attitudes, Practice"]
#2	[mh ^"Patient Participation"]
#3	[mh "Information Services"]
#4	[mh ^"Patient Education as Topic"]
#5	[mh ^"Patient Education Handout"]
#6	[mh ^"patient acceptance of health care"]
#7	[mh "patient satisfaction"]
#8	[mh ^Communication]
#9	[mh "Consumer Health Information"]
#10	((educat* or train* or teach*) near/3 (program* or intervention*)):ti,ab
#11	(patient* near/3 (train* or teach* or educat* or inform*)):ti,ab
#12	((patient or patients) near/3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet* or website* or knowledge or app or apps)):ti,ab
#13	(information* near/3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)):ti,ab
#14	[mh ^Motivation]
#15	motivational interview*:ti,ab
#16	contingency management:ti,ab
#17	biofeedback:ti,ab
#18	bio-feedback:ti,ab
#19	[mh ^goals]
#20	(goal* near/3 set*):ti,ab
#21	[mh ^"decision support techniques"]
#22	decision* aid*:ti,ab
#23	(decision* near/3 support*):ti,ab

#24	[mh "communications media"]
#25	[mh Counseling]
#26	[mh Psychotherapy]
#27	[mh ^"Social support"]
#28	(psycholog* or council* or counsel* or psychotherap* or psychosocial):ti,ab
#29	((support* or advice or advise) near/3 (telephone* or internet or program* or group*)):ti,ab
#30	(behavi* near/3 (therap* or manage* or modif* or chang* or intervention*)):ti,ab
#31	(cogniti* near/3 (therap* or intervention*)):ti,ab
#32	CBT:ti,ab
#33	((anxiety* or anxious*) near/3 (manag* or treat* or therap*)):ti,ab
#34	{or #1-#33}

CINAHL search terms

S1	(MH "Information Services+") OR (MH "Counseling+") OR (MH "Patient Education") OR (MH "Patient Discharge Education") OR (MH "Health Education") OR (MH "Patient Attitudes") OR (MH "Communication+")
S2	(MH "Consumer Health Information") OR (MH "Psychotherapy+")
S3	(MH "Communications Media") OR (MH "Decision Support Techniques") OR (MH "Goals and Objectives") OR (MH "Motivation") OR (MH "Consumer Participation") OR (MH "Attitude to Health")
S4	((educat* or train* or teach*) n3 (program* or intervention*))
S5	(patient* n3 (train* or teach* or educat* or inform*))
S6	((patient or patients) n3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet* or website* or knowledge or app or apps))
S7	(information* n3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*))
S8	motivational interview* OR contingency management OR goal* n3 set*
S9	biofeedback OR bio-feedback OR decision* aid* OR decision* n3 support*
S10	(psycholog* or council* or counsel* or psychotherap* or psychosocial)
S11	((support* or advice or advise) n3 (telephone* or internet or program* or group*))
S12	(behavi* n3 (therap* or manage* or modif* or chang* or intervention*))
S13	(cogniti* n3 (therap* or intervention*))
S14	CBT
S15	((anxiety* or anxious*) n3 (manag* or treat* or therap*))
S16	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

PsycInfo search terms

1	client education/
2	client participation/
3	exp psychotherapy/
4	exp counseling/
5	motivation/
6	exp goals/
7	biofeedback/
8	decision making/
9	exp communications media/
10	health knowledge/

11	health attitudes/
12	exp information/
13	((educat* or train* or teach*) adj3 (program* or intervention*)).ti,ab.
14	(patient* adj3 (train* or teach* or educat* or inform*)).ti,ab.
15	((patient or patients) adj3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet* or website* or knowledge or app or apps)).ti,ab.
16	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab.
17	motivational interview*.ti,ab.
18	contingency management.ti,ab.
19	biofeedback.ti,ab.
20	bio-feedback.ti,ab.
21	(goal* adj3 set*).ti,ab.
22	decision* aid*.ti,ab.
23	(decision* adj3 support*).ti,ab.
24	(psycholog* or council* or counsel* or psychotherap* or psychosocial).ti,ab.
25	((support* or advice or advise) adj3 (telephone* or internet or program* or group*)).ti,ab.
26	(behavi* adj3 (therap* or manage* or modif* or chang* or intervention*)).ti,ab.
27	(cogniti* adj3 (therap* or intervention*)).ti,ab.
28	CBT.ti,ab.
29	((anxiety* or anxious*) adj3 (manag* or treat* or therap*)).ti,ab.
30	or/1-29

F.3.3 Risk

Searches for the following two questions were run as one search:

What is the clinically and cost effective of HAS-BLED compared to other tools in assessing bleeding risk in people with AF?

What is the clinically and cost effective risk stratification tools for stroke or thromboembolic events in atrial fibrillation?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	Risk		SRs RCTs Observational Prognostic (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

Risk search terms

Medline search terms

1	(hasbled or has-bled).ti,ab.
2	(atria adj2 scor*).ti,ab.
3	"HEMORR(2)HAGES".ti,ab.
4	hemorr2hages.ti,ab.

5	((bleed* or hemorrhag* or haemorrhag*) adj3 scor*).ti,ab.
6	((bleed* or hemorrhag* or haemorrhag*) adj3 (risk tool* or risk schem* or risk stratif*)).ti,ab.
7	hemorrhage/ci, ep [Chemically Induced, Epidemiology]
8	proportional hazards models/ or logistic models/ or risk assessment/ or risk factors/
9	decision support systems, clinical/ or decision support techniques/
10	8 or 9
11	(risk tool* or stratification or rating scale* or scoring system* or scoring schem* or risk schem*).ti,ab.
12	10 and 11
13	7 and 12
14	or/1-6,13
15	chads*.ti,ab.
16	cha2ds2*.ti,ab.
17	"cha(2)ds(2)-vasc".ti,ab.
18	(birmingham adj3 (risk tool* or risk scor* or risk system* or risk schem* or risk stratif*)).ti,ab.
19	((stroke or strokes or thrombosis or thrombotic or thromboemboli*) adj6 (risk tool* or risk scor* or risk system* or risk scheme* or risk stratif*)).ti,ab.
20	stroke/ep, pc [Epidemiology, Prevention & Control]
21	thrombosis/ep, pc [Epidemiology, Prevention & Control]
22	thromboembolism/ep, pc [Epidemiology, Prevention & Control]
23	or/20-22
24	proportional hazards models/ or logistic models/ or risk assessment/ or risk factors/
25	decision support systems, clinical/ or decision support techniques/
26	24 or 25
27	(risk tool* or stratification or scoring system* or rating scale* or scoring schem* or risk schem*).ti,ab.
28	23 and 26 and 27
29	or/15-19,28
30	14 or 29

Embase search terms

1	*"HAS BLED Score"/ or (hasbled or has-bled).ti,ab.
2	(atria adj2 scor*).ti,ab.
3	"HEMORR(2)HAGES".ti,ab.
4	hemorr2hages.ti,ab.
5	((bleed* or hemorrhag* or haemorrhag*) adj3 scor*).ti,ab.
6	((bleed* or hemorrhag* or haemorrhag*) adj3 (risk tool* or risk schem* or risk stratif*)).ti,ab.
7	*bleeding/
8	proportional hazards model/ or hazard ratio/ or risk assessment/ or risk factors/
9	decision support system/ or rating scale/ or scoring system/ or "named inventories, questionnaires and rating scales"/
10	8 or 9
11	(risk tool* or stratification or rating scale* or scoring system* or scoring schem* or risk schem*).ti,ab.
12	10 and 11
13	7 and 12
14	or/1-6,13

15	*chads2 score/ or chads*.ti.
16	cha2ds2*.ti,ab.
17	"cha(2)ds(2)-vasc".ti,ab.
18	((birmingham or chads*) adj3 (risk tool* or risk scor* or risk system* or risk schem* or risk stratif*)).ti,ab.
19	((stroke or strokes or thromboemboli* or thrombosis or thrombotic) adj6 (risk tool* or risk scor* or risk system* or risk scheme* or risk stratif*)).ti,ab.
20	*cerebrovascular accident/
21	*thromboembolism/ or *thrombosis/
22	20 or 21
23	proportional hazards model/ or hazard ratio/ or risk assessment/ or risk factors/
24	decision support system/ or rating scale/ or scoring system/ or "named inventories, questionnaires and rating scales"/
25	23 or 24
26	(risk tool* or stratification or scoring system* or rating scale* or scoring schem* or risk schem*).ti,ab.
27	22 and 25 and 26
28	or/15-19,27
29	14 or 28

Cochrane search terms

#1	("has-bled" or hasbled or chads*):ti,ab
#2	cha(2)ds(2)-vasc:ti,ab
#3	cha(2)ds(2):ti,ab
#4	(atria near/2 scor*):ti,ab
#5	HEMORR(2)HAGES:ti,ab
#6	hemorr2hages:ti,ab
#7	((bleed* or hemorrhag* or haemorrhag*) next/3 scor*):ti,ab
#8	((bleed* or hemorrhag* or haemorrhag* or "stroke" or "strokes" or thrombosis or thrombotic or thromboemboli*) near/3 risk*) near/3 (tool* or scal* or schem* or stratif*):ti,ab
#9	{or #1-#8}
#10	MeSH descriptor: [Hemorrhage] this term only and with qualifiers: [Chemically induced - CI, Epidemiology - EP]
#11	MeSH descriptor: [Stroke] this term only and with qualifiers: [Epidemiology - EP, Prevention & control - PC]
#12	MeSH descriptor: [Thrombosis] this term only and with qualifiers: [Epidemiology - EP, Prevention & control - PC]
#13	MeSH descriptor: [Thromboembolism] this term only and with qualifiers: [Epidemiology - EP, Prevention & control - PC]
#14	#10 or #11 or #12 or #13
#15	risk* near/3 (tool* or scal* or schem* or stratif*):ti,ab
#16	(scoring next/2 system*):ti,ab
#17	(rating next/2 scale*):ti,ab
#18	1#15 or #16 or #17
#19	#14 and #18
#20	#9 or #19

F.3.4 Anticoagulation

What is the most clinical and cost-effective antithrombotic therapy for stroke prevention in people with AF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	Anticoagulation		SRs RCTs (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

Anticoagulation search terms

Medline search terms

1	platelet aggregation inhibitors/ or aspirin/ or dipyridamole/
2	aspirin.ti,ab.
3	(clopidogrel or plavix).ti,ab.
4	(ticagrelor or brilique).ti,ab.
5	(prasugrel or efient or effient or prasita).ti,ab.
6	(dipyridamole or persantin or asasantin).ti,ab.
7	(tirofiban or aggrastat).ti,ab.
8	(antiplatelet* or (platelet* adj2 (inhibit* or antagon*))).ti,ab.
9	anticoagulants/ or acenocoumarol/ or coumarins/ or phenindione/ or phenprocoumon/ or warfarin/ or antithrombins/
10	warfarin.ti,ab.
11	(acenocoumarol or phenprocoumon or phenidione or (vitamin k adj2 antagonist*)).ti,ab.
12	((factor xa adj2 inhibit*) or rivaroxaban or xarelto or apixaban or eliquis or dabigatran or pradaxa or argatroban or exembol).ti,ab.
13	or/1-12

Embase search terms

1	*antithrombocytic agent/ or *acetylsalicylic acid/ or *acetylsalicylic acid plus clopidogrel/ or *acetylsalicylic acid plus dipyridamole/ or *clopidogrel/ or *dipyridamole/ or *prasugrel/ or *ticagrelor/
2	aspirin.ti,ab.
3	(clopidogrel or plavix).ti,ab.
4	(ticagrelor or brilique).ti,ab.
5	(prasugrel or efient or effient or prasita).ti,ab.
6	(dipyridamole or persantin or asasantin).ti,ab.
7	(tirofiban or aggrastat).ti,ab.
8	(antiplatelet* or (platelet* adj2 (inhibit* or antagon*))).ti,ab.
9	*anticoagulant agent/ or *antivitamin k/ or *phenindione/
10	*coumarin anticoagulant/ or *acenocoumarol/ or *phenprocoumon/ or *warfarin/
11	*blood clotting factor 10a inhibitor/ or *apixaban/ or *rivaroxaban/
12	*thrombin inhibitor/ or *argatroban/ or *dabigatran/ or *dabigatran etexilate/
13	warfarin.ti,ab.
14	(acenocoumarol or phenprocoumon or phenidione or (vitamin k adj2 antagonist*)).ti,ab.
15	((factor xa adj2 inhibit*) or rivaroxaban or xarelto or apixaban or eliquis or dabigatran or

	pradaxa or argatroban or exembol).ti,ab.
16	or/1-15

Cochrane search terms

#1	MeSH descriptor: [Platelet Aggregation Inhibitors] this term only
#2	MeSH descriptor: [Aspirin] this term only
#3	MeSH descriptor: [Dipyridamole] this term only
#4	aspirin:ti,ab
#5	(clopidogrel or plavix):ti,ab
#6	(ticagrelor or brilique):ti,ab
#7	(prasugrel or efient or effient or prasita):ti,ab
#8	(dipyridamole or persantin or asasantin):ti,ab
#9	(tirofiban or aggrastat):ti,ab
#10	(antiplatelet* or (platelet* near/2 (inhibit* or antagon*))):ti,ab
#11	MeSH descriptor: [Anticoagulants] this term only
#12	MeSH descriptor: [Acenocoumarol] this term only
#13	MeSH descriptor: [Coumarins] this term only
#14	MeSH descriptor: [Phenindione] this term only
#15	MeSH descriptor: [Phenprocoumon] this term only
#16	MeSH descriptor: [Warfarin] this term only
#17	MeSH descriptor: [Antithrombins] this term only
#18	warfarin:ti,ab
#19	(acenocoumarol or phenprocoumon or phenidione or (vitamin k near/2 antagonist*)):ti,ab
#20	((factor xa near/2 inhibit*) or rivaroxaban or xarelto or apixaban or eliquis or dabigatran or pradaxa or argatroban or exembol):ti,ab
#21	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

F.3.5 Monitoring

What is the clinical and cost effectiveness of systematic monitoring of patients with AF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	Monitoring		SRs RCTs Observational (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

Monitoring search terms

Medline search terms

1	monitoring, physiologic/
2	drug monitoring/
3	"continuity of patient care"/
4	*self care/ or self administration/
5	ambulatory care facilities/ or community health centers/ or outpatient clinics, hospital/

6	patient-centered care/
7	*telemedicine/ and (monitor* or followup or follow-up).ti,ab.
8	*home care services/ and telemetry/ and (monitor* or followup or follow-up).ti,ab.
9	((followup or follow-up or outpatient or speciality or anticoagulation or anti-coagulation) adj3 (clinic or clinics* or appointment* or review* or monitor*)).ti,ab.
10	((open or drop-in) adj2 (clinic or clinics)).ti,ab.
11	(time in adj3 range).ti,ab.
12	((regular or short-term or frequent or frequency or infrequent or continuous or continual or intermittent or irregular or schedule or scheduled) adj3 (monitor* or followup* or follow-up* or review or reviews or checkup* or check-up*)).ti,ab.
13	((measur* or review* or check-up* or followup* or follow-up* or monitor*) adj6 (coagulation or rate or rhythmn) adj2 control).ti,ab.
14	((review* or check-up* or followup* or follow-up* or monitor*) adj3 (symptom* or asymptom*)).ti,ab.
15	(self-refer* or self-monitor* or self-test* or home-monitor*).ti,ab.
16	((maintenance or maintain*) adj3 (target range or therapeutic range or ttr or tir)).ti,ab.
17	(symptom* adj2 (diary or diaries)).ti,ab.
18	or/1-17

Embase search terms

1	((followup or follow-up or outpatient or speciality or anticoagulation or anti-coagulation) adj3 (clinic or clinics* or appointment* or review* or monitor*)).ti,ab.
2	((open or drop-in) adj2 (clinic or clinics)).ti,ab.
3	(time in adj3 range).ti,ab.
4	((regular or short-term or frequent or frequency or infrequent or continuous or continual or intermittent or irregular or schedule or scheduled) adj3 (monitor* or followup* or follow-up* or review or reviews or checkup* or check-up*)).ti,ab.
5	((measur* or review* or check-up* or followup* or follow-up* or monitor*) adj6 (coagulation or rate or rhythmn) adj2 control).ti,ab.
6	((review* or check-up* or followup* or follow-up* or monitor*) adj3 (symptom* or asymptom*)).ti,ab.
7	(self-refer* or self-monitor* or self-test* or home-monitor*).ti,ab.
8	((maintenance or maintain*) adj3 (target range or therapeutic range or TIR or TTR)).ti,ab.
9	(symptom* adj2 (diary or diaries)).ti,ab.
10	*patient monitoring/ or *ambulatory monitoring/ or *home monitoring/ or *self monitoring/ or *telemonitoring/
11	*drug monitoring/
12	*physiologic monitoring/
13	*outpatient care/
14	*outpatient department/
15	"evaluation and follow up"/
16	*aftercare/
17	*self care/
18	*drug self administration/
19	*community care/ or *health center/
20	*telemedicine/ and (monitor* or followup or follow-up).ti,ab.
21	or/1-20

Cochrane search terms

#1	MeSH descriptor: [Monitoring, Physiologic] this term only
#2	MeSH descriptor: [Drug Monitoring] this term only
#3	MeSH descriptor: [Continuity of Patient Care] this term only
#4	MeSH descriptor: [Self Care] this term only
#5	MeSH descriptor: [Self Administration] this term only
#6	MeSH descriptor: [Ambulatory Care Facilities] this term only
#7	MeSH descriptor: [Community Health Centers] this term only
#8	MeSH descriptor: [Outpatient Clinics, Hospital] this term only
#9	MeSH descriptor: [Patient-Centered Care] this term only
#10	((followup or follow-up or outpatient or speciality or anticoagulation or anti-coagulation) near/3 (clinic or clinics or appointment* or review or reviews or monitor*)):ti,ab
#11	((open or drop-in) next/2 (clinic or clinics)):ti,ab
#12	(("time in") next/3 range):ti,ab
#13	((regular or short-term or frequent or frequency or infrequent or continuous or continual or intermittent or irregular or schedule or scheduled) near/3 (monitor* or followup* or follow-up* or review or reviews or checkup* or check-up*)):ti,ab
#14	((measur* or review* or checkup* or check-up* or followup* or follow-up* or monitor*) near/6 (coagulation or rate or rhythmn) near/2 control):ti,ab
#15	((review* or checkup* or check-up* or followup* or follow-up* or monitor* or diary or diaries) near/3 (symptom* or asymptom*)):ti,ab
#16	(self-refer* or self-monitor* or self-test* or home-monitor*):ti,ab
#17	((maintenance or maintain*) near/3 ("therapeutic range" or "target range" or TTR or TIR)):ti,ab
#18	MeSH descriptor: [Telemedicine] this term only
#19	(followup* or follow-up* or monitor*):ti,ab
#20	#18 and #19
#21	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #20

F.3.6 Left Atrial Appendage Occlusion

What is the clinical and cost effectiveness of left atrial appendage occlusion compared to anti-thrombotic therapy in the prevention of stroke in people with AF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	LAAO		SRs RCTs (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

LAAO terms

Medline search terms

1	atrial appendage/
2	((heart or atrial or atrium or auricular) adj2 appendage* adj3 (occlu* or clip* or block* or exclu* or clos* or remov*)).ti,ab.
3	(laao or plaao or watchman or plaato).ti,ab.
4	or/1-3

Embase search terms

1	*heart atrium appendage/
2	((heart or atrial or atrium or auricular) adj2 appendage* adj3 (occlu* or clip* or block* or exclu* or clos* or remov*)).ti,ab.
3	(laao or plaao or watchman or plaato).ti,ab.
4	or/1-3

Cochrane search terms

#1	MeSH descriptor: [Atrial Appendage] this term only
#2	((heart or atrial or atrium or auricular) near/2 appendage* near/3 (occlu* or clip* or block* or exclu* or clos* or remov*)):ti,ab
#3	(laao or plaao or watchman or plaato):ti,ab
#4	#1 or #2 or #3

F.3.7 Rate

What is the clinical and cost-effectiveness of using different rate control drug strategies in the pharmacological management of AF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	Rate		SRs RCTs (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

Rate search terms

Medline search terms

1	exp digoxin/
2	(digoxin or lanoxin).ti,ab.
3	amiodarone/
4	(amiodarone or cordarone).ti,ab.
5	(dronedarone or multaq).ti,ab.
6	exp calcium channel blockers/
7	(calcium adj3 (block* or inhibit* or antagonist*)).ti,ab.
8	(amlodipine or amlostin or istin or exforge or diltiazem or optil or tildiem or adizem or angitil or calcicard or dilcardia or dilzem or slozem or viazem or zemtard or felodipine or cardioplen or felogen or felotens or keloc or neofel or parmid or vascalpha or plendil or isradipine or prescal or lacidipine or motens or lercanidipine or zanidip or nicardipine or cardene or nifedipine or adalat or adipine or coracten or fortipine or nifedipress or tensipine or valni or nimodipine or nimotop or verapamil or zolvera or cordilox or securon or univer or verapress or vertab).ti,ab.
9	exp adrenergic beta-antagonists/
10	((beta or b) adj3 (block* or antagonist*)).ti,ab.
11	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.

12	(rate adj2 (drug* or strateg*)).ti,ab.
13	or/1-12

Embase search terms

1	*digoxin/
2	(digoxin or lanoxin).ti,ab.
3	*amiodarone/
4	(amiodarone or cordarone).ti,ab.
5	*dronedarone/
6	(dronedarone or multaq).ti,ab.
7	exp *calcium channel blocking agent/
8	(calcium adj3 (block* or inhibit* or antagonist*)).ti,ab.
9	(amlodipine or amlostin or istin or exforge or diltiazem or optil or tildiem or adizem or angitil or calcicard or dilcardia or dilzem or slozem or viazem or zemtard or felodipine or cardioplen or felogen or felotens or keloc or neofel or parmid or vascalpha or plendil or isradipine or prescal or lacidipine or motens or lercanidipine or zanidip or nicardipine or cardene or nifedipine or adalat or adipine or coracten or fortipine or nifedipress or tensipine or valni or nimodipine or nimotop or verapamil or zolvera or cordilox or securon or univer or verapress or vertab).ti,ab.
10	exp *beta adrenergic receptor blocking agent/
11	((beta or b) adj3 (block* or antagonist*)).ti,ab.
12	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
13	(rate adj2 (drug* or strateg*)).ti,ab.
14	or/1-13

Cochrane search terms

#1	MeSH descriptor: [Digoxin] explode all trees
#2	(digoxin or lanoxin):ti,ab
#3	MeSH descriptor: [Amiodarone] this term only
#4	(amiodarone or cordarone):ti,ab
#5	(dronedarone or multaq):ti,ab
#6	MeSH descriptor: [Calcium Channel Blockers] explode all trees
#7	(calcium near/3 (block* or inhibit* or antagonist*)):ti,ab
#8	(amlodipine or amlostin or istin or exforge or diltiazem or optil or tildiem or adizem or angitil or calcicard or dilcardia or dilzem or slozem or viazem or zemtard or felodipine or cardioplen or felogen or felotens or keloc or neofel or parmid or vascalpha or plendil or isradipine or prescal or lacidipine or motens or lercanidipine or zanidip or nicardipine or cardene or nifedipine or adalat or adipine or coracten or fortipine or nifedipress or tensipine or valni or nimodipine or nimotop or verapamil or zolvera or cordilox or securon or univer or verapress or vertab):ti,ab
#9	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#10	((beta or b) near/3 (block* or antagonist*)):ti,ab
#11	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard

	or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim):ti,ab
#12	(rate near/2 (drug* or strateg*)):ti,ab
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

F.3.8 Rhythm

Searches for the following three questions were run as one search:

What is the most clinical and cost effective antiarrhythmic drug alone or in combination for maintaining sinus rhythm in (a) paroxysmal AF and (b) persistent AF after cardioversion?

What is the most clinical and cost effective means of (excluding ablation) restoring sinus rhythm (a) pharmacological cardioversion, (b) electrical cardioversion or (c) electrical cardioversion combined with antiarrhythmic drugs?

What is the clinical and cost effectiveness of rhythm control (excluding ablation) compared to rate control in the treatment of AF in reducing stroke or improving prognosis?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	Rhythm		SRs RCTs (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

Rhythm search terms

Medline search terms

1	anti-arrhythmia agents/
2	(rhythm adj2 (control* or strateg*)).ti,ab.
3	flecainide/
4	(flecainide or flecanide).ti,ab.
5	propafenone/
6	(propafenone or propafanone or propiophenones).ti,ab.
7	amiodarone/
8	(amiodarone or cordarone).ti,ab.
9	exp adrenergic beta-antagonists/
10	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
11	((beta or b) adj3 (block* or antagonist*)).ti,ab.
12	(dronedarone or multaq).ti,ab.
13	exp calcium channel blockers/
14	(calcium adj3 (block* or inhibit* or antagonist*)).ti,ab.
15	(diltiazem or optil or tildiem or adizem or angitil or calcicard or dilcardia or dilzem or slozem or viazem or zemtard or verapamil or zolvera or cordilox or securon or univer or verapress or vertab).ti,ab.

16	exp digoxin/
17	(digoxin or lanoxin).ti,ab.
18	disopyramide/
19	(disopyramide or rythmodan).ti,ab.
20	(vernakalant or vernakalent).ti,ab.
21	magnesium sulfate/
22	magnesium.ti,ab.
23	(cardiovert* or cardioversion*).ti,ab.
24	electric countershock/
25	(electroversion* adj1 (cardiac or therap*)).ti,ab.
26	((countershock* or conversion*) adj1 (electr* or dc)).ti,ab.
27	or/1-26
28	exp pacemaker, artificial/
29	(pacemaker* or pace maker*).ti,ab.
30	or/28-29
31	(rhythm or rate).ti,ab.
32	30 and 31
33	27 or 32

Embase search terms

1	*antiarrhythmic agent/
2	(rhythm adj2 (control* or strateg*)).ti,ab.
3	*flecainide/
4	(flecainide or flecanide).ti,ab.
5	*propafenone/
6	(propafenone or propafanone or propiophenones).ti,ab.
7	*amiodarone/
8	(amiodarone or cordarone).ti,ab.
9	exp *beta adrenergic receptor blocking agent/
10	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
11	((beta or b) adj3 (block* or antagonist*)).ti,ab.
12	*dronedarone/
13	(dronedarone or multaq).ti,ab.
14	exp *calcium channel blocking agent/
15	(calcium adj3 (block* or inhibit* or antagonist*)).ti,ab.
16	(diltiazem or optil or tildiem or adizem or angitil or calcicard or dilcardia or dilzem or slozem or viazem or zemtard or verapamil or zolvera or cordilox or securon or univer or verapress or vertab).ti,ab.
17	*digoxin/
18	(digoxin or lanoxin).ti,ab.
19	*disopyramide/
20	(disopyramide or rythmodan).ti,ab.

21	*vernakalant/
22	(vernakalant or vernakalent).ti,ab.
23	*magnesium sulphate/
24	magnesium.ti,ab.
25	*cardioversion/
26	(cardiovert* or cardioversion*).ti,ab.
27	(electroversion* adj1 (cardiac or therap*)).ti,ab.
28	((countershock* or conversion*) adj1 (electr* or dc)).ti,ab.
29	or/1-28
30	exp *pacemaker/
31	(pacemaker* or pace maker*).ti,ab.
32	or/30-31
33	(rhythm or rate).ti,ab.
34	32 and 33
35	29 or 34

Cochrane search terms

#1	MeSH descriptor: [Anti-Arrhythmia Agents] this term only
#2	(rhythm near/2 (control* or strateg*)):ti,ab
#3	MeSH descriptor: [Flecainide] explode all trees
#4	(flecainide or flecanide):ti,ab
#5	MeSH descriptor: [Propafenone] this term only
#6	(propafenone or propafanone or propiophenones):ti,ab
#7	MeSH descriptor: [Amiodarone] this term only
#8	(amiodarone or cordarone):ti,ab
#9	MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#10	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim):ti,ab
#11	((beta or b) near/3 (block* or antagonist*)):ti,ab
#12	(dronedarone or multaq):ti,ab
#13	MeSH descriptor: [Calcium Channel Blockers] explode all trees
#14	(calcium near/3 (block* or inhibit* or antagonist*)):ti,ab
#15	(diltiazem or optil or tildiem or adizem or angitil or calcicard or dilcardia or dilzem or slozem or viazem or zemtard or verapamil or zolvera or cordilox or securon or univer or verapress or vertab):ti,ab
#16	MeSH descriptor: [Digoxin] explode all trees
#17	(digoxin or lanoxin):ti,ab
#18	MeSH descriptor: [Disopyramide] this term only
#19	(disopyramide or rythmodan):ti,ab
#20	(vernakalant or vernakalent):ti,ab
#21	MeSH descriptor: [Magnesium Sulfate] this term only
#22	magnesium:ti,ab
#23	MeSH descriptor: [Electric Countershock] this term only

#24	(cardiovert* or cardioversion*):ti,ab
#25	(electroversion* near (cardiac or therap*)):ti,ab
#26	((countershock* or conversion*) near (electr* or dc)):ti,ab
#27	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28	MeSH descriptor: [Pacemaker, Artificial] explode all trees
#29	(pacemaker* or pace maker*):ti,ab
#30	#28 or #29
#31	(rhythm or rate):ti,ab
#32	#30 and #31
#33	#27 or #32

F.3.9 Ablation

Searches for the following three questions were run as one search:

What is the clinical and cost-effectiveness of surgical ablation compared to non ablation therapies?

What is the clinical and cost-effectiveness of percutaneous catheter ablation compared to non ablation therapies?

What is the clinical and cost-effectiveness of surgical ablation compared to catheter ablation in people with AF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	Ablation		SRs RCTs (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

Ablation search terms

Medline search terms

1	exp ablation techniques/
2	catheter ablation/
3	microwaves/
4	ablat*.ti,ab.
5	((high intens* adj6 focus* ultrasound) or epicor or hifu).ti,ab.
6	(radiofrequency or rfa).ti,ab.
7	(cryotherap* or cryoablat*).ti,ab.
8	((maze or cox-maze) adj2 (surg* or procedure*)).ti,ab.
9	thoracic surgery, video-assisted/
10	((video* adj3 (thoracic surger* or thoracoscop*)) or vats or vatss).ti,ab.
11	or/1-10

Embase search terms

1	ablation therapy/
2	catheter ablation/
3	radiofrequency ablation/

4	cryoablation/
5	microwave therapy/
6	ablat*.ti,ab.
7	((high intens* adj6 focus* ultrasound) or epicor or hifu).ti,ab.
8	(radiofrequency or rfa).ti,ab.
9	(cryotherap* or cryoablat*).ti,ab.
10	((maze or cox-maze) adj2 (surg* or procedure*)).ti,ab.
11	((video* adj3 (thoracic surger* or thoracoscop*)) or vats or vatss).ti,ab.
12	*thoracoscopy/
13	or/1-12

Cochrane search terms

#1	MeSH descriptor Ablation Techniques explode all trees
#2	MeSH descriptor Microwaves, this term only
#3	ablat*:ti,ab
#4	((high intens* NEAR/6 focus* ultrasound) or epicor or hifu):ti,ab
#5	(radiofrequency or rfa):ti,ab
#6	(cryotherap* or cryoablat*):ti,ab
#7	((maze or cox-maze) near/2 (surg* or procedure*)):ti,ab
#8	MeSH descriptor: [Thoracic Surgery, Video-Assisted] this term only
#9	((video* near/3 (thoracic surger* or thoracoscop*)) or vats or vatss):ti,ab
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)

F.3.10 Pace and ablate

What is the clinical and cost-effectiveness of atrioventricular junction ablation and pacing compared to usual care in the treatment of AF?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation	Pace and ablate		SRs RCTs (Filters were applied in Medline and Embase only)	No date restriction. Searches run up to 3 October 2013

Pace and ablate search terms

Medline search terms

1	(atrioventric* adj3 (ablat* or modif*)).ti,ab.
2	(pace or pacing or pacemaker*).ti,ab.
3	1 and 2
4	(ablat* and pace).ti,ab.
5	or/3-4
6	((biventricul* or bi-ventricul* or ((dual or double) adj chamber*) or ((AV or atrioventricular) adj (synchron* or sequential)) or ddd or dddr or ddi or ddir or vdd or vddr or vdi or vdir) adj3 (pace or pacing or pacemaker*)).ti,ab.
7	((dual or physiologic*) adj pac*).ti,ab.
8	or/6-7

9	((single or atrial or ventricular) adj pac*).ti,ab.
10	(((single adj (chamber or ventricul*)) or vvi or vvir or aai or aair) adj3 (pace or pacing or pacemaker*)).ti,ab.
11	or/9-10
12	8 and 11
13	cardiac resynchroni#ation therap*.ti,ab.
14	exp pacemaker, artificial/
15	exp cardiac pacing, artificial/
16	or/13-15
17	5 or 12 or 16

Embase search terms

1	(atrioventric* adj3 (ablat* or modif*)).ti,ab.
2	*atrioventricular nodal ablation/
3	or/1-2
4	(pace or pacing or pacemaker*).ti,ab.
5	3 and 4
6	(ablat* and pace).ti,ab.
7	or/5-6
8	((biventricul* or bi-ventricul* or ((dual or double) adj chamber*) or ((AV or atrioventricular) adj (synchron* or sequential)) or ddd or dddr or ddi or ddir or vdd or vddr or vdi or vdir) adj3 (pace or pacing or pacemaker*)).ti,ab.
9	((dual or physiologic*) adj pac*).ti,ab.
10	or/8-9
11	((single or atrial or ventricular) adj pac*).ti,ab.
12	(((single adj (chamber or ventricul*)) or vvi or vvir or aai or aair) adj3 (pace or pacing or pacemaker*)).ti,ab.
13	or/11-12
14	10 and 13
15	cardiac resynchroni#ation therap*.ti,ab.
16	exp *pacemaker/
17	exp *heart pacing/
18	or/15-17
19	7 or 14 or 19

Cochrane search terms

#1	(atrioventric* NEAR/3 (ablat* or modif*)):ti,ab
#2	(pace or pacing or pacemaker*):ti,ab
#3	(#1 AND #2)
#4	(ablat* AND pace):ti,ab
#5	(#3 OR #4)
#6	((biventricul* or bi-ventricul* or ((dual or double) NEAR chamber*) or ((AV or atrioventricular) NEAR (synchron* or sequential)) or ddd or dddr or ddi or ddir or vdd or vddr or vdi or vdir) NEAR/3 (pace or pacing or pacemaker*)):ti,ab
#7	((dual or physiologic*) NEAR pac*):ti,ab
#8	((single or atrial or ventricular) NEAR pac*):ti,ab
#9	(((single NEAR (chamber or ventricul*)) or vvi or vvir or aai or aair) NEAR/3 (pace or pacing or pacemaker*)):ti,ab

#10	(#6 OR #7)
#11	(#8 OR #9)
#12	(#10 AND #11)
#13	MeSH descriptor Pacemaker, Artificial explode all trees
#14	MeSH descriptor Cardiac Pacing, Artificial explode all trees
#15	(cardiac resynchroni?ation therap*):ti,ab
#16	(#13 OR #14 OR #15)
#17	(#5 OR #12 OR #16)

F.4 Economics search

F.4.1 Economics search

Economic searches were conducted in Medline, Embase, HEED, and CRD for NHS EED and HTA.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation			Economic (Medline and Embase only	Medline and Embase 2010. HEED, CRD EED and HTA no date restriction. Searches run up to 3 October 2013

CRD search terms

#1	MeSH DESCRIPTOR atrial fibrillation IN NHSEED,HTA
#2	((atrial near3 fibrillat*) OR (auricular near3 fibrillat*) OR (supraventricul* near3 *arrhythmia*)) IN NHSEED, HTA
#3	#1 OR #2

HEED search terms

1	ax=atrial or auricular or supraventricul*
2	ax=fibrillat* or arrhythmi*
3	cs=1 and 2

F.4.2 Quality of life search

Quality of life searches were conducted in Medline and Embase.

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Atrial fibrillation			Quality of life	No date restriction. Searches run up to 3 October 2013

Appendix G: Clinical evidence tables

G.1 Diagnosis

See previous guideline (CG36) in Appendix S.

G.2 Education

Table 1: Clarkesmith 2013[216]

Study (subsidiary papers)	**Clarkesmith 2013{CLARKESMITH2013} (Beyth 2000{BEYTH2000}, Christensen 2006{CHRISTENSEN2006}, Christensen 2007{CHRISTENSEN2007}, Gadisseur 2003{GADISSEUR2003}, Gadisseur 2004{GADISSEUR2004}, Man-son-hing 1999{MANSONHING1999}, Mcalister 2005{MCALISTER2005}, Polek 2012{POLEK2012}, Thomson 2007{THOMSON2007}, Voller 2000{VOLLER2000}, Voller 2005{VOLLER2005})**
Study type	Systematic Review
Number of studies (number of participants)	8 (n=1067)
Countries and setting	Conducted in Canada, Denmark, Germany, Multiple countries, Netherlands, United Kingdom, USA; Setting: Most of the trials were set in a hospital or anticoagulation clinic setting. One study took place in GP practices, another in a research clinic and one of the trials did not describe the intervention setting
Line of therapy	Adjunctive to current care
Duration of study	Other: Any length of follow up time was included
Method of assessment of guideline condition	Systematic review: method of assessment mixed: Does not report methods
Stratum	Overall
Subgroup analysis within study	Not applicable: None
Inclusion criteria	Varied across included studies
Exclusion criteria	Varied across included studies
Recruitment/selection of patients	Systematic review - no additional details on patient selection
Age, gender and ethnicity	Age - Mean (range): Range from 59 to 75 years. Gender (M:F): 64/36 (average across studies). Ethnicity: Not stated
Extra comments	People with atrial fibrillation. Four of the eight studies included patients with indications for anticoagulants other than

Study (subsidiary papers)	**Clarkesmith 2013{CLARKESMITH2013} (Beyth 2000{BEYTH2000}, Christensen 2006{CHRISTENSEN2006}, Christensen 2007{CHRISTENSEN2007}, Gadisseur 2003{GADISSEUR2003}, Gadisseur 2004{GADISSEUR2004}, Man-son-hing 1999{MANSONHING1999}, Mcalister 2005{MCALISTER2005}, Polek 2012{POLEK2012}, Thomson 2007{THOMSON2007}, Voller 2000{VOLLER2000}, Voller 2005{VOLLER2005})**
	AF. The Cochrane review obtained unpublished data from the authors to provide the outcomes for the sub-set of AF patients only. None
Indirectness of population	No indirectness: None
Interventions	(n=15) Intervention 1: Education - Education (videos, literature, talking interventions). Educational intervention for anticoagulation control. Duration Varied duration among trials. Concurrent medication/care: No additional information Comments: None (n=651) Intervention 2: Usual care. Defined as standard anticoagulation clinic practice, where patients attended routine INR checks (defined as usual care by authors). Duration any follow up was included. Concurrent medication/care: No additional information Comments: Total for comparison with self-monitoring and education=180; education=52 and decision aids=419 (n=145) Intervention 3: Self-monitoring and education. Self-monitoring plus education. Duration Varied among studies. Concurrent medication/care: No additional information - varied within studies (n=411) Intervention 4: Decision aids. Decision aid support. Duration Varied among studies. Concurrent medication/care: No additional information
Funding	Cochrane. 3 of the 8 included trials declared some funding input from industry

RESULTS (NUMBERS ANALYSED): SELF MONITORING AND EDUCATION versus USUAL CARE

Protocol outcome 1: % of INR in therapeutic range
- Actual outcome: Proportion of time spent in therapeutic range: MD: 6.31 (-5.63, 18.25)

Protocol outcome 2: Thromboembolic events:
- Actual outcome: Stroke or thromboembolic events: Group 1: 1/128; Group 2: 3/128

Study (subsidiary papers)	Clarkesmith 2013{CLARKESMITH2013} (Beyth 2000{BEYTH2000}, Christensen 2006{CHRISTENSEN2006}, Christensen 2007{CHRISTENSEN2007}, Gadisseur 2003{GADISSEUR2003}, Gadisseur 2004{GADISSEUR2004}, Man-son-hing 1999{MANSONHING1999}, Mcalister 2005{MCALISTER2005}, Polek 2012{POLEK2012}, Thomson 2007{THOMSON2007}, Voller 2000{VOLLER2000}, Voller 2005{VOLLER2005})
RESULTS (NUMBERS ANALYSED): EDUCATION versus USUAL CARE Protocol outcome 3: % of INR in therapeutic range - Actual outcome: Proportion of time spent in therapeutic range: MD: 7.90 (-6.02,21.82) Protocol outcome 4: Knowledge and understanding: - Actual outcome: Knowledge: MD: 1.10 (-0.69, 2.89) RESULTS (NUMBERS ANALYSED): DECISION AIDS versus USUAL CARE Protocol outcome 5: Hospitalisation - Actual outcome: Hospitalisation: Group 1: 3/53; Group 2: 4/56 Protocol outcome 6: Decision conflict: - Actual outcome: Decision conflict: MD: -0.10 (-0.17, -0.02) Protocol outcome 7: Knowledge and understanding: - Actual outcome: Knowledge – warfarin related: MD: 14.9 (4.60, 25.20)	
Protocol outcomes not reported by the study	Anxiety; Quality of life at Longest endpoint

Table 2: Clarkesmith 2013[217]

Study	Clarkesmith 2013{CLARKESMITH2013A}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=97)
Countries and setting	Conducted in United Kingdom; Setting: Specialist AF/local anticoagulation clinic
Line of therapy	1st line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients attending a specialist AF clinical or local anticoagulation outpatient clinic; documented AF; warfarin naive; accepting of OAC therapy.
Exclusion criteria	Age<18 years; any contraindication to warfarin; previous treatment with warfarin; valvular heart disease; cognitive impairment/ dementia; unable to speak or read English; any disease likely to cause death within the subsequent 12 months.
Age, gender and ethnicity	Age - Mean (SD): intervention: 72 (8.2); control: 73.7 (8.1). Gender (M:F): Intervention: 67.4% male; control: 62.7% male. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Self-monitoring and education. Patients attended one group session (between 1 and 6 patients)for one hour where they were shown a DVD of information about the need for OAC, the risks and benefits associated with OAC therapy, potential interactions with food, drugs and alcohol, and the importance of monitoring and control of their INR. The intervention was developed following discussion with AF patient focus groups and patient interviews and was communicated in a variety of ways (i.e. by expert patients, a cardiology consultant, other healthcare professionals and examples of food/ alcohol dietary components with educational information as a voiceover script). Patients were encouraged to ask questions and complete a worksheet-based exercise following each 10 minute DVD section.. Duration 12 months. Concurrent medication/care: All patients were on OAC therapy. (n=51) Intervention 2: Usual care. All patients received the standard 'yellow booklet' to identify that they are taking OAC therapy. This book contains generic information for all patients taking OAC and includes key safety information including dietary advice, medication and emergency contact details.. Duration 12 months. Concurrent

	medication/care: OAC therapy
Funding	Other (Bayer Healthcare and the University of Birmingham Centre for Cardiovascular Sciences and Aston University.)
RESULTS (NUMBERS ANALYSED): SELF MONITORING AND EDUCATION versus USUAL CARE Protocol outcome 12: Anxiety - Actual outcome: HADs anxiety at 12 months: median IQR: Group 1: 9 (7-12); Group 2: 11 (9-12.7)	
Protocol outcomes not reported by the study	Hospitalisation at Longest endpoint; TTR at Longest endpoint; Stroke and thromboembolic events at Longest endpoint; Decision conflict; Knowledge and understanding; Quality of life at Longest endpoint

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease;; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.3 Referral

Table 3: Hendriks 2012 [434]

Study	Hendriks 2012{HENDRIKS2012}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=712)
Countries and setting	Conducted in Netherlands; Setting: Outpatient care in Maastricht University Medical Centre, Netherlands
Line of therapy	Mixed line
Duration of study	Intervention + follow up: Follow up at least 12 months (mean 22 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: AF documented on an electrocardiogram
Stratum	People with AF
Subgroup analysis within study	Not applicable
Inclusion criteria	All adults referred for newly diagnosed AF documented on an electrocardiogram
Exclusion criteria	Patients excluded in case of any co-morbidity which is unsatisfactorily treated including; unstable and uncontrolled hypertension, unstable heart failure defined as NYHA IV or necessitating hospital admission less than 3 months before inclusion, untreated hyperthyroidism, current or foreseen pacemaker, internal cardioverter defibrillator or cardio resynchronisation therapy, or cardiac surgery less than 3 months before inclusion.
Recruitment/selection of patients	All patients referred for AF by GP or non-cardiology specialists to the outpatient department, Maastricht University Medical Centre between January 2007 and December 2008
Age, gender and ethnicity	Age - Mean (SD): 67 years. Gender (M:F): 418/294 (59%/41%). Ethnicity: Dutch
Indirectness of population	No indirectness
Interventions	(n=356) Intervention 1: Referral to specialist AF services - Specialist service. Care provided in the AF clinic was based on the chronic care model, consisting of nurse-led outpatient care steered by decision support software based on the guidelines and supervised by a cardiologist. Before the first visit patients underwent laboratory testing, electrocardiogram, holter monitoring and echocardiography. At first visit, a nurse specialist took the patients history and informed them about the pathophysiology of AF, its symptoms and possible complications, the results of the diagnostic tests and treatment options. Software determined the individual patient profile based on symptoms, type of AF and stroke risk. At the end of the consultation the nurse specialist was supervised by a cardiologist, endorsing the proposed diagnosis and treatments. Visits to the nurse were scheduled to last 30 minutes. Follow up visits were planned at 3, 6 and 12 months and every 6 months after. Patients could contact the nurse between planned visits. During follow up visits psychosocial support and educational interventions were repeated. Duration At least 12 months.

Study	Hendriks 2012{HENDRIKS2012}
	Concurrent medication/care: All medical records were reviewed for major adverse events and hospitalisation after 1 and 2 years and at end of follow-up. Comments: None (n=356) Intervention 2: Routine management. Usual care by a cardiologist in the outpatient clinic during visits scheduled to last 20 minutes for the first visit and 10 minutes for follow-up visits. During follow-up visits, patients were questioned for major adverse events and hospitalisations. Duration At least 12 months. Concurrent medication/care: All medical records were reviewed for major adverse events and hospitalisation after 1 and 2 years and at end of follow-up. Comments: None
Funding	Study funded by industry (Supported by the University Hospital Maastricht as well as unrestricted educational grants from Boehringer-Ingelheim and Medtronic Bakken Research Centre.)
RESULTS (NUMBERS ANALYSED): SPECIALIST SERVICE versus ROUTINE MANAGEMENT Protocol outcome 1: Rehospitalisation at Latest follow-up - Actual outcome for People with AF: Cardiovascular hospitalisation at Mean 22 months; HR 0.66 (95%CI 0.46 to 0.96) Reported Protocol outcome 2: Adherence to guidelines at Latest follow-up - Actual outcome for People with AF: Adherence to six guidelines recommendations at Mean 22 months; Group 1: 292/356, Group 2: 135/356 Protocol outcome 3: Mortality at Latest follow-up - Actual outcome for People with AF: Cardiovascular mortality at Mean 22 months; HR 0.28 (95%CI 0.09 to 0.85) Reported Protocol outcome 4: Stroke or thromboembolic complications at Latest follow-up - Actual outcome for People with AF: Stroke or thromboembolic complications at Mean 22 months; Group 1: 4/356, Group 2: 11/356	
Protocol outcomes not reported by the study	Disease awareness at Latest follow-up; Health related quality of life at Latest follow-up; Number of patients referred to anticoagulation clinic at Latest follow-up

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease;; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease;

PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.4 Stroke risk tools

Table 4: Baruch 2007[76]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Baruch 2007[76] Country of study: Sweden Study design: Randomised multicentre, parallel-group trials (SPORTIF III and SPORTIF V) Setting: NR Duration of follow-up: 11245 patient years follow-up (mean, 1.5 years/patient)	Patient group: Patients with a diagnosis of AF. Inclusion criteria: Non-valvular chronic or paroxysmal AF patients at high risk of stroke based on ACCP 2001 AF guideline recommendations. Exclusion criteria: Not stated. N: 7329 Age (mean): 76.2 years M/F: 53% male Anticoagulation - Yes, warfarin or ximelagatran.	$CHADS_2$ CHA_2DS_2-VASc ACC/AHA/ESC NICE 2006	**Ischaemic stroke**	159 (1.4 per 100 patient years)	Funding: AstraZeneca, MoIndal, Sweden. Limitations: Authors note that SPORTIF did not have an adequate sample size for low-risk cohorts - impairing the performance of all risk schemes to discriminate risk. Notes: Authors note no difference in hazard ratios or c statistics for warfarin or ximelagatran.
			$CHADS_2$ (1 - 2 points = moderate risk) - 3 strata continuous		
			C statistic	0.65	
			Hazard ratio (95% CI)	2.44 (1.80 - 3.32)	
			P (Hazard ratio)	<0.0001	
			$CHADS_2$ cont.		
			Hazard ratio (95% CI)	1.48 (1.31 - 1.66)	
			C statistics		
			ACCP 2001	0.51	
			ACCP 2004	0.51	

Table 5: Coppens[237]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Coppens 2013[237] Country of study: Multinational Study design: Prospective cohort Setting: Hospital Duration of follow-up: 2.5 years (SD = 1.4 years)	Patient group: Patients with a diagnosis of AF and a $CHADS_2$ score of 1. Inclusion criteria: Patients with a diagnosis of AF and a $CHADS_2$ score of 1 treated with ASA or ASA and clopidogrel from 3 previous trials (AVERROES< ACTIVE-W and ACTIVE-A). Exclusion criteria: Indication for VKAs other than AF, or an indication for clopidogrel, valvular disease requiring surgery, or a high risk of bleeding. AVERROES also excluded patients with severe renal failure or liver transaminases greater than 2 times the upper limit of normal. Daily dose of ASA in ACTIVE and AVERROES 75 - 324mg. Clopidogrel fixed does of 75mg daily in ACTIVE. N: 4670 (2240 - ASA, 2430 - ASA and clopidogrel. Mean age (SD): 65.5 (9) years M/F: 34% female	$CHADS_2$ CHA_2DS_2-VASc	**Ischaemic or non-specified stroke and non-CNS embolus.** Incidence rate, per 100 patient years	205/4670 (11414 patient follow up years) 1.8 (1.6 - 2.1)	Funding: ACTIVE and AVERROES supported by Sanofi-Aventis, Bristol-Myers Squibb and Pfizer. Limitations: none Notes: Stroke was a clinical diagnosis made on the basis of typical symptoms lasting at least 24h.
			CHA_2DS_2-VASc, events per score 1 2 3 - 4	 27/1224 92/1984 86/1462	
			Hazard ratio (95% CI) CHA_2DS_2-VASc, events per score 1 2 3 - 4 C statistic	 1 2.2 (1.5 - 3.5) 2.7 (1.8 - 4.3) 0.587 (0.55 - 0.624)	
			Hazard ratio (95% CI) CHA_2DS_2-VASc, events per score 1 2 - 4 C statistic NRI (95% CI)	 1 2.5 (1.7 - 3.8) 0.567 (0.541 - 0.592) 0.27 (0.11 - 0.41)	

Table 6: Fang 2008[326]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Fang 2008[326] Country of study: USA Study design: Prospective cohort Setting: Californian hospitals Duration of follow-up: median of 6 years (IQR of 31 - 6.7)	Patient group: Adults with a diagnosis of AF enrolled in ATRIA (Anticoagulation and risk factors in atrial fibrillation) study. Inclusion criteria: Adults with non-valvular AF who received care within Kaiser Permanente of North California. Patients included from July 1996 to December 1997 using automated inpatient, outpatient and electrocardiographic databases for diagnosis of AF. Exclusion criteria: Patients with mitral stenosis, documented valvular repair or replacement transient post-operative AF, or concurrent hyperthyroidism. N: 13559 (10932 had periods of time when they did not take warfarin, 5588 not on warfarin at baseline and with continuous follow-up off warfarin for at least 12 months.) Age (mean): 72 years M/F: 43.3% male	$CHADS_2$ (1 - 2 = moderate) ACCP 7th ACCP (age 65 - 75yr + no other risk factors = moderate) (AFI, SPAF and Framingham also reported, but not extracted).	**Thromboembolic events** Ischemic stroke Peripheral emboli	685 (during 32721 person years off warfarin therapy) 643 42	Funding: Supported by Public Health services research grant from the National Institute on Aging, the Eliot B and Edith C Shoolman Fund of Massachusetts General Hospital, a Hartford Geriatrics Health Outcomes Research Scolars Award from the American Geriatrics Society Foundation for Health in Aging from the National Institute on Aging. Limitations: none Notes: Ischaemic stroke identified as neurological deficits of sudden onset that persisted for more than 24hours and were not explained by other aetiologies. Events excluded if occurred during hospitalisation or as a complication from a diagnostic or interventional procedure. Thromboembolic events only included if they occurred when off warfarin.
			C-statistic - all patients (thromboembolism) - 3 strata continuous $CHADS_2$ 7th ACCP	 0.58 0.56	
			C-statistic - not on warfarin(thromboembolism) n = 5588 **3 strata continuous** $CHADS_2$ 7th ACCP	 0.67 0.60	
			Sensitivity analysis - c-statistic $CHADS_2$ cont $CHADS_2$ 3 category score	 0.6 0.58	

Table 7: Friberg 2012[352]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Friberg 2012B[352] Country of study: Sweden Study design: Retrospective cohort Setting: Swedish hospitals Duration of follow-up: 1.4 years (IQR = 1.8 years)	Patient group: Patients with a diagnosis of AF. Inclusion criteria: Patients with a diagnosis of AF identified through the Swedish National Hospital Discharge Registry (July 2005 - December 2008) Exclusion criteria: Patients with 'silent' AF and AF who were taken care of in the primary care or other open clinics not affiliated with a hospital during follow-up. N: 170291 Age (mean): 76.2 years M/F: 53% male Never used warfarin: 90490 Warfarin at index: 68307 Began warfarin during follow-up: 12498 Stopped warfarin during follow-up: 3956 Exclusions: 7167 = died in conjunction with the index generating hospital contact 528 = patients with valvular AF	$CHADS_2$ CHA_2DS_2-VASc ACC/AHA/ESC NICE 2006 (also reported, but not extracted: AF investigators, SPAF, Framingham)	**<u>Ischaemic stroke (without anticoagulation)</u>** *<u>CHA_2DS_2-VASc (cont.)</u>* C-statistic (95% CI) *<u>CHA_2DS_2-VASc</u>* C-statistic (95% CI) Sensitivity Specificity *<u>$CHADS_2$ (cont.)</u>* C-statistic (95% CI) *<u>$CHADS_2$</u> (0 = low, 1 - 2 = intermediate, >2 = high risk)* C-statistic (95% CI) Sensitivity Specificity NRI (ref CHA_2DS_2-VASc) *<u>$CHADS_2$</u> (0 = low, 1 = intermediate, <u>≥</u>2 = high risk)* C-statistic (95% CI) Sensitivity Specificity NRI (ref CHA_2DS_2-VASc) *<u>ACC/AHA/ESC</u>*	 0.67 (0.66 - 0.68) 0.56 (0.56 - 0.57) 1.00 0.06 0.66 (0.66 - 0.67) 0.62 (0.61 - 0.62) 0.98 0.15 0.07 0.65 (0.64 - 0.65) 0.98 0.15 0.07	Funding: NR Grants from Swedish Heart and Lung Foundation, The Stockholm County Council and the Board of Benevolence of the Swedish Order of Freemasons. Limitations: none Notes: Events within 14 days of the index date were not counted due to likely to have been given at discharge of hospital period that started with an event.

	due to mitral stenosis 5112: valvular surgery.		C-statistic (95% CI) Sensitivity Specificity *NICE 2006* C-statistic (95% CI) Sensitivity Specificity	0.62 (0.61 - 0.62) 0.98 0.15 0.61 (0.60 - 0.62) 1.00 0.09	
			Stroke/TIA/systemic emboli (without anticoagulation) *CHA_2DS_2-VASc (cont.)* C-statistic (95% CI) *CHA_2DS_2-VASc* C-statistic (95% CI) Sensitivity Specificity *$CHADS_2$ (cont.)* C-statistic (95% CI) *$CHADS_2$ (0 = low, 1 - 2 = intermediate, >2 = high risk)* C-statistic (95% CI) Sensitivity Specificity *$CHADS_2$ (0 = low, 1 = intermediate, ≥2 = high risk)* C-statistic (95% CI) Sensitivity Specificity	 0.67 (0.67 - 0.68) 0.56 (0.56 - 0.57) 1.00 0.07 0.66 (0.65 - 0.66) 0.61 (0.61 - 0.62) 0.97 0.16 0.64 (0.64 - 0.65) 0.97 0.16	

			ACC/AHA/ESC	
			C-statistic (95% CI)	0.62 (0.61 - 0.62)
			Sensitivity	0.98
			Specificity	0.16
			NICE 2006	
			C-statistic (95% CI)	0.61 (0.60 - 0.62)
			Sensitivity	1.00
			Specificity	0.09
			Event rates/100 years at risk - (without anticoagulation)	
			Ischaemic stroke	
			CHA_2DS_2-VASc	
			Low	0.2
			Intermediate	0.6
			High	6.2
			$CHADS_2$ (0 = low, 1 - 2 = intermediate, >2 = high risk)	
			Low	0.6
			Intermediate	3.6
			High	9.0
			$CHADS_2$ (0 = low, 1 = intermediate, ≥2 = high risk)	
			Low	0.6
			Intermediate	3.0
			High	6.6
			ACC/AHA/ESC	
			Low	0.6
			Intermediate	2.8

			High *NICE 2006* Low Intermediate High	6.6 0.2 2.2 6.4	

			Event rates/100 years at risk - <u>(without anticoagulation)</u> ***<u>Stroke/TIA/systemic emboli</u>*** *<u>CHA_2DS_2-VASc</u>* Low Intermediate High *<u>$CHADS_2$</u> (0 = low, 1 - 2 = intermediate, >2 = high risk)* Low Intermediate High *<u>$CHADS_2$</u> (0 = low, 1 = intermediate, <u>≥</u>2 = high risk)* Low Intermediate High *<u>ACC/AHA/ESC</u>* Low Intermediate High *<u>NICE 2006</u>* Low Intermediate High	 0.3 1.0 8.9 0.9 5.2 12.3 0.9 4.3 9.1 0.8 3.9 9.2 0.3 0.5 9.0	

			C statistic (SD) ACCP 2001 $CHADS_2$ (3 strata, 1-2 = moderate)	 0.58 (0.01) 0.7 (0.02)	

Table 8: Gage 2004 [363]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Gage 2004[363] Country of study: Multi-national Study design: Prospective cohort (from 6 separate trials) Setting: Data from 6 trials	Patient group: Patients with non-valvular AF. Inclusion criteria: Patients with non-valvular AF who took aspirin at doses ranging between 75 and 325mg daily. Patients included from the following trials: (All received aspirin) AFASAK-I, n = 336 PATAF, n = 319 EAFT, n = 404 Low risk SPAF III, n = 891 (aspirin + warfarin 1.25mg) AFASAK-2, n = 169	$CHADS_2$ ACCP (AFI, SPAF and Framingham also reported, but nor extracted).	Ischaemic stroke (n) Incidence rate C statistic (SD) ACCP 2001 $CHADS_2$ (3 strata, 1-2 = moderate)	207 (during 4887 patient years of aspirin therapy). 4.2/100 patient-years 0.58 (0.01) 0.7 (0.02)	Funding: Supported by the American Heart Association, National Institutes of Health, Danish Heart Foundation, Zorg Onderzoek Nederland Prevention fund, Netherlands Heart Foundation, Bayer Germany, UK Stroke Association, University Hospital Utrecht and University Hospital Rotterdam.

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Duration of follow-up: 1.9 years (maximum of 6.6 years)	(aspirin + warfarin 2mg) High risk SPAF III, n = 290 Exclusion criteria: None reported. N: 2580 Mean age (SD): 72 (9) years M/F: 27% women				Limitations: Several of the authors were involved in the development of the risk stratification schemes tested in these analyses. Notes:

Table 9: Larsen 2012[571]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Larsen 2012 Country of study: Denmark Study design: Prospective cohort Setting: NR Duration of follow-up: 5.4 years (±	Patient group: Patients with a diagnosis of AF. Inclusion criteria: Aged between 50 - 64, living in urban areas of Copenhagen and Aarhus, without a cancer diagnosis with AF and atrial flutter. Exclusion criteria: Patients with simultaneous diagnosis of stroke, thromboembolism and transient ischaemic attack or patients who died on the same day they were	$CHADS_2$ CHA_2DS_2-VASc	**Stroke - 5 year follow-up** *$CHADS_2$* AUC (95% CI) CHA_2DS_2-VASc AUC (95% CI)	 0.64 (0.56 - 0.71) 0.66 (0.59 - 0.72)	Funding: The Danish Council for Strategic Research and The Danish Cancer Society. Limitations: none
			Mortality - 5 year follow-up *$CHADS_2$* AUC (95% CI) CHA_2DS_2-VASc AUC (95% CI)	 0.62 (0.59 - 0.66) 0.63 (0.59 - 0.66)	
			NRI cases at 1 year (95% CI)	17% (9 - 26)	

3.7 years)	diagnosed with AF were excluded. AF patients with prescriptions of anticoagulant agents, warfarin or phenprocoumon within 180 days to the outcome event or end of follow up were excluded. N: 1603 non-anticoagulated patients Age (mean): 66.6years M/F: 967 men, 636 women Exclusions:		NRI cases at 5 years (95% CI)	32% (27 - 36)	
			Incidence rate at 1 year (per 100 person years) Stroke Mortality	 3.4 13.6	
			Incidence rate at 5.4 years (per 100 person years) Stroke Mortality	 1.9 5.6	

Table 10: Li 2012 [594]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Li 2012 Country of study: China Study design: Prospective cohort (retrospectively assessed)	Patient group: Patients hospitalised with acute stroke Inclusion criteria: Patients hospitalised for acute stroke with non-valvular AF between 2007 and 2008. Eligible patients were defined as having AF or flutter by self-report or by electrocardiography on admission, without mitral or aortic valve disease. Exclusion criteria:	$CHADS_2$ CHA_2DS_2-VASc	Stroke recurrence $CHADS_2$ C statistic OR (95% CI) CHA_2DS_2-VASc statistic OR (95% CI)	 0.53 1.15 (1.01 - 1.32) 0.55 1.14 (1.05 - 1.24)	Funding: Ministry of Science and Technology and the Ministry of Health of the People's Republic of China National Science and Technology Major Project of China and State Key Development Program for Basic Research of China.
			Mortality $CHADS_2$ C statistic OR (95% CI)	 0.53 1.12 (0.99 - 1.28)	

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Setting: Hospitals Duration of follow-up: 1 year	N: 1297 (185 with anti-coagulants, 1112 without) Age: >75: 243 (18.7%) 65 - 74: 408 (31.5%) <64: 646 (49.8%) M/F: 679 (52.4%) female		CHA_2DS_2-VASc statistic OR (95% CI)	0.57 1.20 (1.11 - 1.31)	Limitations: Notes:

Table 11: Lip 2010[607]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Lip 2010[607] Country of study: Study design: Prospective cohort Setting: Swedish hospitals Duration of	Patient group: Patients with a diagnosis of AF. Inclusion criteria: Anticoagulated patients participating in the SPORTIF III and V trials (randomised, multicentre parallel group trials comparing ximelgatran [36mg twice daily] with warfarin [dose adjusted to maintain INR 2 - 3]for prevention of stroke and systemic embolism in patients with non-valvular persistent paroxysmal or permanent AF..	$CHADS_2$ CHA_2DS_2-VASc ACC/AHA/ESC 8th ACCP NICE 2006 (Framingham also reported, but not extracted).	Total events thromboembolism **Events thromboembolism** $CHADS_2$ - classical Low Intermediate High $CHADS_2$ - revised Low Intermediate High NICE 2006 Low Intermediate	184 0/238 87/7276 97/3716 0/238 31/3563 153/7431 0/2 32/3651	Funding: Two authors have received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for the treatment of AF and thrombosis, including AstraZeneca. One author is an employee of AstraZeneca and one author received a grant from Bayer

follow-up: Up to 9 years. Total of 11233 patient years of follow up.	Exclusion criteria: None reported N: 7329 Age (mean): not reported (refers to original trial) M/F: not reported (refers to original trial)		High ACC/AHA/ESC 2006 Low Intermediate High ACCP 2008 Low Intermediate High CHA_2DS_2-VASc Low Intermediate High	152/7580 0/212 29/3469 155/7551 0/212 29/3479 155/7541 0/2 3/653 181/10578	healthcare and sponsorship from AstraZeneca and Boehringer-Ingelheim. Limitations: none

			Predictive ability		
			$CHADS_2$ - classical		
			C Statistic	0.637 (0.607, 0.674)	
			Hazard ratio	2.26 (1.71, 3.00)	
			$CHADS_2$ - revised		
			C Statistic	0.637 (0.607, 0.674)	
			Hazard ratio	2.50 (1.72, 3.63)	
			NICE 2006		
			C Statistic	0.575 (0.547, 0.600)	
			Hazard ratio	2.28 (1.56, 3.34)	
			ACC/AHA/ESC 2006		
			C Statistic	0.587 (0.557, 0.611)	
			Hazard ratio	2.58 (1.75, 3.79)	
			ACCP 2008		
			C Statistic	0.587 (0.557, 0.612)	
			Hazard ratio	2.59 (1.76, 3.81)	
			CHA_2DS_2-VASc		
			C Statistic	0.647 (0.613, 0.678)	
			Hazard ratio	3.75 (1.20, 11.73)	

Table 12: Olesen 2011[711]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Olesen 2011 Country of study: Denmark Study design: Retrospective cohort Setting: Hospital Duration of follow-up: 1, 5 and 10 years	Patient group: Patients with AF or flutter that were not treated with vitamin K antagonists. Inclusion criteria: as above. As treatment may be changed or intensified in relation to hospital admission, they started follow-up seven days after discharge. Exclusion criteria: if patients died or had a thromboembolism in this seven day quarantine period. Excluded patients if they had received VKA or heparins. N: 73,538 Age, 75 or over: 43864 (59.7%) 65-74: 14544 (19.8%) Female gender (%): 51.2%	$CHADS_2$ CHA_2DS_2-VASc	Event rate thromboembolism Per 100 person years at 1 year follow-up: $CHADS_2$ Low: Intermediate: High:	 1.67 (1.47-1.89) 4.75 (4.45-5.07) 12.27 (11.84-12.71)	Funding: None Limitations: Retrospective cohort from registry database Notes: None
			Event rate thromboembolism Per 100 person years at 1 year follow-up: CHA_2DS_2-VASc Low: Intermediate: High:	 0.78 (0.58-1.04) 2.01 (1.70-2.36) 8.82 (8.55-9.09)	
			Categorical c-statistics at 1 year follow up	$CHADS_2$: score 0-6: 0.663 (0.634-0.691) 3 groups: 0.722 (0.694-0.748) CHA_2DS_2-VASc: Score 0-9: 0.661 (0.633-0.690) 3 groups: 0.850 (0.829-0.871)	
			continuous c-statistics at 1 year follow up	$CHADS_2$: score 0-6: 0.691 (0.663-0.719) 3 groups: 0.722 (0.694-0.748)	

				CHA_2DS_2-VASc: Score 0-9: 0.682 (0.653-0.709) 3 groups: 0.852 (0.830-0.873)	

Table 13: Olesen 2012[713]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Olesen 2012B[713] Country of study: Denmark Study design: Retrospective cohort Setting: Hospital Duration of follow-up: 1 year	Patient group: Patients with a non-valvular AF or atrial flutter. Inclusion criteria: Patients identified from the national patient register with a non-valvular AF or atrial flutter during 1997 - 2008. Follow up was started 7 days after discharge. Exclusion criteria: Previous diagnosis of mitral or aortic valve disease or aortic valve surgery. Patients who died or had thromboembolism within 7 days of discharge. Patients receiving VKA or heparin were excluded. N: 47576 ($CHADS_2$ 0: 19444, $CHADS_2$ 1: 28132)	$CHADS_2$ CHA_2DS_2-VASc	**Event rate thromboembolism/100 person years** **$CHADS_2$ (0 - 1)** 1 year Events Stroke rate (95%CI) 12 years Events Stroke rate (95%CI) **$CHADS_2$ (0)** 1 year Events Stroke rate (95%CI) 12 years Events Stroke rate (95%CI) **$CHADS_2$ (1)** 1 year	 1405 3.49 (3.31 - 3.68) 4599 2.46 (2.39 - 2.53) 275 1.59 (1.41 - 1.79) 1182 1.28 (1.21 - 1.35)	Funding: Authors received various travel and research grants or acted as consultants for AstraZeneca, Boehringer-Ingelheim, Lundbeck Foundation, Sanofi-Aventis, Cardiome, Merck, BMS/Pfizer, Bayer, Astellas, Daiichi-Sankyo, Biotronik and Portola. Limitations: Retrospective cohort study Notes: None

	Age, mean (SD): 69.4 (14.7) Female gender (%): 22017 (46.3)		Events Stroke rate (95%CI) 12 years Events Stroke rate (95%CI)	1130 4.92 (4.65 - 5.22) 3417 3.61 (3.49 - 3.73)	
			Event rate thromboembolism/100 person years CHA_2DS_2-VASc = 0 1 year Events Stroke rate (95%CI) 12 years Events Stroke rate (95%CI) CHA_2DS_2-VASc = 1 1 year Events Stroke rate (95%CI) 12 years Events Stroke rate (95%CI) CHA_2DS_2-VASc = 2 1 year Events Stroke rate (95%CI) 12 years Events Stroke rate (95%CI) CHA_2DS_2-VASc = 3 1 year	 58 0.84 (0.65 - 1.08) 299 0.76 (0.68 - 0.85) 159 1.79 (1.53 - 2.09) 662 1.44 (1.34 - 1.56) 435 3.67 (3.34 - 4.03) 1489 2.89 (2.74 - 3.04)	

			Events	660
			Stroke rate (95%CI)	5.75 - 5.33 - 6.21)
			12 years	
			Events	1933
			Stroke rate (95%CI)	4.22 (4.04 - 4.41)
			CHA_2DS_2-VASc = 4	
			1 year	
			Events	93
			Stroke rate (95%CI)	8.18 (6.68 - 10.02)
			12 years	
			Events	216
			Stroke rate (95%CI)	4.93 (4.32 - 5.64)
			Thromboembolism	(confidence intervals estimated from graph)
			Hazard ratio - 1 year follow up	
			CHA_2DS_2-VASc 0 (ref)	1
			CHA_2DS_2-VASc 1	2.10 (1.6 - 2.9)
			CHA_2DS_2-VASc 2	4.20 (3.2 - 5.0)
			CHA_2DS_2-VASc 3	6.52 (5 - 9)
			CHA_2DS_2-VASc 4	9.10 (6.7 - 13)
			Thromboembolism	
			C statistic - 1 year	
			$CHADS_2$ 0 - 1	0.632 (0.619 - 0.646)
			CHA_2DS_2-VASc	0.663 (0.650 - 0.676)
			CHA_2DS_2-VASc at 1 year	
			(with event) reclassified to higher risk	1307/1405 (93.0%)
			(without event) reclassified to higher risk	36410/46171 (78.9%)
			NRI	14.2%

Table 14: Van Staa 2011[883]

Study details	Patients	Stroke risk score	Outcome measures	Effect size	Comments
Van Staa 2011[883] Country of study: UK Study design: Prospective cohort Setting: UK general practice Duration of follow-up:	Patient group: AF patients Inclusion criteria: Patients aged ≥18 years with a documented record of AF (from January 1990 to December 2008). Exclusion criteria: Patients with rheumatic valve disease/ N: 79844 Mean age (SD): 73.3 (12.5) years M/F: 50.3% male Anticoagulation history, n (%): 16060 (20.1)	ACCP 2001 ACCP 2004 ACCP 2008 NICE 2006 ACC/AHA/ESC CHA_2DS_2-VASc (3 categories) CHA_2DS_2-VASc cont $CHADS_2$ 2001(3 categories) $CHADS_2$ 2001 cont $CHADS_2$ 2008(3 categories) $CHADS_2$ 2008 cont (AFI, SPAF, Hart, van Walraven, van Latum	**Ischaemic stroke - c statistic (95% CI)** ACCP 2001 ACCP 2004 ACCP 2008 NICE 2006 ACC/AHA/ESC CHA_2DS_2-VASc (3 categories) CHA_2DS_2-VASc cont $CHADS_2$ 2001(3 categories) $CHADS_2$ 2001 cont $CHADS_2$ 2008(3 categories) $CHADS_2$ 2008 cont	 0.62 (0.6 - 0.63) 0.62 (0.6 - 0.63) 0.64 (0.62 - 0.67) 0.64 (0.62 - 0.66) 0.64 (0.62 - 0.67) 0.60 (0.59 - 0.61) 0.67 (0.64 - 0.69) 0.65 (0.62 - 0.67) 0.66 (0.63 - 0.69) 0.6 (0.57 - 0.64) 0.66 (0.63 - 0.69)	Funding: The General Practice Research Database is funded by the MHRA, the Medical Research Council, various universities, contract research organisations and pharmaceutical companies. Limitations: none

Mean 4.0 years (percentiles 5, 95 = 0.2, 11.0) Follow up to start of warfarin treatment Mean 2.4 years (percentiles 5, 95 = 0.1, 9.1)		and Framingham also reported, but not extracted).	**Death resulting from stroke - c statistic (95% CI)** ACCP 2001 ACCP 2004 ACCP 2008 NICE 2006 ACC/AHA/ESC CHA_2DS_2-VASc (3 categories) CHA_2DS_2-VASc cont $CHADS_2$ 2001(3 categories) $CHADS_2$ 2001 cont $CHADS_2$ 2008(3 categories) $CHADS_2$ 2008 cont	 0.63 (0.62 - 0.64) 0.62 (0.61 - 0.63) 0.68 (0.65 - 0.70) 0.68 (0.66 - 0.69) 0.68 (0.65 - 0.70) 0.61 (0.61 - 0.62) 0.74 (0.71 - 0.76) 0.70 (0.68 - 0.73) 0.72 (0.69 - 0.74) 0.71 (0.68 - 0.74) 0.78 (0.75 - 0.80)	

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.5 Anticoagulation

Table 15: Active 2009[12]

Study	Active 2009{ACTIVE2009}
Study type	RCT (Patient randomised; Parallel)

Study	Active 2009{ACTIVE2009}
Number of studies (number of participants)	1 (n=7554)
Countries and setting	Conducted in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Hong Kong (China), Hungary, Italy, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, USA; Setting: Multicentre, 580 centers in 33 countries
Line of therapy	Mixed line
Duration of study	Intervention time: 3.6 years
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Enrolled if they had AF or in the previous 6 months
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for ACTIVE (either ACTIVE A or ACTIVE W) if they had atrial fibrillation at enrolment or had had at least two episodes of intermittent atrial fibrillation in the previous 6 months. In addition, patients were required to have at least one of the following risk factors for stroke: an age of 75 years or more; systemic hypertension during treatment; previous stroke, transient ischemic attack, or non–central nervous system systemic embolism; a left ventricular ejection fraction of less than 45%; peripheral vascular disease; or an age of 55 to 74 years and diabetes mellitus or coronary artery disease.
Exclusion criteria	Patients were excluded if they required a K antagonist or clopidogrel or had any of the following risk factors for haemorrhage: documented peptic ulcer disease within the previous 6 months; a history of intracerebral haemorrhage; significant thrombocytopenia (platelet count <50×109 per litre); or on-going alcohol abuse.
Recruitment/selection of patients	Study was coordinated by the Population Health Research Institute at McMaster University
Age, gender and ethnicity	Age - Mean (SD): 71 (10.2). Gender (M:F): 58/42. Ethnicity: Mixture
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Extra comments	13% history of stroke or TIA
Indirectness of population	No indirectness
Interventions	(n=3772) Intervention 1: Antiplatelets - Aspirin + Clopidogrel. Clopidogrel (75mg/d) and aspirin (75 to 100 mg/d). Duration 3.6 yrs. Concurrent medication/care: Patients undergoing cardioversion at any point during the trial were to be treated with an open label Vitamin K antagonist for 4 weeks before and after cardioversion and were then to resume the assigned study treatment. Medications at baseline, VKA (8%), Aspirin (83%), Clopidogrel (2%), Antiarrhythmic agent (22%)

Study	Active 2009{ACTIVE2009}
	(n=3782) Intervention 2: Antiplatelets - Aspirin. Aspirin (75 to 100 mg/d). Duration 3.6 yrs. Concurrent medication/care: Patients undergoing cardioversion at any point during the trial were to be treated with an open label Vitamin K antagonist for 4 weeks before and after cardioversion and were then to resume the assigned study treatment. Medications at baseline, VKA (8%), Aspirin (83%), Clopidogrel (2%), Antiarrhythmic agent (22%)
Funding	Equipment / drugs provided by industry (Sanofi-Aventis and Bristol-Myers Squibb)
RESULTS (NUMBERS ANALYSED): ASPIRIN + CLOPIDOGREL versus ASPIRIN Protocol outcome 1: Ischaemic stroke at Latest endpoint - Actual outcome: Ischaemic stroke at 3.6 years; Group 1: 235/3772, Group 2: 343/3782 Protocol outcome 2: All cause mortality at Latest endpoint - Actual outcome: Death from any cause at 3.6 years; Group 1: 825/3772, Group 2: 841/3782 Protocol outcome 3: Thromboembolic complications at Latest endpoint - Actual outcome: Non-central nervous system systemic embolism at 3.6 years; Group 1: 54/3772, Group 2: 56/3782 Protocol outcome 4: Haemorrhagic stroke at Latest endpoint - Actual outcome: Haemorrhagic stroke at 3.6 years; Group 1: 30/3772, Group 2: 22/3782 Protocol outcome 5: Major bleeding at 30 days - Actual outcome: Major bleeding (major and fatal) at 3.6 years; Group 1: 251/3772, Group 2: 162/3782	
Protocol outcomes not reported by the study	Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 16: Active writing group of the active investigators 2006[13]

Study	Active writing group of the active investigators 2006{ACTIVE2006A}
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=)

Study	Active writing group of the active investigators 2006{ACTIVE2006A}
Countries and setting	Not reported
Line of therapy	Mixed line
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	ECG evidence of AF at least one of the following: age 75 years or older, on treatment for systemic hypertension, previous stroke, transient ischaemic attack, or non-CNS systemic embolus, LV dysfunction, PAD. If patients were 55-74 and did not have one of the other inclusion criteria they were required to have diabetes mellitus requiring drug therapy or previous CAD.
Exclusion criteria	Contraindication for clopidogrel or for oral anticoagulant (such as prosthetic mechanical heart valve); documented peptic ulcer disease within the previous 6 months; previous intracerebral haemorrhage; significant thrombocytopenia; or mitral stenosis.
Age, gender and ethnicity	Age - Mean (SD): 70.2 (9.4). Gender (M:F): 66:34. Ethnicity:
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Indirectness of population	No indirectness
Interventions	(n=3371) Intervention 1: Anticoagulants - Warfarin (Vitamin K Antagonists). Vitamin K antagonist INR 2-3. Duration 1.28 years. Concurrent medication/care: Unclear if patients continued with baseline medication (n=3335) Intervention 2: Antiplatelets - Aspirin + Clopidogrel. Clopidogrel 75mg/d and aspirin 75-100 mg/d. Duration 1.28 years. Concurrent medication/care: Unclear if patients continued with baseline medication
Funding	Not reported

RESULTS (NUMBERS ANALYSED): ORAL ANTICOAGULATION THERAPY versus ASPIRIN + CLOPIDOGREL

Protocol outcome 1: All cause mortality at Latest endpoint
- Actual outcome: All-cause mortality at 1.28 years; Group 1: 158/3371, Group 2: 159/3335

Protocol outcome 2: Thromboembolic complications at Latest endpoint
- Actual outcome: Major bleeding at 1.28 years; Group 1: 93/3371, Group 2: 101/3335
- Actual outcome: Non-CNS embolus at 1.28 years; Group 1: 4/3371, Group 2: 18/3335

Study	Active writing group of the active investigators 2006{ACTIVE2006A}
Protocol outcome 3: Haemorrhagic stroke at Latest endpoint - Actual outcome: Haemorrhagic stroke at 1.28 years; Group 1: 15/3371, Group 2: 5/3335 Protocol outcome 4: Major bleeding at 30 days - Actual outcome: Ischaemic stroke at 1.28 years; Group 1: 93/3371, Group 2: 101/3335	
Protocol outcomes not reported by the study	Ischaemic stroke at Latest endpoint; Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 17: Aguilar 2005[19]

Study	Aguilar 2005{AGUILAR2005}
Study type	Systematic Review
Number of studies (number of participants)	3 (n=1965)
Countries and setting	Conducted in Denmark, Spain, USA
Line of therapy	1st line
Duration of study	Follow up (post intervention): Mean duration of follow up averaged at 1.3 years per participant
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants with AF documented by electrocardiogram (ECG).
Stratum	Overall
Subgroup analysis within study	Sys review – pre-specified in protocol
Inclusion criteria	Participants with AF documented by ECG either intermittent (paroxysmal) or sustained (constant) were included.
Exclusion criteria	Mitral stenosis or prosthetic cardiac valves were not included.
Age, gender and ethnicity	Age - Mean (SD): 70 years. Gender (M:F): 1218 / 747. Ethnicity: Unknown
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Indirectness of population	No indirectness
Interventions	(n=1082) Intervention 1: Antiplatelets - Aspirin. Dose varied in the three studies: 75mg/day, 125mg per day or alternate day and 325mg/day. Duration Long-term (minimum of 4 weeks). Concurrent medication/care: Not given in

Study	Aguilar 2005{AGUILAR2005}
	systematic review (n=883) Intervention 2: Control - No treatment. No treatment given in two studies and one used placebo.. Duration Long-term (minimum of 4 weeks). Concurrent medication/care: Information not provided in systematic review.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): ASPIRIN versus NO TREATMENT Protocol outcome 1: Ischaemic stroke at Latest endpoint - Actual outcome: Ischaemic stroke; Group 1: 39/1032, Group 2: 52/933 Protocol outcome 2: All cause mortality at Latest endpoint - Actual outcome: All cause mortality; Group 1: 72/1082, Group 2: 87/995 Protocol outcome 3: Thromboembolic complications at Latest endpoint - Actual outcome: Systemic emboli; Group 1: 4/1032, Group 2: 6/933 Protocol outcome 4: Haemorrhagic stroke at Latest endpoint - Actual outcome: Intracranial hemorrhage; Group 1: 3/1032, Group 2: 2/933 Protocol outcome 5: Major bleeding at 30 days - Actual outcome: All major extracranial bleeds; Group 1: 9/838, Group 2: 8/842	
Protocol outcomes not reported by the study	Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 18: Aguilar 2005[20]

Study (subsidiary papers)	Aguilar 2005{AGUILAR2005A} (Connolly 1991{CONNOLLY1991}, Ezekowitz 1992{EZEKOWITZ1992}, Singer 1990{SINGER1990})

Study (subsidiary papers)	Aguilar 2005{AGUILAR2005A} (Connolly 1991{CONNOLLY1991}, Ezekowitz 1992{EZEKOWITZ1992}, Singer 1990{SINGER1990})
Study type	Systematic Review
Number of studies (number of participants)	5 (n=2313)
Countries and setting	Conducted in Canada, Denmark, USA; Setting: Studies from USA (3 studies), Canada and Denmark were included
Line of therapy	Mixed line
Duration of study	Intervention time: Long-term intervention of at least 4 weeks or more
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: AF documented by electrocardiogram
Stratum	Overall
Subgroup analysis within study	Sys review – pre-specified in protocol: double blind compared to open label studies
Inclusion criteria	Long-term treatment (more than four weeks) with oral anticoagulants compared with control or placebo in patients with chronic non-valvular AF.
Exclusion criteria	Participants with prior stroke or TAI at any time before study entry were excluded; those with mitral stenosis or prosthetic cardiac valves were also excluded. Trials involving iatrogenic cardioversion for recent onset AF were excluded. Trials testing vitamin K antagonists in which the mean INR was not prolonged beyond the normal range were excluded. All trials excluded those with major cardiac valvular disease or with perceived contraindications to VKA therapy.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 69 years. Gender (M:F): 74/26%. Ethnicity: Not reported
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Extra comments	. None
Indirectness of population	No indirectness: Not applicable
Interventions	(n=1154) Intervention 1: Anticoagulants - Warfarin (Vitamin K Antagonists). Warfarin. Intensity of anticoagulation was adjusted using the PTR in three trials and using the INR in two trials. Target intensities varied, with INR ranges of 2-3 and 2.8-4.2 and PTR of 1.2-1.5 (2 studies) to 1.3 to 1.8.. Duration Minimum of 4 weeks. Concurrent medication/care: Not reported (n=1159) Intervention 2: Control - Placebo or no treatment. Placebo. Duration Minimum of 4 weeks. Concurrent medication/care: 4 studies in the control group did not allow the use of aspirin or other antithrombotic agents. In one study 45% of the control group took aspirin in various doses by participant self-selection.

Study (subsidiary papers)	Aguilar 2005{AGUILAR2005A} (Connolly 1991{CONNOLLY1991}, Ezekowitz 1992{EZEKOWITZ1992}, Singer 1990{SINGER1990})
Funding	Funding not stated (Cochrane review)
RESULTS (NUMBERS ANALYSED): WARFARIN (VITAMIN K ANTAGONISTS) versus PLACEBO OR NO TREATMENT Protocol outcome 1: Ischaemic stroke at Latest endpoint - Actual outcome: Ischaemic stroke at least 4 weeks; Group 1: 22/1154, Group 2: 69/1159 Protocol outcome 2: All cause mortality at Latest endpoint - Actual outcome: All cause mortality at least 4 weeks Protocol outcome 3: Thromboembolic complications at Latest endpoint - Actual outcome: Systemic emboli at least 4 weeks; Group 1: 3/1154, Group 2: 7/1159 Protocol outcome 4: Haemorrhagic stroke at Latest endpoint - Actual outcome: Intracranial haemorrhage at least 4 weeks; Group 1: 5/1154, Group 2: 2/1159 Protocol outcome 5: Major bleeding at 30 days - Actual outcome: Major extracranial bleeds at least 4 weeks; Group 1: 17/1154, Group 2: 16/1159	
Protocol outcomes not reported by the study	Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 19 Aguilar 2007[21]

Study	Aguilar 2007{AGUILAR2007B}
Study type	Systematic Review
Number of studies (number of participants)	6 (n=2892)
Countries and setting	Conducted in Denmark, Greece, Netherlands, Spain, USA; Setting:
Line of therapy	1st line

Study	Aguilar 2007{AGUILAR2007B}
Duration of study	Other:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Sys review – pre-specified in protocol
Inclusion criteria	We included participants with AF documented by electrocardiogram either intermittent (paroxysmal) or sustained (constant).
Exclusion criteria	We did not include those with concomitant mitral stenosis or prosthetic cardiac valves.
Recruitment/selection of patients	We identified all unconfounded, randomized trials in which long-term (more than 4 weeks) adjusted dose-oral anticoagulant treatment was compared with antiplatelet therapy in patients with chronic non-valvular AF. We considered trials in which the intervention was masked (double-blinded where both the clinician and the patient are unaware of the intervention) and those in which the intervention was given open label. We excluded trials involving iatrogenic cardioversion for recent onset AF.
Age, gender and ethnicity	Age - Other: range of ages but all adults, from 6 papers. Gender (M:F): Approximately 50%. Ethnicity:
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Indirectness of population	No indirectness
Interventions	(n=1444) Intervention 1: Anticoagulants - Warfarin (Vitamin K Antagonists). Warfarin INR>1.5 or other coumarins (such as acenocumarol) . Duration 6 months to 3.5 years. Concurrent medication/care: Unclear (n=1448) Intervention 2: Antiplatelets - Aspirin. Aspirin or other platelet anti-aggregants. Duration 6 months to 3.5 years. Concurrent medication/care: Unclear
Funding	No funding
RESULTS (NUMBERS ANALYSED): ANTICOAGULANTS versus ANTIPLATELET Protocol outcome 1: Ischaemic stroke at Latest endpoint - Actual outcome: Ischaemic stroke; Group 1: 91/4815, Group 2: 170/4783 Protocol outcome 2: All cause mortality at Latest endpoint - Actual outcome: Death from any cause; Group 1: 271/4480, Group 2: 271/4447 Protocol outcome 3: Thromboembolic complications at Latest endpoint	

Study	Aguilar 2007{AGUILAR2007B}
- Actual outcome: Systemic embolism; Group 1: 12/4815, Group 2: 26/4783 Protocol outcome 4: Haemorrhagic stroke at Latest endpoint - Actual outcome: Haemorrhagic stroke; Group 1: 41/4810, Group 2: 20/4776 Protocol outcome 5: Major bleeding - Actual outcome: Major bleeding (major and fatal); Group 1: 103/4810, Group 2: 105/4776	
Protocol outcomes not reported by the study	Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 20: Chen 2012[189]

Study	Chen 2012{CHEN2012B}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=786)
Countries and setting	Conducted in China; Setting: 75 institutions in China
Line of therapy	1st line
Duration of study	Follow up (post intervention): 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Medical history, electrocardiogram and/or Holter recordings
Stratum	Overall
Subgroup analysis within study	Not applicable: None
Inclusion criteria	At least one of the following conditions: age 60 years or over, well controlled mild to moderate hypertension and diastolic blood pressure, transient ischemic attack, ischemic stroke or systemic embolism after 6 months; left ventricular dysfunction, and/or diabetes mellitus. Patients were able to complete the entire study period and cooperate with the follow-up and were not presently participating in any other clinical trials
Exclusion criteria	Presently taking warfarin or aspirin for any reason, cardiovascular factors including cardioversion was planned within 3 months of enrolment; cardiac valvular disease documented by echocardiography; severe left ventricular dysfunction; myocardial infarction within 6 months; coronary artery bypass graft surgery within 6 months; percutaneous coronary intervention within months; unstable angina pectoris; thrombus in the left sided heart

Study	Chen 2012{CHEN2012B}
	chamber documented by echocardiography; uncontrolled severe hypertension; or Wolff-Parkinson-White syndrome. Non cardiac factors including allergic to warfarin or aspirin; severe lung disease; TIA, ischemic stroke or systemic embolism within 6 months; history of a haemorrhagic stroke; requirement for treatment with other NSIADs due to non-cardiac diseases
Recruitment/selection of patients	Patients with non valvular AF lasting for one month or more were recruited between November 2001 and December 2004
Age, gender and ethnicity	Age - Mean (range): 67 years. Gender (M:F): 270/170. Ethnicity: Chinese
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Extra comments	None. None
Indirectness of population	No indirectness: None
Interventions	(n=239) Intervention 1: Anticoagulants - Warfarin (Vitamin K Antagonists). Standard intensity warfarin (INR 2.1-2.5). Duration 15 months. Concurrent medication/care: An initial dose of 1-3 mg/d of warfarin was prescribed after the baseline INR values were measured. Then the INR values were measured every 1-2 days after the initial dose on which the next dose was adjusted. The frequency of the INR measurements was reduced to once a week when a stable target value was achieved and was further reduced to once a month following the first month Comments: None (n=201) Intervention 2: Antiplatelets - Aspirin. Fixed dose of 200 mg/d. Duration 15 months. Concurrent medication/care: No further details Comments: None
Funding	Academic or government funding (Grant from the10th National Five-year Project of China)

RESULTS (NUMBERS ANALYSED): WARFARIN versus ASPIRIN

Protocol outcome 1: Ischaemic stroke at Latest endpoint
- Actual outcome: Ischaemic stroke at 15 months; Group 1: 1/239, Group 2: 8/201

Protocol outcome 2: All cause mortality at Latest endpoint
- Actual outcome: Mortality at Mean 15 months; Group 1: 5/239, Group 2: 6/201

Protocol outcome 3: Thromboembolic complications at Latest endpoint

Study	Chen 2012{CHEN2012B}
- Actual outcome: Thromboembolic events at 15 months; Group 1: 7/239, Group 2: 16/201 Protocol outcome 4: Haemorrhagic stroke at Latest endpoint - Actual outcome: Haemorrhagic stroke at 15 months; Group 1: 1/239, Group 2: 0/201 Protocol outcome 5: Major bleeding at 30 days - Actual outcome: Major bleeding at 15 months; Group 1: 7/239, Group 2: 1/201	
Protocol outcomes not reported by the study	Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 21: Chen 2012[189]

Study	Chen 2013{CHEN2013}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1162)
Countries and setting	Conducted in China; Setting: NR
Line of therapy	1st line
Duration of study	Follow up (post intervention): 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged ≥65 years; had indicated at least two documented AF episodes in the previous six months with a duration of <3 days [confirmed by electrocardiography (ECG) or Holter]; patients that demonstrated palpitations, chest tightness, dizziness and sweating; and patients that were either at a middle or high‐risk of a stroke.
Exclusion criteria	Patients with non‐atherosclerosis AF (rheumatic heart disease, cardiomyopathy, hyperthyroidism and electrolyte disturbances); AF due to reversible underlying disease (acute myocardial infarction, acute myocarditis and untreated hyperthyroidism); AF induced by electrophysiological examination, coronary angiography or pacemaker implantation; patients with a recent history of cardiothoracic surgery, gastrointestinal and intracranial bleeding or other bleeding; severe liver or renal dysfunction; cancer or blood disease; and acute inflammation of the respiratory tract or urinary

Study	Chen 2013{CHEN2013}
	tract.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): Group A: 72.4±4.9 ; Group C: 72.8±4.5; Group D: 72.2±4.9; Group E: 72.8±4.5; Group F: 71.9±4.3. Gender (M:F): Male (%) Groups A: 108 (62.4); Group C 141 (61.8); Group D: 72.2±4.9; Group E: 72.8±4.5; Group F: 71.9±4.3. Ethnicity: Chinese
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Extra comments	group A: high risk; group C: high risk; group D: high risk; group E: middle risk; group F: middle risk. Group B omitted from our analysis due to low INR range
Indirectness of population	No indirectness
Interventions	(n=361) Intervention 1: Antiplatelets - Aspirin. 150 mg/day. Duration unclear. Concurrent medication/care: NR Comments: Includes patients classed as at middle and high risk of stroke (n=650) Intervention 2: Anticoagulants - Warfarin (Vitamin K Antagonists). 2.5 mg/day. Target INR range: group C and F: 1.7-2.5; group D 2.6-3.0. Duration unclear. Concurrent medication/care: NR Comments: Includes patients classed as at middle and high risk of stroke
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): ASPIRIN versus WARFARIN (VITAMIN K ANTAGONISTS)

Protocol outcome 1: Ischaemic stroke at Latest endpoint
- Actual outcome: ischaemic stroke at up to 5 years; Group 1: 17/361, Group 2: 9/650

Protocol outcome 2: All cause mortality at Latest endpoint
- Actual outcome: Death at up to 5 years; Group 1: 9/361, Group 2: 10/650

Protocol outcome 3: Thromboembolic complications at Latest endpoint
- Actual outcome: PE at up to 5 years; Group 1: 6/361, Group 2: 4/650

Protocol outcome 4: Haemorrhagic stroke at Latest endpoint
- Actual outcome: Cerebral haemorrhage at up to 5 years; Group 1: 3/361, Group 2: 16/650

Study	Chen 2013{CHEN2013}
Protocol outcome 5: Major bleeding at 30 days - Actual outcome: Major bleeding at up to 5 years; Group 1: 8/361, Group 2: 25/650	
Protocol outcomes not reported by the study	Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 22: Connolly 2011[229]

Study	Connolly 2011{CONNOLLY2011B}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=5599)
Countries and setting	Conducted in Multiple countries
Line of therapy	Mixed line
Duration of study	Intervention time: 1.1 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: had AF documented 6 months prior or evidence on 12-lead ECG on day of screening
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis: CHAD score
Inclusion criteria	Patients were eligible if they were 50 years of age or older and had atrial fibrillation documented in the 6 months before enrolment or by 12-lead electrocardiography on the day of screening. Patients also had to have at least one of the following risk factors for stroke: prior stroke or transient ischemic attack, an age of 75 years or older, arterial hypertension (receiving treatment), diabetes mellitus (receiving treatment), heart failure (New York Heart Association class 2 or higher at the time of enrolment), a left ventricular ejection fraction of 35% or less, or documented peripheral-artery disease.
Exclusion criteria	In addition, patients could not be receiving vitamin K antagonist therapy, either because it had already been demonstrated to be unsuitable for them or because it was expected to be unsuitable. The reasons that vitamin K antagonist therapy was unsuitable for the patient had to be documented on the study case-report forms. The key exclusion criteria were the presence of conditions other than atrial fibrillation for which the patient required long-term anticoagulation, valvular disease requiring surgery, a serious bleeding event in the previous 6 months or a high

Study	Connolly 2011{CONNOLLY2011B}
	risk of bleeding (e.g., active peptic ulcer disease, a platelet count of <100,000 per cubic millimetre or haemoglobin level of <10 g per decilitre, stroke within the previous 10 days, documented haemorrhagic tendencies, or blood dyscrasias), current alcohol or drug abuse or psychosocial issues, life expectancy of less than 1 year, severe renal insufficiency (a serum creatinine level of >2.5 mg per decilitre [221 µmol per litre] or a calculated creatinine clearance of <25 ml per minute), an alanine aminotransferase or aspartate aminotransferase level greater than 2 times the upper limit of the normal range or a total bilirubin more than 1.5 times the upper limit of the normal range, and allergy to aspirin.
Recruitment/selection of patients	522 centers in 36 countries
Age, gender and ethnicity	Age - Mean (SD): 70 (9). Gender (M:F): 59:41. Ethnicity: Mixed
Further population details	1. Age of study: 2000 and later (CHAD score). 2. Time in therapeutic range (INR): Not applicable / Not stated / Unclear
Extra comments	14% prior stroke. Subgroup analysis on patients with different CHAD scores. Major bleeding: Aspirin vs. Apixaban CHAD 0-1= 6 vs. 6. CHAD 2 =14 vs. 14. CHAD >3 =19 vs. 24.
Indirectness of population	No indirectness: 14% prior stroke
Interventions	(n=2808) Intervention 1: Anticoagulants - Apixaban (Direct factor Xa inhibitors). Apixaban 5mg 2x day. Duration 1.1 years. Concurrent medication/care: Medications at baseline, ACE or ARB (64%), Verapamil or diltiazem (9%), Beta-blockers (56%), Digoxin (29%), Amiodarone (11%), Statin (31%) (n=2791) Intervention 2: Antiplatelets - Aspirin. Aspirin 81 to 324 mg/day. Duration 1.1 years. Concurrent medication/care: Medications at baseline, ACE or ARB (64%), Verapamil or diltiazem (9%), Beta-blockers (55%), Digoxin (27%), Amiodarone (12%), Statin (31%)
Funding	Equipment / drugs provided by industry (Bristol-Myers Squibb, Pfizer, Boehringer-Ingelheim, Sanofi-Aventis, Portola and Merch)

RESULTS (NUMBERS ANALYSED): APIXABAN (DIRECT FACTOR XA INHIBITORS) versus ASPIRIN

Protocol outcome 1: Ischaemic stroke at Latest endpoint
- Actual outcome: Ischaemic stroke at 1.1years; Group 1: 35/2808, Group 2: 93/2791

Protocol outcome 2: All cause mortality at Latest endpoint
- Actual outcome: Death from any cause at 1.1 years; Group 1: 111/2808, Group 2: 140/2791

Study	Connolly 2011{CONNOLLY2011B}
Protocol outcome 3: Thromboembolic complications at Latest endpoint - Actual outcome: Systemic embolism at 1.1 years; Group 1: 2/2808, Group 2: 13/2791 Protocol outcome 4: Hospitalisation at Latest endpoint - Actual outcome: Hospitalisation for cardiovascular cause at 1.1 years; Group 1: 367/2808, Group 2: 455/2791 Protocol outcome 5: Haemorrhagic stroke at Latest endpoint - Actual outcome: Haemorrhagic stroke at 1.1 years ; Group 1: 6/2808, Group 2: 9/2791 Protocol outcome 6: Major bleeding at 30 days - Actual outcome: Major bleeding at 1.1 years; Group 1: 44/2808, Group 2: 39/2791	
Protocol outcomes not reported by the study	Quality of life at Latest endpoint

Table 23: Dewilde 2013[282]

Study	Dewilde 2013{DEWILDE2013}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=563)
Countries and setting	Conducted in Belgium, Netherlands
Line of therapy	Mixed line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Only patients scheduled for PCI can be included tough this intervention would also take place without this study.
Exclusion criteria	cardiogenic shock, contra-indication for aspirin or clopidogrel, allergy to aspirin or clopidogrel, documented peptic ulcer disease within the previous six months, pregnancy and previous intracerebral haemorrhage or

Study	Dewilde 2013{DEWILDE2013}
Recruitment/selection of patients	All eligible patients referred to the study centres
Age, gender and ethnicity	Age - Mean (SD): 70 (7). Gender (M:F): 80:20. Ethnicity: NA
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Indirectness of population	Serious indirectness: 69% had AF at baseline, 25% had ACS
Interventions	(n=284) Intervention 1: Anticoagulants and dual antiplatelets - Anticoagulants and antiplatelets. Warfarin + clopidogrel 75mg/day + aspirin 80mg/day = 284. Duration 1 years. Concurrent medication/care: Other cardiac medications were given at the discretion of the attending physician (n=279) Intervention 2: Anticoagulants and antiplatelets. Warfarin + clopidogrel 75mg/day. Duration 1 year. Concurrent medication/care: Other cardiac medications were given at the discretion of the attending physician
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): WARFARIN+CLOPIDOGREL+ASPIRIN versus ANTICOAGULANTS AND ANTIPLATELETS Protocol outcome 1: All cause mortality at Latest endpoint - Actual outcome: All-cause mortality at 1 year; Group 1: 18/284, Group 2: 7/279 Protocol outcome 2: Haemorrhagic stroke at Latest endpoint - Actual outcome: Ischaemic stroke at 1 year; Group 1: 8/284, Group 2: 2/279 - Actual outcome: Haemorrhagic stroke at 1 year; Group 1: 0/284, Group 2: 1/279 Protocol outcome 3: Major bleeding at 30 days - Actual outcome: Major bleeding at 1 year; Group 1: 16/284, Group 2: 9/279	
Protocol outcomes not reported by the study	Ischaemic stroke at Latest endpoint; Thromboembolic complications at Latest endpoint; Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 24: Hart 2008[423]

Study	Hart 2008{HART2008A}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=593)
Countries and setting	Conducted in USA; Setting: Clinic
Line of therapy	Mixed line
Duration of study	Intervention time: 2.3 years
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Documented cerebrovascular disease
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	History of AF, patients were >45 years old and had one of the following: multiple atherothrombotic risk factors or clinically documented coronary artery, cerebrovascular, or peripheral arterial disease.
Exclusion criteria	Receiving oral anticoagulants
Recruitment/selection of patients	Run by Cleveland Clinic Cardiovascular Coordinating Center
Age, gender and ethnicity	Age - Mean (SD): 70. Gender (M:F): Define. Ethnicity: 94% White
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Extra comments	15% prior stroke
Indirectness of population	No indirectness
Interventions	(n=298) Intervention 1: Antiplatelets - Aspirin + Clopidogrel. Clopidogrel (75mg/d) and low dose aspirin (75-162 mg/d). Duration 28 months. Concurrent medication/care: From the larger sample, patients were on nitrates (23%), diuretics (48%), calcium antagonists (36%), beta-blockers (55%), ACEi (63%), ARBs (25%), statins (76%), anti-diabetic mediations (14%), other lipid lowering medication (41%) (n=285) Intervention 2: Antiplatelets - Aspirin. Low dose aspirin (75-162 mg/d). Duration 28 months. Concurrent medication/care: From the larger sample, patients were on nitrates (23%), diuretics (48%), calcium antagonists (36%), beta-blockers (55%), ACEi (63%), ARBs (25%), statins (76%), anti-diabetic mediations (14%), other lipid lowering medication (41%)
Funding	Equipment / drugs provided by industry (Sanofi-Aventis and Bristol-Myers Squibb)

Study	Hart 2008{HART2008A}
RESULTS (NUMBERS ANALYSED): ASPIRIN + CLOPIDOGREL versus ASPIRIN Protocol outcome 1: Ischaemic stroke at Latest endpoint - Actual outcome: Ischemic stroke at 28 months; Group 1: 14/298, Group 2: 14/285 Protocol outcome 2: All cause mortality at Latest endpoint - Actual outcome: All-cause mortality at 28 months; Group 1: 29/298, Group 2: 25/285 Protocol outcome 3: Hospitalisation at Latest endpoint - Actual outcome: Rehospitalisation at 28 months; Group 1: 41/298, Group 2: 43/285 Protocol outcome 4: Haemorrhagic stroke at Latest endpoint - Actual outcome: Primary intracerebral hemorrhage at 28 months; Group 1: 1/298, Group 2: 0/285 Protocol outcome 5: Major bleeding at 30 days - Actual outcome: Intracranial bleeds, severe/fatal extracranial hemorrhage at 28 months; Group 1: 9/298, Group 2: 4/285	
Protocol outcomes not reported by the study	Thromboembolic complications at Latest endpoint; Quality of life at Latest endpoint

Table 25: Mant 2007[641]

Study	Mant 2007{MANT2007}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=973)
Countries and setting	Conducted in United Kingdom
Line of therapy	Mixed line
Duration of study	Intervention time: 2.7 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG or primary care records of diagnosed AF and verified by cardiologist
Stratum	Overall

Study	Mant 2007{MANT2007}
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged over 75 years or over and had AF or AF flutter.
Exclusion criteria	rheumatic heart disease, a major non-traumatic haemorrhage within the previous 5 years; intracranial haemorrhage; endoscopically proven peptic ulcer disease in the previous year; oesophageal varices; allergic hypersensitivity to either of the study drugs; a terminal illness as judged by primary physician; surgery within the past 3 months; or blood pressure greater than 180/100 mmHg. Should not be on warfarin
Recruitment/selection of patients	General practices
Age, gender and ethnicity	Age - Mean (SD): 81.5 (4.3). Gender (M:F): Define. Ethnicity: NA
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Extra comments	13% had prior stroke
Indirectness of population	No indirectness
Interventions	(n=488) Intervention 1: Anticoagulants - Warfarin (Vitamin K Antagonists). Warfarin INR 2-3. Duration 2.7 years. Concurrent medication/care: Not provided (n=485) Intervention 2: Antiplatelets - Aspirin. Aspirin 75mg/d. Duration 2.7 years. Concurrent medication/care: None provided
Funding	Academic or government funding (Medical Research Council)

RESULTS (NUMBERS ANALYSED): WARFARIN (VITAMIN K ANTAGONISTS) versus ASPIRIN

Protocol outcome 1: Ischaemic stroke at Latest endpoint
- Actual outcome: Ischaemic stroke at 2.7 years; Group 1: 10/488, Group 2: 32/485

Protocol outcome 2: All cause mortality at Latest endpoint
- Actual outcome: All-cause mortality at 2.7 years; Group 1: 107/488, Group 2: 108/485

Protocol outcome 3: Thromboembolic complications at Latest endpoint
- Actual outcome: Systemic embolism at 2.7 years; Group 1: 1/488, Group 2: 3/485

Protocol outcome 4: Haemorrhagic stroke at Latest endpoint

Study	Mant 2007{MANT2007}
- Actual outcome: Haemorrhagic stroke at 2.7 years; Group 1: 6/488, Group 2: 5/485 Protocol outcome 5: Major bleeding at 30 days - Actual outcome: All major haemorrhages (including intracranial) at 2.7 years; Group 1: 19/488, Group 2: 20/485	
Protocol outcomes not reported by the study	Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 26: Rash 2007[767]

Study	Rash 2007{RASH2007}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in United Kingdom; Setting:
Line of therapy	Mixed line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Screening clinic
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>80 and <90 years of age, were ambulant and had permanent AF.
Exclusion criteria	Had one of the following: one more falls (without formal gait assessment) or syncopal episode within the last 12 months; epileptiform seizures; alcoholic liver disease or excess alcohol intake (>21 and >14 units per week for males and females) previous history of thromboembolism (stroke, transient ischaemic attack, systemic embolus); gastrointestinal or genitourinary bleeding in the previous 6 months; previous intracranial haemorrhage; BP>180/100; abnormal resting prothrombin time; Folstein mental state examination score <26; previous intolerance/allergy warfarin or aspirin; already taking warfarin.
Recruitment/selection of patients	Outpatient clinics and Hospital
Age, gender and ethnicity	Age - Mean (range): 83 (80-90). Gender (M:F): Define. Ethnicity: not available
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Extra comments	Primary prevention of stroke
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Anticoagulants - Warfarin (Vitamin K Antagonists). Warfarin INR 2-3. Duration 1 year. Concurrent medication/care: None listed (n=39) Intervention 2: Antiplatelets - Aspirin. 300mg/d. Duration 1 year. Concurrent medication/care: Not listed
Funding	No funding
RESULTS (NUMBERS ANALYSED): WARFARIN (VITAMIN K ANTAGONISTS) versus ASPIRIN	

Protocol outcome 1: Ischaemic stroke at Latest endpoint - Actual outcome: Stroke (ischaemic) at 1 year; Group 1: 0/36, Group 2: 0/39 Protocol outcome 2: All cause mortality at Latest endpoint - Actual outcome: Death at 1 year; Group 1: 1/36, Group 2: 2/39 Protocol outcome 3: Haemorrhagic stroke at Latest endpoint - Actual outcome: Stroke (Haemorrhagic) at 1 year Protocol outcome 4: Major bleeding at 30 days - Actual outcome: Serious bleeding at 1 year; Group 1: 0/36, Group 2: 3/39	
Protocol outcomes not reported by the study	Thromboembolic complications at Latest endpoint; Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 27: Sato 2006[800]

Study	**Sato 2006{SATO2006}**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=871)
Countries and setting	Conducted in Japan; Setting: 13 centres and 76 affiliated hospitals in Japan
Line of therapy	1st line

Study	Sato 2006{SATO2006}
Duration of study	Intervention time: Median 810 days (range 15 to 1365 days)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Documented by ECG at least twice within 12 months
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a history of stroke or TIA less than 1 year previously were exceptionally eligible if both the patient and physician agreed.
Exclusion criteria	Prosthetic heart valve, rheumatic heart disease, mitral valve disease, uncontrolled hypertension, hyperthyroidism, severe heart failure, and a past history of symptomatic thromboembolic disease within a year, previous intracranial bleeding, or gastrointestinal hemorrhage within 6 months. Patients with other indications for anticoagulant therapy or antiplatelet agents were excluded. Patients whose attending physicians considered it inappropriate for them to join the study were excluded.
Recruitment/selection of patients	Patients with chronic or intermittent AF from centres and hospitals in Japan
Age, gender and ethnicity	Age - Mean (SD): 65 years. Gender (M:F): 70%/30%. Ethnicity: Japanese
Further population details	1. Age of study: 2000 and later (2006). 2. Time in therapeutic range (INR): Not applicable / Not stated / Unclear (Not applicable).
Extra comments	Patients with chronic or intermittent AF. None
Indirectness of population	No indirectness
Interventions	(n=426) Intervention 1: Antiplatelets - Aspirin. Aspirin dose 150-200mg per day selected by the attending physician and also depending on the aspirin formulation available at each hospital. Patients were instructed to take aspirin every morning after breakfast. Treatment with 330mg of aspirin on alternative days was also permitted. . Duration Long-term. Concurrent medication/care: If patients taking anticoagulant or antiplatelets they were required to discontinue their treatment for at least 2 weeks before randomisation. Sporadic use of aspirin or anti-inflammatory agents was discouraged. Other medications were not prohibited during this trial. Comments: Low dose aspirin used (n=445) Intervention 2: Control - No treatment. No treatment. Duration Long-term. Concurrent medication/care: Patients taking anticoagulant or antiplatelet medicine were required to discontinue their treatment for at least two weeks before randomisation. Sporadic use of aspirin and non-steroidal anti-inflammatory agents was discouraged. Other medications were not prohibited during the trial. Comments: None

Study	Sato 2006{SATO2006}
Funding	Academic or government funding (Supported in part by a research grant for cardiovascular disease from the Ministry from Health and Welfare of Japan, by research funds for Prevention of Stroke in Patients with AF from the Japan Circulation Society, and by a research grant from the Osaka Heart club.)
RESULTS (NUMBERS ANALYSED): ASPIRIN versus NO TREATMENT Protocol outcome 1: Ischaemic stroke at Latest endpoint - Actual outcome: Ischaemic stroke at Long-term follow-up; Group 1: 13/426, Group 2: 16/445 Protocol outcome 2: All cause mortality at Latest endpoint - Actual outcome: Mortality at Mean follow up 768 days; Group 1: 10/426, Group 2: 9/445 Protocol outcome 3: Haemorrhagic stroke at Latest endpoint - Actual outcome: Haemorrhagic stroke at Long-term follow-up; Group 1: 4/426, Group 2: 2/445 Protocol outcome 4: Major bleeding at 30 days - Actual outcome: Major bleeding at Long-term follow up; Group 1: 3/426, Group 2: 0/445	
Protocol outcomes not reported by the study	Thromboembolic complications at Latest endpoint; Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 28: Saxena 2004[801]

Study	Saxena 2004{SAXENA2004}
Study type	Systematic Review
Number of studies (number of participants)	1 (n=455)
Countries and setting	Conducted in Multiple countries; Setting: 12 European countries and 1 in Israel
Line of therapy	2nd line
Duration of study	Intervention + follow up: Mean duration of follow up was 2.3 years

Study	Saxena 2004{SAXENA2004}
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Electrocardiographically proven
Stratum	Overall: None
Subgroup analysis within study	Not applicable: None
Inclusion criteria	Over 25 years who had a TIA or minor ischaemic stroke in the previous three months were eligible if AF had been electrocardiographically proven.
Exclusion criteria	AF secondary to other disorders such as hyperthyroidism were excluded. Other exclusions included: contraindication to, or an absolute indication for, aspirin; were taking non-steroid anti-inflammatory drugs, other anti-platelet aggregating drugs, or oral anticoagulants; and had no other sources of cardiac emboli, such as prosthetic valves, cardiac aneurysm, atrial myxoma, cardiothoracic ratio exceeding 0.65, myocardial infarction in the preceding 3 month.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 71 (7) years (includes placebo group). Gender (M:F): 59% / 41% (includes placebo group). Ethnicity: Unknown
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Extra comments	None
Indirectness of population	No indirectness: None
Interventions	(n=225) Intervention 1: Anticoagulants - Combinations. Physicians were free in their choice of oral anticoagulants but treatment was adjusted to obtain INR 2.5-4 (target 3). Duration Minimum 12 months. Concurrent medication/care: None Comments: None (n=230) Intervention 2: Antiplatelets - Aspirin. 300 mg per day. Duration Minimum 12 month. Concurrent medication/care: None Comments: This study had two groups: group 1 randomised participants to three arms anticoagulation, aspirin
Funding	Funding not stated (Cochrane review)
RESULTS (NUMBERS ANALYSED): ANTICOAGULANT versus ANTIPLATELET Protocol outcome 1: Major bleeding - Actual outcome: Major extrancranial bleed at Long-term follow-up; Group 1: 13/225, Group 2: 2/214 Protocol outcome 2: Haemorrhagic stroke at Latest endpoint	

Study	Saxena 2004{SAXENA2004}
- Actual outcome: Intracranial bleed; Group 1: 0/225, Group 2: 1/214	
Protocol outcomes not reported by the study	Ischaemic stroke at Latest endpoint; All cause mortality at Latest endpoint; Thromboembolic complications at Latest endpoint; Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

Table 29: Saxena 2004[802]

Study (subsidiary papers)	Saxena 2004{SAXENA2004A} (Van latum 1993{VANLATUM1993})
Study type	Systematic Review
Number of studies (number of participants)	2 (n=485)
Countries and setting	Conducted in Multiple countries; Setting: One study was conducted in 16 departments of Veterans Affairs medical centres (VA-SPINAF study). The EAFT study was conducted from 108 centres in 12 European countries and one from Israel.
Line of therapy	2nd line
Duration of study	Intervention time: EAFT study: mean follow up 2.3 years; VA-SPINAF study: mean follow-up 1.7 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Electrocardiogram
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with non-rheumatic AF and a previous TIA or minor ischaemic stroke
Exclusion criteria	Not reported in systematic review. EAFT study excluded patients that had AF secondary to other disorders such as hyperthyroidism.
Recruitment/selection of patients	Patients recruited that met the eligibility criteria.
Age, gender and ethnicity	Age - Mean (SD): 69 years. Gender (M:F): EAFT study reported average 56.5% men. VA-SPINAF study was 100% men.. Ethnicity: Not reported
Further population details	1. Age of study: 2. Time in therapeutic range (INR):
Indirectness of population	No indirectness

Study (subsidiary papers)	Saxena 2004{SAXENA2004A} (Van latum 1993{VANLATUM1993})
Interventions	(n=246) Intervention 1: Anticoagulants - Combinations. EAFT study physicians free in choice of oral anticoagulant (most choosing courmarin derivatives) but treatment was adjusted to obtain INR 2.5-4 (target value 3). VA-SPINAF study used sodium warfarin given as 2mg - goal to maintain the prothrombin tie ratio to 1.2 to 1.5 corresponding to an INR of 1.4 to 2.8. Duration Long-term treatment. Concurrent medication/care: Not reported in SR. EAFT: Patients not included in randomisation if they had a contraindication to, or an absolute indication for, aspirin; were taking non-steroid anti-inflammatory drugs, other antiplatelet aggregating drugs or oral anticoagulants. VA-SPINAF: patients required to discontinue warfarin treatment for at least six months before randomisation. Aspirin and other non-steroidal anti-inflammatory agents were withdrawn if both the patient and his physician agreed. Sporadic use of aspirin or non-steroidal anti-inflammatory agents was discouraged. (n=239) Intervention 2: Control - Placebo. Matching placebo tablets. Duration Long-term use. Concurrent medication/care: No further details
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): ANTICOAGULANT versus NO TREATMENT Protocol outcome 1: Major bleeding - Actual outcome: Major extrancranial bleed at Long-term follow-up; Group 1: 13/225, Group 2: 3/214	
Protocol outcomes not reported by the study	All-cause mortality at Latest endpoint; Thromboembolic complications at Latest endpoint; Hospitalisation at Latest endpoint; Haemorrhagic stroke at Latest endpoint; Quality of life at Latest endpoint

Table 30: Van Latum 1993[882]

Study (subsidiary papers)	**Van latum 1993[882]**
Study type	RCT (Patient randomised; Parallel)
Funding	Study funded by industry (Netherlands Heart foundation grant, Bayer Germany the UK stroke Association, Bayer subsidiaries in all participating countries, the University Hospitals of Utrecht and Rotterdam, and numerous others who helped to sponsor the annual

	meetings).
Number of studies (number of participants)	1 (N=1007)
Countries and setting	Conducted in Multiple countries; Setting: 108 centres in 12 European countries and from 1 in Israel
Line of therapy	2nd line
Duration of study	Long-term follow up - mean 2.3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis ~ Electrocardiographically proven at time, or in paroxysmal AF, in the preceding 24 months, and if echocardiography showed no evidence of rheumatic valvular disease
Stratum	Overall
Subgroup analysis within study	Not applicable: None
Inclusion criteria	Patients over 25 years who had a TIA or minor ischaemic stroke in the previous 3 months were eligible if AF had been electrocardiographically proven at the time or, in paroxysmal AF, in the preceding 24 months, and if echocardiography showed no evidence of rheumatic valvular disease.
Exclusion criteria	Patients with AF secondary to disorders such as hyperthyroidism were excluded. Patients were randomised unless contraindication to, or an absolute indication for, aspirin; were taking non steroid anti-inflammatory drugs other antiplatelet aggregating drugs or oral anticoagulants; and had no other sources of cardiac emboli, such as prosthetic valves, cardiac aneurysm, atrial myxoma, cardiothoracic ratio exceeding 0.65, myocardial infarction in the preceding 3 months.
Recruitment/selection of patients	None
Age, gender and ethnicity	Age - Mean (SD): 73 (SD 8). Gender (M:F): 56% male. Ethnicity: European and Israeli
Further population details	1. Age of study: Before 2000 (1993). 2. Time in therapeutic range (INR): Not applicable / Not stated / Unclear (None).
Extra comments	None . None
Intervention 1	Intervention 1: Antiplatelets ~ Aspirin. 300mg/day. Duration Long-term. Concurrent medication/care: None (N=404) Further details: Comments: None Intervention 2: Control ~ Placebo. Matching placebo supplied by Bayer. Duration Long-term. Concurrent medication/care: None reported(N=378) Comments: None

RESULTS (NUMBERS ANALYSED): ASPIRIN versus NO TREATMENT Protocol outcome 1: All cause mortality at Latest endpoint - Actual outcome: Mortality at Long-term follow-up; Group 1: 102/404, Group 2: 99/378 Protocol outcome 2: Major bleeding - Actual outcome: Major bleeding at Long-term follow up; Group 1: 6/404, Group 2: 4/378 Protocol outcome 3: Systemic embolic - Actual outcome: systemic embolic at Long-term follow up; Group 1: 6/404, Group 2: 9/378	
Protocol outcomes not reported by the study	Ischaemic stroke, Haemorrhagic stroke, Hospitalisation at Latest endpoint; Quality of life at Latest endpoint

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.6 Bleeding stroke risk tools

Table 31: Apostolakis 2012 [45]

Study details	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Apostolakis 2012A[45] Country of study: UK and	Patient group: AF undergoing anticoagulation randomised to vitamin K antagonist Inclusion criteria: as above	$HEMORR_2HAGES$ HAS-BLED ATRIA	C statistic for major bleeding	HAS-BLED 0.65 (0.56-0.73) SE 0.046 $HEMORR_2HAGES$ 0.6 (0.51-0.69) SE 0.043 Atria 0.61 (0.51-0.70) SE 0.048	Funding: AMADEUS study funded by Sanofi-Aventis Limitations:
			Cox regression analysis for major	$HEMORR_2HAGES$ >1: 1.8 (0.9-3.5) p=0.08	

Netherlands Study design: Retrospective analysis of AMADEUS RCT (VKA arm) Setting: NR Duration of follow-up: 429±118 days	Exclusion criteria: history of active malignancy, alcohol abuse, or major bleeding. All patients N: 2292 Age (mean): 70.2±9.1 years M/F: 65% male		bleeding: HR (95% CI)	HAS-BLED>2: 2.4 (1.3-4.6) p 0.006 ATRIA>3: 2.3 (1.1-5.1) p= 0.03	Retrospective analysis No genetic information for HEMORR$_2$HAGES scores. Exclusion criteria from RCT included history of bleeding which is a component of the scores. Notes: NR
			Comparison of AUCs or C indices for major bleeding	AUC difference (95% CI) HAS-BLED vs HEMORR$_2$HAGES 0.04 (-0.03 to 0.12), z score 1.1, p=0.23 HAS-BLED vs ATRIA 0.04 (-0.06 to 0.14), z score 0.85, p=0.04 ATRIA vs HEMORR$_2$HAGES 0.0 (-0.09 to 0.09), z score 0.04, p=0.97	

Table 32: Apostolakis 2013 [44]

	Patients	Bleeding risk score	Outcome measures- all 'any clinically relevant bleeding'*	Effect size	Comments
Apostoakis 2013[44] Country of study: multiple countries Study design:	Patient group: AF undergoing anticoagulation randomised to vitamin K antagonist Inclusion criteria: as above Exclusion criteria: history of active malignancy, alcohol abuse, or major bleeding.	CHA_2DS_2-VASc $CHADS_2$ HAS-BLED	HAS-BLED	AUC 0.6 SE under the non-parametic assumption 0.02 95% CI 0.56-0.63 p value (null hypothesis: true area=0.5) <0.0001	Funding: Sanofi Limitations: Limited comparability to other studies due to definition of outcome No genetic information for
			$CHADS_2$	AUC 0.51 SE under the non-parametic assumption 0.02 95% CI 0.47-0.55 p value (null hypothesis: true	

Post hoc analysis of AMADEUS study Setting: NR Duration of follow-up: 429±118	All patients N: 2293 Age (mean): 70.2±9.1 M/F: 65% male			area=0.5) 0.590	HEMORR$_2$HAGES scores. Exclusion criteria from RCT included history of bleeding which is a component of the scores. Notes: *'any clinically relevant bleeding' included major and clinically relevant non-major bleeding events. 'major bleeding' was bleeding that was fatal, intracranial or affected another critical anatomical site, or overt bleeding with a drop in Hb≥20g/L or requiring transfusion of two or more units of erythrocytes. 'clinically relevant non-major bleeding' was defined as overt bleeding that did not satisfy the criteria for major bleeding but that met defined criteria and included repetitive epistaxis for >5 min at least twice
			CHA_2DS_2-VASc	AUC 0.53 SE under the non-parametic assumption 0.02 95% CI 0.49-0.57 p value (null hypothesis: true area=0.5) 0.125	
			AUC difference HAS-BLED vs. $CHADS_2$	0.085 Z 3.93 P <0.001	
			AUC difference HAS-BLED vs. CHA_2DS_2-VASc	0.065 Z 3.23 P 0.001	
			Net reclassification improvement HAS-BLED vs $CHADS_2$	(95%) categorical 0.13 (0.05-0.21) P 0.001 (95%) continuous 0.16 (0..03-0.29) P 0.017	
			Net reclassification improvement HAS-BLED vs CHA_2DS_2-VASc	(95%) categorical 0.10 (0.004-0.19) P 0.04 (95%) continuous 0.29 (0..16-0.42) P <0.001	

					in 24h, haematuria (spontaneous or lasting >24h), haematemesis, and subcutaneous haematomas of >25cm^2 if spontaneous, or > 100cm^2 if after trauma.

Table 33: Fang 2011 [327]

Study details	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Fang 2011[327] Country of study: USA Study design: Retrospective cohort Setting: Kaiser Permanente of	Patient group: non-valvular, non-transient atrial fibrillation Inclusion criteria: as above Exclusion criteria: All patients N: 13,559 Age (mean): 56±8 years M/F: 81/34 Drop outs: 20	The Anticoagulation and Risk factors In Atrial fibrillation (ATRIA) study – internal validation study.	Major bleeding	307/6123	Funding: National Institute on Aging, the National Heart, Lung and Blood Institute, the Eliot B. and Edith C. Shoolman fund of the Massachusetts General Hospital (Boston, MA) and a research grant from Daiichi Sankyo, Inc. Limitations: Retrospective study some baseline details
			Bleeding risk classification n (%) patients in each risk category	Low: 0 to 3 Moderate: 4 High: 5 to 10	
			Major bleeding events by risk category in validation cohort, n (%)	Low: 0.8% Moderate: 2.6% High: 5.8%	
			Net reclassification improvement	Atria risk score – Referent HEMORR$_2$HAGES: 28.9%	

Northern California, a large integrated healthcare system. Duration of follow-up: NR					(age and sex) not provided and duration of follow-up not reported Notes: Major bleeding defined as fatal, requiring transfusion of 2 U packed blood cells, or haemorrhage into a critical anatomical site (e.g. intracranial, retroperitoneal). Internal validation for atria score.

Table 34: Friberg 2012 [351]

Study details	Patients	Prognostic factor	Outcome measures	Effect size	Comments
Friberg 2012[352] Country of study: USA Study design:	Patient group: AF patients Inclusion criteria: All individuals with a diagnosis of AF at any Swedish hospital between 1 July 2005 and 31 December 2008 were identified through the Swedish National Hospital Discharge Registry (HDR) by the	HAS-BLED HEMORR$_2$HAGES In the whole cohort, 1600 (0.6/100 years at risk) intracranial bleeds and 5810 (2.3/100 years at risk) major bleeding events occurred.	Major bleeding	5810 (2.3/100 years at risk)	Funding: National Institute on Aging (R01 AG15478 and K23 AG028978), the National Heart, Lung and Blood Institute (U19 HL91179 and RC2HL101589), the Eliot B. and Edith C.
			Intracranial bleeding	1600 (0.6/100 years at risk)	
			Intracranial bleed (HAS-BLED)	OAC 0.6 (0.58-0.62)	
			C statistics (OAC group)	HAS-BLED: 0.61 [0.59-0.62] HEMORR$_2$HAGES: 0.63 [0.61-0.64]	

Retrospective cohort Setting: Kaiser Permanente of Northern California, a large integrated healthcare system. Duration of follow-up: 26.2 months (median), range 1-97 months	ICD-10 code I489 with or without any of the specifying sub codes A–F. Exclusion criteria: Patients with 'silent' AF and patients with AF who were taken care of in the primary care or in other open clinics not affiliated with a hospital during follow-up All patients N: 182,678 We studied 182 678 subjects with AF, of which 170 291 (mean age 76.2 years, 53% male) fulfilled our criteria of non-valvular AF and survival of the first 14 days after index date and were prospectively followed for an average of 1.5 years (259 798 years at risk). Of these patients, 90 490 (53%) never used warfarin, and 68 307 (40%) had warfarin at index. There were another 12 498 patients without warfarin at baseline who began to use warfarin during follow-up and 3956 patients with warfarin at baseline who stopped taking it during follow-up.				Shoolman fund of the Massachusetts General Hospital (Boston, MA) and a research grant from Daiichi Sankyo, Inc. Limitations: Labile INR data and genetic factors not available for the scores.

Table 35: Gage 2006 [364]

Study details	Patients	Prognostic factor	Outcome measures	Effect size	Comments
Gage 2006[364] Country of study: USA Study design: Retrospective cohort Setting: Registry of hospital patients Duration of follow-up: 3,138 pt-years	Patient group: All individuals with a diagnosis of AF at any Swedish hospital between 1 July 2005 and 31 December 2008 were identified through the Swedish National Hospital Discharge Registry (HDR) by the ICD-10 code I489 with or without any of the specifying sub codes A–F. Inclusion criteria: see above Exclusion criteria: Patients with 'silent' AF and patients with AF who were taken care of in the primary care or in other open clinics not affiliated with a hospital during follow-up All patients N: 3971 (validation) We studied 182 678 subjects with AF, of which 170 291 (mean age 76.2 years, 53% male) fulfilled our criteria of non-valvular AF and survival of the first 14 days after index date and were prospectively followed for an average of 1.5 years (259 798 years at risk). Of these patients,	$HEMORR_2HAGES$ In the whole cohort, 1600 (0.6/100 years at risk) intracranial bleeds and 5810 (2.3/100 years at risk) major bleeding events occurred.	Major bleeding	5810 (2.3/100 years at risk)	Funding: Agency for Health Care Research and Quality and by the American Heart Association. Limitations: Retrospective study Definition of major bleeding not fully clear Major bleeding: ICD-9-CM codes for major bleeds except those unrelated to antithrombotic therapy
			Intracranial bleeding	1600 (0.6/100 years at risk)	
			Bleeding risk classification n (%) patients in each risk category	Low: 0–1 Intermediate: 2–3 High: ≥4 Among those on warfarin (n=1604) Low: 717 (44.7%) Intermediate: 694 (43.3%) High: 193 (12.0%)	
			Major bleeding events by risk category in validation cohort, n (%)	Low: 15 (2.1%) Intermediate: 35 (5.0%) High: 17 (8.8%)	
			Intracranial bleed (HAS-BLED)	OAC 0.6 (0.58-0.62)	
			Classification	Low: 22 (1.1%) Intermediate: 14 (1.9%) High: 12 (4.9%)	
			Bleeding risk classification n (%) patients in each risk category	Low: 0–1 Intermediate: 2–3 High: ≥4 Among those on warfarin (n=1604) Low: 717 (44.7%) Intermediate: 694 (43.3%)	

	90 490 (53%) never used warfarin, and 68 307 (40%) had warfarin at index. There were another 12 498 patients without warfarin at baseline who began to use warfarin during follow-up and 3956 patients with warfarin at baseline who stopped taking it during follow-up.			High: 193 (12.0%)	
			C statistic (on warfarin)	HEMORR$_2$HAGES: 0.67 (SD 0.04)	

Table 36: Gallego 2012 [366]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Gallego 2012[366] Country of study: Spain Study design: Prospective cohort Setting: outpatient anticoagulation clinic	Patient group: anticoagulated patients with permanent or paroxysmal AF who were stabilised for at least 6 months on oral anticoagulation Inclusion criteria: INR between 2.0 and 3.0 during the previous 6 month clinic visits Anticoagulation with acenocoumarol Exclusion criteria:	HAS-BLED	C statistic for major bleeding	0.7 (0.64-0.76) p<0.001	Funding: partially supported by Sociedad Espanola de Cardiologia, RECAVA (Re Tematica de Investigacion Cooperativa en Enfermedades Cardiovasculares) RD06/0014/039, from ISCIII and PI081531-FEDER (Fondo Europeo de Desarrollo egional) from Instituto de Salud Carlos III.
			Haemorrhagic death	8 (0.4%/ year)	
			Number of haemorrhagic events	75 (3.6%/year)	
			Univariable analysis for the composite of major bleeding events	HAS-BLED HR 1.96 (1.60-2.41); p<0.001 HAS-BLED≥3 HR 3.68 (2.37-5.78); p<0.001 CHADS$_2$ 1.23 (1.03-1.47), p=0.022	

Duration of follow-up: median 861 days (718-1016)	Patients with prosthetic heart valves Acute coronary syndrome Stroke (ischemic and embolic) Valvular AF Any hemodynamic instability Hospital or surgical admission in the preceding 6 months All patients N: 965 Age (median): 76 years; IQR 70-81 M/F: 50% M Drop outs: NR				Limitations: Risk in lowest group not reported Notes: Bleeding events were assessed by the 2005 International Society on Thrombosis and Haemostasis criteria. Their definition was: fatal bleeding, and/or symptomatic bleeding in a critical area or organ such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding a causing a fall in haemoglobin level of 20g per L or more, or leading to transfusion of 2 or more units of whole blood or red cells.

Table 37: Guo 2012 [404]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Guo 2012[44,404] Country of study: China Study design: cohort Setting: hospital Duration of follow-up: 1.9 years (median) IQR 1.4-2.6	Patient group: patients with AF Inclusion criteria: pre-existing diagnosis of permanent, persistent or paroxysmal AF, development of new-onset AF during their current admission. Exclusion criteria: NR All patients N: 1034 Age (median): 75 (63-83) Female, n (%): 281 (27.1%)	CHA_2DS_2-VASc $CHADS_2$ HAS-BLED	Major bleeding according to HAS-BLED criteria (bleeds per 100 patient-year+ 95% CI)	Patients not on warfarin Risk score: 0: 1.8 (0.1-9.7) 1: 2.1 (0.4-6.1) 2: 1.8 (0.6-4.1) 3: 1.4 (0.4-3.6) ≥4: 4.0 (1.3-9.1) Patients on warfarin risk score: 0: 3.0 (0.1-15.8) 1: 0 (0-7.8) 2: 3.6 (0.1-18.4) 3: 2.5 (0.1-13.2) ≥4: 9.1(0.2-41.3)	Funding: NR Limitations: not all results data shown No validated HAS-BLED score in a Chinese population Gender selection bias Limited number of patients on warfarin, for analysis of bleeding risk factors. Some patients had degenerative valvular disease could have impacted TE/ bleeding events.
			Thromboembolic event rate in non-anticoagulated patients	$CHADS_2$ risk score: 0: 0 1: 2.9 2: 4.9 3: 3.4 ≥4: 4.9	
			Incidence of thromboembolic events in patients without warfarin (% in risk category)	$CHADS_2$ Low: 0 Intermediate: 6 (2.9%) High: 27 (4.6%) C statistic(95% CI): 0.58 (0.5-0.67) P value: 0.109 CHA_2DS_2-VASc	

				Low: 0 (0%) Intermediate: 0 (0%) High: 32 (4.5%) C statistic(95% CI): 0.72 (0.64-0.81) P value: <0.001	
			Major bleeding	Non-anticoagulated pts HAS-BLED score: 2: 1.8 (0.6-4.1) ≥3: 2.2 (1.0-4.2) C statistic 0.61 (0.51-0.71) Anticoagulated pts HAS-BLED score: 3: 2.5%/ year ≥4: 9.1%	
			Stroke/ TE	C statistic $CHADS_2$: 0.58 (0.5-0.67) p= 0.109 CHA_2DS_2-VASc: 0.72 (0.64-0.81) p=<0.001	
			NRI Use of CHA_2DS_2-VASc compared to $CHADS_2$	16.6% (3.9-29.1%)	

Table 38: Lip 2012 [605]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Lip 2012C[605] Country of study: France Study design: Retrospective cohort Setting: 4 hospital institution Duration of follow-up:	Patient group: non-valvular AF or atrial flutter Inclusion criteria: as above Exclusion criteria: Valvular disease Missing values on VKA treatment All patients N: 1254+4260+1282 Age (mean): HAS-BLED high risk: 77.7 HAS-BLED moderate risk: 73.8 HAS-BLED low risk: 49.0 M/F: High: 38.9% female Moderate: 39.5% female Low: 30.7% female Drop outs: NR	HAS-BLED HEMORR$_2$HAGES ATRIA	C statistics (95% CIs) HAS-BLED (as a continuous variable)	0.61 (0.59-0.63) all patients 0.61 (0.58-0.65) patients on VKA 0.60 (0.56-0.64) patients not on VKA	Funding: NR Limitations: Generic information not available (apart from serum creatinine and haematocrit). Inpatient population; may not be relevant to outpatient setting. Notes: Major bleeding defined as bleeding with a reduction in Hb level of at least 20g/L, or with transfusion of at least 1 unit of blood, or symptomatic bleeding in a critical area or organ (e.g. intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular or
			C statistic HAS-BLED (as a categorical variable)	0.59 (0.57-0.61) all patients 0.58 (0.55-0.61) patients on VKA 0.60 (0.54-0.64) patients not on VKA	
			C statistic HEMORR$_2$HAGES (as a continuous variable)	0.58 (0.56-0.61) all patients 0.59 (0.56-0.62) patients on VKA 0.59 (0.54-0.63) patients not on VKA	
			C statistic HEMORR$_2$HAGES (as a categorical variable)	0.54 (0.51-0.56) all patients 0.53 (0.50-0.57) patients on VKA 0.55 (0.50-0.59) patients not on VKA	
			C statistic ATRIA (as a continuous variable)	0.59 (0.57-0.62) all patients 0.60 (0.56-0.63) patients on VKA 0.59 (0.55-0.64) patients not on VKA	
			C statistic ATRIA (as a categorical variable)	0.54 (0.52-0.57) all patients 0.55 (0.52-0.59) patients on VKA 0.47 (0.42-0.51) patients not on VKA	
			Hazard ratio of major bleeding (continuous variable)	HAS-BLED: 1.40 (0.31-1.51) HEMM: 1.48 (1.35-1.61) ATRIA: 1.26 (1.20-1.31)	
			Hazard ratio of major bleeding (categorical variable)	HAS-BLED: 1.85 (1.60-2.13) HEMM: 1.80 (1.49-2.17) ATRIA: 1.61 (1.41-1.84)	

			Major bleeding event rates (95% CI) per 100 person years	High risk (has-bled ≥3) n= 1254 158 events; event rate 1.26 (1.07-1.47) Moderate risk (has-bled 1-2) n=4620 events 343; event rate 0.74 (0.67-0.83) Low risk (has-bled 0) n=1282 events 49; event rate 0.38 (0.28-0.51) P value for 2 sided chi squared test <0.001	pericardial, or intramuscular with compartment syndrome), or bleeding that causes death.

Table 39: Lip 2011 [615]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Lip 2011E[615] Country of study: SPORTIF III from 23 countries and SPORTIF V from North America Study design: Retrospective cohort Setting: Trial	Patient group: non valvular AF at moderate to high risk of thromboembolism. Inclusion criteria: age 18 and older, persistent or paroxysmal AF and at least 1 of the following stroke risk factors: hypertension, age 75 years and older, previous stroke, transient ischaemic attack or systemic embolic event; left ventricular dysfunction, age 65 years and older with diabetes mellitus. Exclusion criteria: NR All patients N: 7329	HAS-BLED HEMORR$_2$HAGES	C statistic for HAS-BLED	0.66 (0.61-0.70) for warfarin patients 0.65 (0.61-0.68) for all patients 0.66 (0.55-0.74) for warfarin naïve at baseline 0.6 (0.53-0.68) for warfarin and aspirin	Funding: SPORTIF III and V studies were sponsored by AstraZeneca. Limitations: Generic information not available (apart from serum creatinine and haematocrit). Retrospective study Notes: Major bleeding defined as fatal or clinically overt bleeding associated with either transfusion of ≥20 g/l decrease in
			C statistic for HEMORR$_2$HAGES	0.61 (0.56-0.65) in warfarin patients 0.62 (0.52-0.72)in all patients 0.62 (0.52-0.72) for warfarin naïve at baseline 0.58 (0.51-0.66) for warfarin and aspirin	
			Hazard ratios for HAS-BLED	Moderate vs low: 4.31 (1.99-9.33) High vs moderate: 2.02 (1.41-2.90) High vs low: 8.56 (3.86-188.98)	
			Hazard ratios for HEMORR$_2$HAGES	Moderate vs low: 2.19 (1.55-3.10) High vs moderate: 0.34 (0.08-1.38) High vs low: 0.75 (0.18-3.06)	

Duration of follow-up: NR	Age (mean) – no bleed: 70.9 and with bleeding event: 73.9 years M/F: 69/31% Drop outs: NR				haemoglobin or bleeding involving a critical anatomic site other than the brain parenchyma.

Table 40: Naganuma 2012 [681]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Naganuma 2012[681] Country of study: Japan Study design: Retrospective cohort Setting: Outpatient setting Duration of follow-up: Median 27 months	Patient group: consecutive non valvular AF patients aged 70 years or over who were taking warfarin and undergoing PT-INR measurements between May 2001 and December 2006. Identified patients from the automated outpatient accounting databases of the department of Cardiology at Tokyo Women's medical University hospital. Inclusion criteria: As above. Exclusion criteria: Patients with mitral valve disease, history of valvular repair or replacement, or concurrent hyperthyroidism. All patients N: 845	HAS-BLED	Hazard ratio for major bleeding events: HAS-BLED ≤3 vs <3	HR 2.8 (1.7-4.6) p=<0.001 Has-bled 1-2 n=346 rate (n) 2.0 (7) Has-bled ≥3 n-499 rate (n) 5.6(28)	Funding: supported by funds from the Japan Research Promotion Society for Cardiovascular diseases. Limitations: NO details on imputation. Retrospective Notes: Major bleeding events defined as intracranial haemorrhage observed by imaging or surgery, intraocular haemorrhage leading to a substantial loss of vision, gastrointestinal

	Age (median): 74 (70-91) M/F: 69.5/30.5% Drop outs: 36				haemorrhage or other sever haemorrhage that was fatal or required an endoscopic haemostasis, a surgical intervention, hospital admission or a blood transfusion.

Table 41: Oldgren 2011 [708]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Oldgren 2011[708] Country of study: 44 countries Study design: Retrospective cohort Setting: Trial Duration of follow-up: Median 2 years	Patient group: Inclusion criteria: documented AF and at least one of the following risk factors for stroke: previous stroke or transient ischemic attack; congestive heart failure or reduced left ventricular ejection fraction; and aged at least 75 years or at least 65 years with diabetes mellitus, hypertension or coronary artery disease. Exclusion criteria: severe heart valve disorder, recent stroke, increased risk for haemorrhage, creatinine clearance less than 30mL/min, or active lever disease.	$CHADS_2$	Major bleeding rate in all participants, %/year	0 to 1 rate 2.26 2 rate 3.11 3 to 6 rate 4.42 P <0.001 (for linear trend)	Funding: Study funded by Boehringer-Ingelheim and coordinated by the Population Health Research Institute. Limitations: Retrospective Notes: Did not provide outcomes listed in protocol for this question. Major bleeding was defined as a reduction in haemoglobin level of at least 20g/L or

	All patients N: 18113 Age (median): 71 M/F: 11514/6598 Drop outs: NR				transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ.

Table 42: Olesen 2011 [711]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Olesen 2011A[709] Country of study: Denmark Study design: Retrospective cohort Setting: Nationwide data on patients admitted to hospital with AF	Patient group: From the national patient registry, all patients with non-valvular AF were identified between 1997 and 2006 with or without oral anticoagulation. Inclusion criteria: as above Exclusion criteria: no previous diagnoses of mitral or aortic valve disease and no mitral or aortic valve surgery. Follow up was started seven days after discharge. Patients were excluded if they died or had a thromboembolism in this seven day quarantine period. Patients who had received vitamin K antagonists.	HAS-BLED HEMORR$_2$HAGES	Major bleeding events during 1 year of follow-up in non OAC cohort	Has-bled low (score 0-1) 2,54 (2.34-2.76) Has-bled intermediate (score 2) 5.4 (5.08-5.75) Has-bled high (score≥3) 7.68 (7.3-8.08) Haemorrhages low (score 0-1) 2.48 (2.29-2.68) Haemorrhages intermediate (score 2-3) 5.53 (5.25-5.82). Haemorrhages high (score≥4) 11.23 (10.56-11.95)	Funding: NR Limitations: Retrospective Genetic and labile INR information not available for the scores Notes: Outcome was hospitalisation or death from major bleeding, including gastrointestinal bleeding, intracranial bleeding, bleeding form the urinary tract or airway bleeding.
			Major bleeding events during 1 year of follow-up in OAC cohort	Has-bled low (score 0-1) 2.66 (2.40-2.94) Has-bled intermediate (score 2) 5.54 (5.15-5.96) Has-bled high (score≥3) 8.11 (7.61-8.64) Haemorrhages low (score 0-1) 3.06 (2.83-3.32)	

Duration of follow-up: Follow up at 1, 5 and 10 years	All patients: 118584 Patients with no treatment with VKAs or heparins (non OAC cohort): N: 73813 Patients in treatment with VKAs and heparins (OAC cohort): N: 44771 Age: NR M/F: NR Drop outs: 184 patients discharged within seven days from study end, 2022 patients died within seven days from discharge, 490 experienced a major bleeding within seven days from discharge.			Haemorrhages intermediate (score 2-3) 6.33 (5.95-6.73). Haemorrhages high (score≥4) 12.16 (11.09-13.34)	
			Hazard ratio of major bleeding (unadjusted cox proportional hazard analyses) in non OAC cohort	Has-bled: Low 1.00 Mod 2.10 (1.89-2.33) High 2.95 (2.95-3.26) HEMORR$_2$HAGES: Low 1.00 Mod 2.18 (1.99-2.4) High 4.34 (3.92- 4.8)	
			Hazard ratio of major bleeding (unadjusted cox proportional hazard analyses) in OAC cohort	Has-bled: Low 1.00 Mod 2.07 (1.83-2.34) High 3.00 (2.67-3.38) HEMORR$_2$HAGES: Low 1.00 Mod 2.04 (1.85-2.26) High 3.87 (3.43-4.38)	
			C stats (continuous scores)	Non OAC cohort Has-bled (0-8) 0.806 (0.777-0.833) Hae (0-11) 0.758 (0.727-0.788) OAC cohort Has-bed (0-8) 0.795 (0.759-0.829) Hem (0-11) 0.771 (0.733-0.806)	
			C stats (categorical scores)	Non OAC cohort Has-bled 0.815 (0.786-0.842) Hem 0.769 (0.738-0.798) OAC cohort	

				Has-bled 0.795 (0.759-0.829) Hem 0.782 (0.745-0.816)	

Table 43: Pisters 2010 [741]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Pisters 2010[741] Country of study: USA Study design: Retrospective cohort Setting: from Euro heart survey on AF Duration of follow-up: 3,138 pt-years	Inclusion criteria: All individuals with a diagnosis of AF at any Swedish hospital between 1 July 2005 and 31 December 2008 were identified through the Swedish National Hospital Discharge Registry (HDR) by the ICD-10 code I489 with or without any of the specifying sub codes A–F. Exclusion criteria: NR All patients: N: Derivation- n=3978 Validation- n=3071, 66.8 (12.8); 59% male	HAS-BLED	C statistic	Overall: Has-bled: 0.72 (0.65-0.79) Haemorrhages: 0.66 (0.57-0.74) OAC only: Has-bled: 0.69 [0.59-0.80] Haemorr$_2$hages: 0.64 [0.53-0.75]	Funding:NR Limitations: Retrospective study Definition of major bleeding not fully clear. Genetic data not available for score. Major bleeding: Requiring hospitalisation &/or causing drop of Hb ≥2g/l, need for blood transfusion that was not a haemorrhagic stroke
			Number of bleeds by HAS-BLED classification Low=score 0-1 Intermediate=2 High=>2	Low: 22 (1.1%) Intermediate: 14 (1.9%) High: 12 (4.9%) Total bleeds: 48/3071	
			Outcome measures	Effect size	

Table 44: Roldan 2011 [782]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Roldan 2011D[782] Country of study: Spain/US Study design: Prospective cohort but baseline from retrospective outpatient registry Setting: outpatient anticoagulation clinic Duration of follow-up: Median 828 days	Patient group: consecutive patients with permanent/paroxysmal AF from outpatient anticoagulation clinic, who were stabilised on oral anticoagulation therapy for at least 6 months (INR 2-3). Inclusion criteria: see above Exclusion criteria: Valvular AF or prosthetic heart values, any acute coronary syndrome, stroke (embolic or ischemic) or hemodynamic instability in the preceding 6 months, as well as any hospital admissions or surgical interventions during the same period. All patients N: 829 Age (median and IQR): 76 (70-80) M/F: 416/413	HAS-BLED	Hazard ratio for major bleeding events (multivariate analysis) – continuous variables	HAS-BLED: 1.90 (1.53-2.37) P<0.001	Funding: Partially supported by Sociedad Espanola de Cardiologi, RD06/0014/039, (RECAVA) from ISCIII; and P1081531-FEDER from ISCIII. . Limitations: NR Notes: Bleeding events were assessed following 2005 International Society on Thrombosis and Haemostasis criteria.
			Major bleeding episodes	N=68/829 Event rate: 3.6% per year	

Table 45: Roldan 2013 [781]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Roldan 2013[781] Country of study: Spain Study design: Prospective cohort but baseline from retrospective outpatient registry Setting: Outpatient clinic Duration of follow-up: 952 days (median) 785-1074	Patient group: anticoagulated patients with permanent or paroxysmal AF who were stabilised for at least 6 months on oral anticoagulation Inclusion criteria: INR between 2.0 and 3.0 during the previous 6 month clinic visits Anticoagulation with acenocoumarol Exclusion criteria: Patients with prosthetic heart valves Acute coronary syndrome Stroke (ischemic and embolic) Valvular AF Any hemodynamic instability Hospital or surgical admission in the preceding 6 months All patients N: 937 Age (median): 76 M/F: 49%M	HAS-BLED ATRIA	C statistic	Has-bled (quantitative) 0.71 (0.68-0.74) Atria (quantitative) 0.68 (0.65-0.71) Atria (0-4 vs≥5) 0.59 (0.55-0.62) Has-bled (0-2 vs≥3) 0.68 (0.65-0.71)	Funding: partially supported by Sociedad Espanola de Cardiologia, [RD06/0014/039], (RECAVA) from ISCIII, Beca Cajamurcia FFIS2010, and PIII/1256 from ISCIII. Limitations: Only stable, warfarin experienced patients were included, leading to possible selection bias Notes: Bleeding events were assessed by the 2005 International Society on Thrombosis and Haemostasis criteria. Their definition was: fatal bleeding, and/or symptomatic bleeding in a critical area or organ such as
			Hazard ratio of major bleeding	HAS-BLED≥3vs<3: 4.55 (2.82-7.34) ATRA≥5<5: 3.05 (1.87-4.97)	
			HR ratio of major bleeding (continuous variable)	HAS-BLED: 2.23 (1.82-2.73) ATRA: 1.34 (1.22-1.47)	

					intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding a causing a fall in haemoglobin level of 20g per L or more, or leading to transfusion of 2 or more units of whole blood or red cells.

Table 46: Roldan 2013 [780]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Roldan 2013B[44,404,780] Country of study: NR Study design: Retrospective cohort	Patient group: AF patients on anticoagulation Inclusion criteria: permanent or paroxysmal AF on OAC Exclusion criteria: prosthetic heart valves, acute coronary syndrome, stroke (ischaemic or embolic), valvular AF, any haemodynamic instability, hospital admissions or surgical intervention in the preceding 6	CHA_2DS_2-VASc $CHADS_2$ HAS-BLED	Major bleeding $CHADS_2$ vs. HAS-BLED	$CHADS_2$ C-statistic (95% CI) 0.59 (0.56-0.62) HAS-BLED C-statistic (95% CI) 0.69 (0.67-0.72) P value $CHADS_2$ vs. HAS-BLED<0.001 NRI 38.26% SD 7.3 P <0.001	Funding: Partially supported by Sociedad Espanola de Cardiologia, RD06/0014/039, (RECAVA) from ISCIII; and PI11/1256-FEDER from ISCIII Limitations: only pts with stable OAC were included therefore those more likely to have adverse events
			Major bleeding CHA_2DS_2-VASc vs. HAS-BLED	CHA_2DS_2-VASc C-statistic (95% CI) 0.58 (0.55-0.60) HAS-BLED C-statistic (95% CI) 0.69 (0.67-0.72) P value CHA_2DS_2-VASc vs. HAS-BLED<0.001	

Setting: NR Duration of follow-up: median 996 (802-1254 days)	months. All patients N: 1370 Age (median): 76 (IQR 71-81) M/F: 47% male			NRI 37.6% SD 7.81 P <0.001	were excluded
			Cox regression analysis for the composite of major haemorrhagic events (univariable analysis HR/ 95% CI)	HAS-BLED 1.94 (1.66-2.28) p <0.001 CHA_2DS_2-VASc 1.22 (1.09-1.37) p 0.001 CHA_2DS_2 1.31 (1.38-1.52) p <0.001	
			Predictive value of scores for bleeding events by themselves (multivariable analysis) HR (95% CI)	HAS-BLED 2.02 (1.67-2.45) p <0.001 CHA_2DS_2 0.94 (0.79-1.12) p 0.488	
			Predictive value of scores for bleeding events adjusted by HAS-BLED score (multivariable analysis) HR (95% CI).	HAS-BLED 2.02 (1.67-2.45) p <0.001 CHA_2DS_2-VASc 0.96 (0.83-1.10) p 0.566	

Table 47: Seet 2013 [805]

	Patients	Bleeding risk score	Outcome measures	Effect size	Comments
Seet 2013[805] Country of study: US Study design:	Patient group: Ischemic stroke patients with persistent AF or flutter or 2 or more episodes of AF or flutter, at least 2 weeks apart in the 12 months before enrolment.	HAS-BLED $HEMORR_2HAGES$	Major bleeding events	41/100 9.79 bleeds per 100 patient years	Funding: Rochester epidemiology Project was supported by the National Institute on Aging of the National Institutes of Health.
			Cumulative major bleeding events by year after warfarin treatment	Year 1: 14% Year 5: 26%	
			C statistic (assumed	HAS-BLED: 0.72	

Prospective cohort but baseline from outpatient registry Setting: outpatient after stroke Duration of follow-up: 419 person years. Follow up from Jan 1985-until death or until August 2011.	Baseline information used to derive scores before initiation of warfarin. Inclusion criteria: see above Exclusion criteria: patients with amaurosis fugax and TIA All patients N: 100 Age (mean): 79.3 (11.5) M/F: 68% females No patients lost to follow up		continuous)	HEMORR$_2$HAGES: 0.76	Limitations: Genetic information not available. Major bleeding defined as fatal or clinically overt bleeding associated with either transfusion of 2 or more units of blood or greater than or equal to 20 g/L decrease in haemoglobin or bleeding involving a critical anatomic site. Intracranial haemorrhage was counted as major bleeding event.

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.7 Left Atrial Appendage Occlusion (LAAO)

Table 48: Holmes 2009[461] and Reddy{Reddy, 2013 REDDY2013A /id}

Study	Holmes 2009{HOLMES2009A} {Reddy, 2013 REDDY2013A /id}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=707)
Countries and setting	Conducted in Multiple countries; Setting: 59 sites in the USA and Europe.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2.3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Baseline neurological assessment by a neurologist. For patients who had a history of stroke, a CT or MRI scans taken at baseline. Patients also had an echocardiographic examination to assess other echocardiographic exclusion criteria.
Stratum	People who can take anticoagulants: Study included people who could take anticoagulants
Subgroup analysis within study	Not applicable: None
Inclusion criteria	CHADS2 risk score of 1 or more (at least one of the following; previous stroke or transient ischaemic attack, congestive heart failure, diabetes mellitus, hypertension, or were 75 years or older).
Exclusion criteria	Contraindications to warfarin comorbidities other than atrial fibrillation that required chronic warfarin use, LAA thrombus, a patent foramen ovale with atrial septal aneurysm and right-to-left shunt, mobile aortic atheroma, and symptomatic carotid artery disease.
Recruitment/selection of patients	Enrolment from February 2005 to June 2008.
Age, gender and ethnicity	Age - Mean (SD): Intervention group: 71.7 (8.8) and control group: 72.7 (9.2). Gender (M:F): 497/210. Ethnicity: Mixed: Asian, Black/African- American, White, Hispanic, Hawaiian, Other. (>91% white)
Further population details	None
Extra comments	Patients aged 18 years or older with paroxysmal, persistent, or permanent non-valvular atrial fibrillation.
Indirectness of population	No indirectness: Patients with AF and indication for anticoagulation.
Interventions	(n=244) Intervention 1: Anticoagulants - Warfarin. Warfarin - target international normalised ratio (INR) between 2.0-3.0. Duration 24 months. Concurrent medication/care: Monitoring of the INR done by the patients treating physician at least every two weeks for six months and at least once a month thereafter (n=463) Intervention 2: Left atrial appendage occlusion. Watchman device - self expanding nickel titanium frame

Study	Holmes 2009{HOLMES2009A} {Reddy, 2013 REDDY2013A /id}
	structure with a fixation barbs and a permeable polyester fabric cover. The device ranges in diameter from 21-33 mm to accommodate varying LAA anatomy and size. Implanted via a trans-septal approach by use of a catheter based delivery system to seal the ostium of the LAA. Duration Operation time and antithrombotics for length of study.. Concurrent medication/care: Warfarin for 45 days to facilitate device endothelialisation. Patients discontinued warfarin therapy if the 45 day TEE showed either complete closure of the LAA or if there was residual peri-device flow. After stopping warfarin treatment, once daily clopidogrel and aspirin were prescribed until completion of the 6 month visit, from which point aspirin was continued alone.
Funding	Study funded by industry (Atritech)
RESULTS (NUMBERS ANALYSED): LAAO versus WARFARIN Protocol outcome 1: Mortality - latest endpoint at Longest endpoint - Actual outcome: Mortality (all cause) at 2.3 years follow up; Group 1: 34/463, Group 2: 26/244 Protocol outcome 2: Ischaemic stroke at Longest endpoint - Actual outcome: Ischaemic stroke at 2.3 years follow up; Group 1: 19/463, Group 2: 8/244 Protocol outcome 3: Haemorrhagic stroke at Longest endpoint - Actual outcome: Haemorrhagic stroke at 2.3 years follow up; Group 1: 3/463, Group 2: 7/244 Protocol outcome 4: Procedural complications at Longest endpoint - Actual outcome: Primary safety at 2.3 years follow up; Group 1: 54/463, Group 2: 20/244 Protocol outcome 5: Thromboembolic complications at Longest endpoint - Actual outcome: Systemic embolism at 2.3 years follow up; Group 1: 3/463, Group 2: 0/244	
Protocol outcomes not reported by the study	Major bleeding at Longest endpoint; Hospitalisation at Longest endpoint; Quality of life at Longest endpoint

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV=

electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.8 Rate versus rhythm control strategies

Table 49: Carlsson et al 2003[176]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Carlsson, Jorg, et al. "Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study." Journal of the	Design: Open randomised controlled pilot trial Enrolment: Not described (see inclusion criteria) Randomisation: Computer generated codes per study centre, blocks of 10 patients, randomization by calling the study centre. Allocation	n = 200 Drop-outs: None Crossover: NA	Inclusion criteria: 18 years or older with one or more of following: AF for >4 weeks; left atrial size >45 mm; congestive heart failure, NYHA class II or greater; left ventricular ejection fraction <45%; or ≥ 1 prior cardioversion with arrhythmia recurrence. Exclusion criteria: Permanent AF >2 years, a history of paroxysmal AF, left atrial size >70 mm, LVRF <20%, Wolff-Parkinson-White syndrome, history of AV node ablation or modification, contraindications against oral anticoagulation, primarily success-less cardioversion within 4 weeks before randomisation, pregnancy, or malignant or other concomitant disease that would most likely limit the patient's life expectancy to <3 years.	Rhythm control by cardioversion and class I antiarrhythmic agents or sotalol in the absence of coronary heart disease and in patients with a normal left ventricular function. Patients with coronary heart disease or an impaired LV function	Rate control using beta-blockers, digitalis, calcium antagonists or atrioventricular node ablation/ modification. All patients were anticoagulated.	0-36 months	Death Cardiopulmonary resuscitation Cerebrovascular event Systemic embolism	Medtronic Gmb,Dusseldorf, Germany and by Arbeitsgemeinschaftleitender kardiologischer Krankenhausaerzte, Germany

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
American College of Cardiology 41.10 (2003): 1690-96. [176]	concealment: Not described Blinding: open trial Sample size calculation: The number of patients, based on a 33% relative risk reduction in the rhythm control group, was calculated to be 2,000 (80% power). This trial is a pilot to test the assumed event rates after the first 200 patients. ITT analysis: Yes		Demographics and baseline characteristics Drug therapy: See description of comparison	received a beta-blocker and/or amiodarone. In case of a recurrence, repeated cardioversion was performed. All patients were anticoagulant-ed.				

Results:	Rhythm control group N=100	Rate control group N=100	Effect estimate
Combined primary end point: death, stroke, or transient ischemic attack, systemic embolism and CPR	9/100	10/100	RR 0.90 [0.38, 2.12]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Al- cause mortality		4/100		8/100		RR 0.50 [0.16, 1.61]		
Stroke or thromboembolic complications		5/100 (Stroke/TIA)		2/100 (1 stroke/TIA; 1 systemic embolism)		RR 2.50 [0.50, 12.59]		
Bleeding		11/100		8/100		RR 1.38 [0.58, 3.27]		
Hospitalization for cardiovascular disease		54/100		26/100		RR 2.08 [1.42, 3.03]		
Sinus rhythm at last follow-up		38/100		9/100		RR 4.22 [2.16, 8.26]		
Quality of Life assessed by SF-36 at last follow-up								
General health		56 ± 8		53 ± 12		MD 3.00 (0.17,5.83)		
Physical functioning		69 ± 12		62 ± 15		MD 7.00 (3.24, 10.76)		
Physical role function		62 ± 19		55 ± 21		MD 7.00 (1.45, 12.55)		
Bodily pain		74 ± 15		72 ± 17		MD 2.00 (-2.44,6.44)		
Mental health		72± 10		69± 10		MD 3.00 (0.23, 5.77)		
Social functioning		83± 13		79± 13		MD 4.00 (0.40, 7.60)		
Role emotional		71± 17		75± 18		MD -4.00 (-8.85, 0.85)		
Vitality		53± 10		49± 12		MD 4.00 (0.94, 7.06)		

Table 50: Dorian et al 2003[296]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Dorian, Paul and Iqwal Mangat. . "Quality of life variables in the selection of rate versus rhythm control in patients with atrial fibrillation: observations from the Canadian Trial of Atrial Fibrillation." Cardiac electrophysiology review 7.3 (2003): 276-79.[296]	Design: Multicentre RCT With methods described in protocol paper Enrolment: See Roy et al. Randomisation: See Roy et al Allocation concealment: NA Blinding: NA Sample size calculation: See Roy et al ITT analysis: NA	n = 294 completed baseline questionnaires; 264 had complete baseline and 3 month data and 170 patients completed baseline, 3 month and 12 month date; sub-study of Canadian Trial of Atrial Fibrillation Drop-outs: Not stated	Inclusion criteria: Not stated Exclusion criteria: Patients with NYHA class III or IV heart failure; patients with previous failure of rhythm control medications, or intolerance to any of the 3 drugs. Demographics and baseline characteristics Drug therapy: See description of comparison	Effect of anti-arrhythmic treatment with amiodarone on health related quality of life using SF-36 form.	Effect of rate control with sotalol or propafenone on patient perceived health related quality of life using SF-36 form.	12 months	Physical and mental health per SF-36.	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		Crossover: Not stated						

Results at 3 months:	Rhythm control group (amiodarone)	Rate control group (sotalol or propafenone)	SF-36 score
Overall improvement at 3 months in both groups	---	---	41.9±9.2 to 43 ±9.2 physical health
			47.5±10.4 to 49.0 ±9.8 for mental health
Quality of life improvements	Data not available	Data not available	QoL improvements were similar in the amiodarone group compared to the sotalol or propafenone group for SF-36

Table 51: Hagens et al 2005[409]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hagens, Vincent E., et al. "Rate control versus rhythm control for patients	Design: Randomised prospective study Enrolment: 31 centres in the Netherlands	n = 261 Drop-outs: Not stated Crossover: Not stated	Inclusion criteria: Patients with CHF in NYHA functional classes II and III Exclusion criteria: Not stated Demographics and baseline characteristics: See below	Rhythm control consisted of serial electrical cardioversion with institution of	Rate control was achieved using negative chronotropic drugs including digitalis, beta blocker and nondihydro-	Maxi-mum 3 years; Mean 2.3 ± 0.6 years.	Composite of cardiovascular death, hospitalisation for CHF, thrombo-embolic complication	Not stated Van Gelder paper cites RACE trial

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
with persistent atrial fibrillation with mild to moderate heart failure: results from the RAte Control versus Electrical cardioversion (RACE) study." American heart journal 149.6 (2005): 1106-11 [409]	Randomisation: Not described Allocation concealment: NA Blinding: NA Sample size calculation: No power calculation was performed for this sub-study of the RACE trial. ITT analysis: Yes		Drug therapy: See description of comparison	antiarrhythmic drugs (sotalol, class IC drugs or amiodarone).	pyridine calcium channel blocker.		, bleeding, pacemaker implantation or severe adverse effects of antiarrhythmic drugs.	funding as follows: Centre for Health Care Insurance; Inter-university Cardio-logy Institute in the Netherlands and by an unrestricted grant from 3M Pharma.

Results at mean of 2.3 ±0.6 years :	Rhythm control N=131	Rate control N=130	Measure of effect RR [95% CI]
Composite results, n(%)	24.4 (32)	22.3 (29)	1.08 [0.64, 1.83]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cardiovascular mortality n(%)		6.1 (8)		11.5 (15)		0.50 [0.19, 1.28]		
Thromboembolic complications n(%)		8.4 (11)		6.2 (8)		1.32 [0.47, 3.71]		
Bleeding n(%)		3.1 (4)		8.5 (11)		1.32 [0.47, 3.71]		
Quality of life		93 patient		90 patients		At baseline and also at the end of the study there were no differences between the groups. Total values not provided. See Hagen 2004.		

Table 52: Hagens et al 2004[407]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hagens, V. E., et al. "Effect of rate or rhythm control on quality of life in persistent	Design: Randomised prospective study Enrolment: 31 centres in the Netherlands	n = 352 Drop-outs: Not stated Crossover: Not stated	Inclusion criteria: Patients who completed the self- administered QoL questionnaire at baseline, after one year and at the end of follow-up Exclusion criteria: Patients who died and patients who did not complete the QoL questionnaire at either baseline, one year	Rhythm control consisted of serial electrical cardioversion with institution of antiarrhythmi	Rate control was achieved using negative chronotropic drugs including digitalis, beta blocker and nondihydro-pyridine	Maxi-mum 3 years; Mean 2.3 ± 0.6 years.	Quality of life as measured by SF36	Centre for Health Care Insuranc e; Inter-universit y Cardio-

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
atrial fibrillation: Results from the rate control versus electrical cardio-version (RACE) study." Journal of the American College of Cardiology 43.2 (2004): 241-47. [407]	Randomisation: Not described Allocation concealment: NA Blinding: NA Sample size calculation: No power calculation was performed for this sub-study of the RACE trial. ITT analysis: Yes		or at the end of the study Demographics and baseline characteristics: See below Drug therapy: See description of comparison	c drugs (sotalol, class IC drugs including flecanide /propafenone or amiodarone).	calcium channel blocker.			logy Institute in the Netherlands and by an unrestricted grant from 3M Pharma.

Results: SF-36 QoL scores	Rhythm control N=177	Rate control N=175	Measure of effect Change from baseline to study end
General health – baseline General health – 12 months General health – Study End	54 (18) 58 (20) 54 (20)	54 (19) 58 (18) 57 (18)	Absolute change from baseline: Rhythm group: 0; rate group +3 Effect size for rhythm group: 0

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
							Effect size for rate group 0.16	
Physical functioning – baseline Physical functioning – 12 months Physical functioning – Study End		64 (24) 67 (24) 64 (27)		62 (24) 62 (23) 59 (25)			Absolute change from baseline: Rhythm group: 0; rate group -3 Effect size for rhythm group: 0 Effect size for rate group -0.12	
Mental health – baseline Mental health – 12 months Mental health – Study End		74 (18) 76 (19) 76 (18)		73 (18) 77 (18) 76 (17)			Absolute change from baseline: Rhythm group: +2; rate group +3 Effect size for rhythm group: 0.11 Effect size for rate group 0.17	
Role physical – baseline Role physical – 12 months Role physical – Study End		50 (44) 61 (43) 55 (45)		45 (46) 59 (42) 53 (44)			Absolute change from baseline: Rhythm group: +5; rate group +8 Effect size for rhythm group: 0.11 Effect size for rate group: 0.18	
Bodily pain – baseline Bodily pain – 12 months Bodily pain – Study End		81 (21) 82 (22) 80 (22)		80 (22) 81 (21) 79 (23)			Absolute change from baseline: Rhythm group: -1; rate group -1 Effect size for rhythm group: -0.05 Effect size for rate group -0.04	
Social functioning – baseline		78 (22)		76 (24)			Absolute change from baseline:	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Social functioning – 12 months Social functioning – Study End		79 (25) 80 (23)		81 (21) 81 (21)			Rhythm group: +2; rate group +5 Effect size for rhythm group: 0.09 Effect size for rate group 0.22	
Role emotional – baseline Role emotional – 12 months Role emotional – Study End		70 (42) 74 (39) 74 (38)		73 (41) 76 (38) 73 (39)			Absolute change from baseline: Rhythm group: +4; rate group 0 Effect size for rhythm group: 0.10 Effect size for rate group 0	
Vitality – baseline Vitality – 12 months Vitality – Study End		60 (21) 62 (21) 62 (21)		60 (22) 59 (20) 59 (21)			Absolute change from baseline: Rhythm group: +2; rate group -1 Effect size for rhythm group: 0.10 Effect size for rate group -0.05	
Comments: When the scores on the SF-36 subscales at 12 month follow-up and study end were compared between the rate and rhythm control groups, no significant differences were found in any of the eight subscales. The absolute differences between the scores at baseline and study end were not statistically different between rate and rhythm control.								

Table 53: Hohnloser et al and Gronefeld et al 2003[394,453]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hohnloser, S. H., K. H. Kuck, and J. Lilienthal. "Rhythm or rate control in atrial fibrillation--Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial." Lancet 356.9244 (2000): 1789-94.[453] And Gronefeld, G. C., et al. "Impact of rate versus rhythm control on	Design: Open randomised pilot trial. Enrolment: Not described (see inclusion criteria) Randomisation: Computer generated codes per study centre, blocks of 6 patients Allocation concealment: Not described Blinding: open trial Sample size calculation: A sample size of 130 patients in each group allowed detection of a	n = 252 Drop-outs: None Crossover: 5 patients from rate control and 6 patients crossed over from rhythm control.	Inclusion criteria: Patients 18-75 years presenting with symptomatic persistent AF of between 7 days and 360 days duration. Exclusion criteria: Congestive heart failure; NYHA class I; unstable angina; acute MI within 30 days; AF with an average rate of fewer than 50 BPM; known sick sinus syndrome; AF in the setting of Wolff-Parkinson-White syndrome; CABG or valve replacement within past 3 months; ECG documentation of intra-cardiac thrombus formation; central or peripheral embolization within the past 3 months; hypertrophic cardiomyopathy; amiodarone therapy within the past 6 months; acute thyroid dysfunction; pacemaker therapy; contraindications for systemic anticoagulation therapy; pregnancy., Demographics and baseline characteristics: See below Drug therapy: See description of comparison	Rhythm control by amiodarone 600 mg for 3 weeks and then cardioversion if necessary. Maintenance of sinus rhythm was attempted by administration of amiodarone 200 mg/day. Treatment of recurrent atrial fibrillation was left to treating physician.	Rate control diltiazem 90 mg two or three times a day. Additional therapy was left to discretion of treating physician.	12 months	Symptom improvement, including elimination of palpitations, reduction in frequency of episodes of dyspnoea, reduction of dizzy spells.	Sanofi and Park Davis

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
quality of life in patients with persistent atrial fibrillation: Results from a prospective randomized study." European Heart Journal 24.15 (2003): 1430-36. [394]	difference between rates of 50% and 70% with 90% power. ITT analysis: Yes							

Results:	Rhythm control group N=127	Rate control group N=125	Effect estimate RR
Overall symptomatic improvement	70 (55%)	76 (60%)	0.91 [0.73, 1.12]
All cause mortality	2 (2%)	2 (2%)	0.98 [0.14, 6.88]
Restoration of sinus rhythm at one year	71 (56%)	12.5 (10%)	5.30 [3.09, 9.08]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hospital admission		87 (69%)		30 (24%)			2.85 [2.04, 3.98]	
Quality of Life assessed by SF-36 at last follow-up		N=81		N=84				
General health		55 ± 20		50 ± 17			MD 5.00 [-0.67, 10.67]	
Physical functioning		71 ± 26		67 ± 26			MD 4.00 [-3.94, 11.94]	
Physical role function		58 ± 51		52 ± 57			MD 6.00 [-10.49, 22.49]	
Bodily pain		77 ± 36		77 ± 31			MD 0.00 [-10.27, 10.27]	
Mental health		71± 17		68± 20			MD 3.00 [-2.66, 8.66]	
Social functioning		84± 29		80± 28			MD 4.00 [-4.70, 12.70]	
Role emotional		62± 45		65± 51			MD -3.00 [-17.66, 11.66]	
Vitality		57± 21		55± 19			MD 2.00 [-4.12, 8.12]	

Table 54: Ogawa et al 2009 and Yamashita et al 2003[703,920]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ogawa, Satoshi, et al. "Optimal treatment strategy for patients with paroxysmal atrial fibrillation: J-RHYTHM Study." Circulation journal 73.2 (2009): 242-48. [703] and Yamashita, Takeshi, et al. "Investigation of the optimal treatment strategy for atrial fibrillation in Japan." Circulation journal 67.9	Design: Randomised multicentre study Enrolment: Not described Randomisation: Method not described Allocation concealment: Not described Blinding: open trial Sample size: 2600 cases were calculated on the basis of projected incidence of rate control related events of 15% and expected event decrease rate in the rhythm control group as 30%.	n =823 Drop-outs: 62 Crossover: Not stated	Inclusion criteria: Patients with PAF treated by either rate or rhythm control Exclusion criteria: Persistent AF lasting 1 year or longer and permanent AF; initial episode of paroxysmal AF; AF that has occurred within 1 month of the onset of MI; transient AF associated with cardiac surgery; requirement of continuous treatment with beta blockers and calcium antagonists, excluding dihydropyridines, that affect the heart rate; AF with a history of 2 or more electrical cardioversions; contraindication for anticoagulation therapy; pregnancy or possibility of pregnancy and breast feeding; judgment by attending physician that patient participation would be inappropriate. Demographics and baseline characteristics: See table below Drug therapy: See description of comparison	Rhythm control with antiarrhythmic drugs selected according to "The Japanese Guideline for Atrial Fibrillation Management" All patients received anticoagulants.	Rate control using beta-blockers, calcium channel blockers and digitalis. All patients received anticoagulants.	Mean 578 days	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure requiring intravenous administration of diuretics and physical/psychological disability requiring alteration of the assigned treatment strategy. Secondary endpoints were patient QoL	Japanese Circulation Society and Japanese Heart Foundation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
(2003): 738-41. [920]	ITT analysis: Yes						scores on Japanese Society of Electrocardiology's AF QoL Questionnaire and the efficacy and safety of drugs required in AF treatment.	

Results:	Rhythm control group N=419	Rate control group N=404	Effect estimate RR (incidence)
Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure requiring intravenous administration of diuretics and physical/psychological disability requiring alteration of the assigned treatment strategy (%)	64 (15.3)	89 (22)	RR 0.69 [0.52, 0.93]
All cause mortality (%)	4 (1.0)	3 (0.7)	RR 1.29 [0.29, 5.71]
Symptomatic stroke (%)	9 (2.1)	11 (2.7)	RR 0.79 [0.33, 1.88]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Systemic embolism (%)		1 (0.2)		1 (0.2)			RR 0.96 [0.06, 15.36]	
Major bleeding (%)		2 (0.5)		1 (0.2)			RR 1.93 [0.18, 21.18]	
Heart failure (%)		2 (0.5)		6 (1.5)			RR 0.32 [0.07, 1.58]	
Maintenance of sinus rhythm at three years		305 (72.7)		177 (43.9)			RR 3.43 [2.56, 4.59]	

Table 55: Opolski et al 2004[717]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Opolski, Grzegorz, et al. "Rate control vs rhythm control in patients with non-valvular persistent atrial fibrillation: the results	Design: Prospective, randomised, open multicentre clinical trial Enrolment: Not described (see inclusion criteria) Randomisation: Permuted block	n = 200 Drop-outs: None Crossover: NA	Inclusion criteria: 50 -75 years of age and AF had to be known to be present for at least 7 days but not for >2 years. Only patients with a first clinically overt persistent episode of AF were enrolled. Exclusion criteria: Documented inefficiency; intolerance to or contraindications for treatment with antiarrhythmic drugs; presence of arrhythmia associated with an acute reversible condition; thyroid	Rhythm control by cardioversion prior to drug treatment with propafenone, disopyrmide, or sotalol. Beta blockers were given if clinically	Rate control using beta-blockers, digitalis, calcium channel blockers or a combination of these drugs. Cardioversion and atrioventricular ablation with	Mean of 1.7 ± 0.4 years with a maximum of 2.5 years	Primary composite endpoint; all-cause mortality; thrombo-embolic events and major bleeding complications	Polish government research grant

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study." Chest 126.2 (2004): 476-86. [717]	design with equal allocation and stratified centrally by a steering centre of the Chair and Department of Cardiology. Allocation concealment: Not described Blinding: open trial Sample size calculation: Not described ITT analysis: Yes		dysfunction; pregnancy or lactation; history of MI within 3 months preceding enrolment; acute myocarditis; cardiac surgery during the previous 30 days; severe cardiac disability; hypotension; history of TIA; history of haemorrhagic stroke; ischemic stroke during the 3 months preceding entrance into the trial; any mitral stenosis or other valvular disease suitable for surgical treatment; R-R intervals exceeding 3 s; ventricular response to AF of <90 beats/min; bundle branch block or QT segment prolongation; alcoholism; contraindications to anticoagulation therapy; liver, kidney, or CNS damage; advanced chronic lung disease, malignancy; or any non-cardiac illness associated with a life expectancy of <1 year; or participation in another study; women of childbearing potential. Demographics and baseline characteristics: See table below Drug therapy: See description of comparison	indicated. All patients were anticoagulant-ed.	pacemaker placement were alternative non-pharmaco-logic strategies. All patients were anticoagulant-ed.			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Results:	Rhythm control group N= 104	Rate control group N=101	Effect estimate
Composite end point (mortality, thromboembolic events and major bleeding)	Not stated	Not Stated	OR 1.98 [95% CI 0.28-22.3]
All cause mortality	3(2.9%)	1(1%)	RR 2.97 [0.30, 29.04]
Bleeding (major)	8 (7.7%)	5 (5%)	RR 1.55 [0.53, 4.59]
Thromboembolic complications	3(2.9%) - stroke	1(1%) – pulmonary embolism	RR 2.97 [0.30, 29.04]
Hospitalisation	1.03 per person (13/104)	0.05 per person (5/101)	RR 2.52 [0.93, 6.83] P=0.001
AF at follow up	38/104 (36.5%)	101/101 (100%)	RR 0.37 [0.29, 0.47]

Table 56: Roy et al 2008[789]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Roy, Denis, et al. "Rhythm control versus rate control for atrial fibrillation	Design: Multicentre RCT Enrolment: May 2001 to June 2005 Randomisation: Permuted blocks	n = 682 rhythm control; 694 rate control Drop-outs:35	Inclusion criteria: LVEF of 35% or less within 6 months of enrolment; a history of congestive heart failure defined as NYHA class II or IV in previous 6 months or hospitalisation for heart failure in previous 6 months or LVEF of 25% or less; a history of AF with at least one episode lasting for ≥ 6 hours or requiring cardioversion within	Aggressive rhythm control: amiodarone and either sotalol or dofetilide if required;	Rate control: Adjusted doses of beta blockers with digitalis to achieve the targeted heart rate of less	The follow-up period ended on June 30, 2007.	The primary outcome was death from cardiovascular causes. Secondary outcomes were death	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
and heart failure." New England journal of medicine 358.25 (2008): 2667-77.[788] CTAF trial	of various sizes and stratified according to the study centre. Allocation concealment: NA Blinding: Not possible as patients may have received cardioversion, pacemaker or ablation. Sample size calculation: 1374 patients required to demonstrate with 80% power a reduction of 25% in rate of death from cardiovascular causes in the rhythm control group. ITT analysis: Yes	rhythm control; 44 rate control Crossover: 142 patients (21%) in the rhythm control group crossed over to the rate control group due to inability to maintain sinus rhythm. 66 patients (10%) in the rate control group crossed over to the rhythm control	the previous 6 months; and, eligibility for long term therapy in either study group. Exclusion criteria: Persistent AF for more than 12 months; a reversible cause of AF or heart failure ; decompensated heart failure within 48 hours before intended randomization; the use of antiarrhythmic drugs for other arrhythmias; second degree or third degree AV block (bradycardia of <50 beats per minute); a history of the long-QT-syndrome; previous ablation of an AV node; anticipated cardiac transplantation within 6 months; renal failure requiring dialysis; lack of birth control in women of child-bearing potential; an estimated life expectancy of less than 1 year; and an age of less than 18 years. Demographics and baseline characteristics Drug therapy: See description of comparison	electric cardioversion within 6 weeks after randomization in patients who did not have conversion to SR after antiarrhythmic drug therapy; if necessary a second cardioversion was recommended within 3 months after enrolment; additional cardio-versions were recommended for subsequent recurrences of AF; installation of a permanent pacemaker	than 80 beats per minute at rest and less than 110 beats per minute during a 6 minute walk test. AV nodal ablation and pacemaker therapy were recommended for patients who did not meet rate-control target with drug therapy. Therapies for heart failure: Treatment with an ACE inhibitor or ARA was recommended for all patients. Maximum tolerated doses of beta blockers were	The mean follow-up was 37 ± 19 months	from any cause, stroke, worsening congestive heart failure, hospitalization, quality of life, cost of therapy and a composite of death from cardiovascular causes, stroke, or worsening congestive heart failure.	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
		group due to worsening heart failure.		was recommended if bradycardia prevented the use of anti-arrhythmic drugs. Therapies for heart failure: Treatment with an ACE inhibitor or ARA was recommended for all patients. Maximum tolerated doses of beta blockers were recommended for patients in both groups. Anticoagulation was recommended for all patients. The	recommended for patients in both groups. Anticoagulation was recommended for all patients. The use of an implantable defibrillator and ventricular-resynchronisation therapy was recommended.			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				use of an implantable defibrillator and ventricular-resynchronization therapy was recommended.				

Results at 48 months:	Rhythm control group N=682	Rate control group N=694	Measure of effect HR/RR
Death from cardiovascular causes	182/682 (27%)	175/692 (25%)	HR 1.06 [95% CI 0.86-1.30] unadjusted HR 1.05 [95% CI 0.85-1.29] adjusted
Probability of death from any cause	217/682 (32%)	228/694 (33%)	HR 0.97 [95% CI 0.80-1.17]
Probability of stroke	20/682(3%)	28/694 (4%)	HR 0.74 [95% CI 0.40-1.35]
Worsening heart failure	191/682 (28%)	215/694 (31%)	HR 0.87 [95% CI 0.72-1.06]
Composite outcome: death from cardiovascular causes, stroke or worsening heart failure	293/682 (43%)	319/694 (46%)	HR 0.90 [95% CI 0.77-1.06]
Hospitalisation	436/682 (64%)	409/694 (59%)	RR 1.08 [1.00, 1.18]

Table 57: Shelton et al 2009[811]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Shelton, R. J., et al. "A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II Study)." Heart 95.11 (2009): 924-30. [811]	Design: Open randomised controlled trial Enrolment: Patients identified among referrals to heart failure clinic at Castle Hill Hospital, Cottingham, Kingston-Upon-Hull, UK Randomisation: Block randomisation with variable block-size Allocation concealment: Not described Blinding: open trial	n = 61 Drop-outs: None (2 deaths) Crossover: If rhythm treatment unsuccess-ful	Inclusion criteria: 18 years or older with Persistent AF and chronic symptomatic heart failure (NYHA ≥ Class II symptoms) with evidence of systolic dysfunction on ECG. Exclusion criteria: Patients in whom oral anticoagulants were contraindicated. Demographics and baseline characteristics: See table below Drug therapy: See description of comparison	Rhythm control with oral amiodarone; if AF persisted after 2 months, cardioversion was performed. If unsuccessful after multiple attempts, patients were crossed over to rate control protocol. All patients received anticoagulants.	Rate control using beta-blockers and digoxin. All patients received anticoagulants.	1 year	The primary outcome was QoL using SF-36vII at 1 year. Secondary outcome of interest was sinus rhythm.	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	Sample size: 59 patients permitted detection of a medium to large effect size (0.6-1.0 SDs of the primary outcome measure) with 80% power and 5% significance. calculation ITT analysis: Yes							

Results:	Rhythm control group N=30	Rate control group N=31	Effect estimate
All cause mortality n (%)	1 (3.33)	1 (3.23)	RR 1.03 [0.07, 15.78]
Quality of life, SF36vII	Values not provided	Values not provided	Patients assigned to rhythm control had a greater improvement in QoL over 1 year compared with rate control; p=0.020 as a whole; p= 0.050 for mental functioning and p=0.029 for physical functioning.
Quality of life for patients in sinus rhythm at 1 year (in rhythm group) with	Values not provided	Values not provided	There was greater improvement in QoL in patients assigned to rhythm control

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
those who had adequately rate controlled AF (in the rate control group), SF36vII						group; p=0.016 as a whole; p= 0.038 for mental functioning and p=0.024 for physical functioning.		

Table 58: Van Gelder 2002[879]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Van Gelder, Isabelle C., et al. "A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation." New England journal of medicine	Design: Randomised prospective study Enrolment: 31 centres in the Netherlands from June 1, 1998-July 1, 2001 Randomisation: Not described Allocation concealment: NA Blinding: NA	n = 522 Drop-outs: Not stated Crossover: Not stated	Inclusion criteria: Patients with recurrent persistent atrial fibrillation or flutter, in whom oral anticoagulation was not contraindicated; patients were required to have undergone one electrical cardioversion during the previous two years, with a maximum of two. Exclusion criteria: If arrhythmia had lasted longer than one year; patients with NYHA class IV heart failure, current or previous treatment with amiodarone, or a pacemaker. Demographics and baseline characteristics: See below	Rhythm control consisted of serial electrical cardioversion with institution of antiarrhythmic drugs (sotalol, class IC drugs including flecainide or propafenone or amiodarone).	Rate control was achieved using negative chronotropic drugs including digitalis, beta blocker and nondihydro-pyridine calcium channel blocker.	Maxi-mum 3 years; Mean 2.3 ± 0.6 years.	Composite of cardiovascular death, hospitalisation for CHF, thrombo-embolic complication, bleeding, pacemaker implantation or severe adverse effects of antiarrhythmic drugs.	Centre for Health Care Insurance; Inter-university Cardio-logy Institute in the Netherlands and by an unrestricted

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
347.23 (2002): 1834-40. [879]	Sample size calculation: With a significant level of 5%, a power of 80% and an assumed 30% incidence of the primary end point, 260 patients per group re required. ITT analysis: Yes		Drug therapy: See description of comparison					grant from 3M Pharma.

Results at mean of 2.3 ±0.6 years :	Rhythm control N=266	Rate control N=256	Measure of effect
Composite results, n (%)	60 (22.6)	44 (17.2)	HR of rate compared to rhythm: 0.73 [90% CI 0.53, 1.01]
Cardiovascular mortality (incidence , n (%)	18 (6.8)	18 (7.0)	RR 0.96 [95 % CI 0.51, 1.81]
Heart failure (incidence) , n (%)	12 (4.5)	9 (3.5)	RR 1.28 [95 % CI 0.55, 2.99]
Thromboembolic complications (incidence), n (%)	21 (7.9)	14 (5.5)	RR 1.44 [95% CI 0.75, 2.78]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Bleeding (incidence) , n (%)		9 (3.4)		12 (4.7)		RR 0.72 [95% CI 0.31, 1.68]		

Table 59: Wyse et al 2002, Saksena et al 2011, Fruendberger 2007[350,796,915]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Wyse, D. G., et al. "A comparison of rate control and rhythm control in patients with atrial fibrillation." New England journal of medicine 347.23 (2002): 1825-33.[915] And Saksena, Sanjeev, et	Design: Randomised, multicentre comparison Enrolment: 213 individual clinical sites and their satellite sites (see inclusion criteria) Randomisation: Stratified according to clinical site. Patients were not assigned randomly to specific initial drug therapy. The further study	n =4060 Drop-outs: 71 withdrew consent; 26 survival unknown Crossover: 248 crossed over from rate to rhythm control ; 86 of these crossed back to rate	Inclusion criteria: 65 years or who had other risk factors for stroke or death. Overriding criteria was AF which was likely to be recurrent; AF likely to cause illness or death; long term treatment for AF; anticoagulant therapy was not contraindicated; patient was eligible to undergo trials of at least two drugs in both treatment strategies; and treatment with either strategy could be initiated immediately after randomisation. Exclusion criteria: Not stated Demographics and baseline characteristics Drug therapy: See description of comparison	Rhythm control Drugs chosen by the treating physician and may include cardioversion. Drugs could include amiodarone, disopyramide, dofetilide, flecainide, moricizine, procainamide, propafenone, quinidine,	Rate control using beta-blockers, digoxin, calcium antagonists or a combination of these drugs. Heart rate control during AF was assessed both at rest and during activity, usually during a 6 minute walk. After standard approaches to treatment,	Mean 3.5 years; maximum 6 years. Data truncated at 5 years.	Overall mortality; a composite endpoint comprised death, disabling stroke, disabling anoxic encephalopathy, major bleeding and cardiac arrest.	National Heart, Lung and Blood Institute; Electrophysiology Research Foundation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
al. "Cardiovascular outcomes in the AFFIRM Trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Manage-ment). An assessment of individual antiarrhythmic drug therapies compared with rate control with propensity score-matched analyses." Journal of the American College of	by Saksensa et al included the development of propensity scores matched cohorts to account for possible confounding variables that might be related to drug selection among the anti-arrhythmia group. Allocation concealment: Not described Blinding: not described. Sample size calculation: Not described ITT analysis: Primary analysis was ITT	control by the end of the study		sotalol and combinations of these drugs. After standard approaches to treatment, patients could be considered for non-pharmacologic therapy, such as ablation, a maze procedure or pacing, as appropriate to their randomisation. Patients were also anticoagulated until SR has been maintained for at least 4, preferably 12	patients could be considered for non-pharmacologic therapy, such as ablation, a maze procedure or pacing, as appropriate to their randomisation. Patients were continuously anticoagulated.			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cardiology 58.19 (2011): 1975-85. [796] AND Freudenberger, Ronald S., et al. "Comparison of rate versus rhythm control for atrial fibrillation in patients with left ventricular dysfunction (from the AFFIRM Study)." American journal of cardiology 100.2 (2007): 247-52. [350]				consecutive weeks.				
Results:		**Rhythm control group N=2033**		**Rate control group N=2027**		**Effect estimate**		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Composite endpoint (death, disabling stroke, disabling anoxic encephalopathy, major bleeding and cardiac arrest) n (%)		445 (32)		416 (32.7)			RR 1.07 [0.95, 1.20]	
All cause mortality at 5 years (Wyse et al 2002) n (%)		356 (17.5)		310 (15.3)			HR 1.15 [95% CI 0.99, 1.34] (rate vs. rhythm) Log rank p value 0.08 RR 1.14 [1.00, 1.32] - incidence (rhythm vs. rate)	
All cause mortality (time to death) (Saksena et al 2011)		Not provided		Not provided			HR 1.149 [95% CI 0.987,1.338]	
All cause mortality (time to death) amiodarone vs. rate (Saksena et al 2011)		Not provided		Not provided			HR 1.198 [95% CI 0.935,1.533]	
All cause mortality (time to death) sotalol vs. rate (Saksena et al 2011)		Not provided		Not provided			HR 1.002 [95% CI 0.750,1.337]	
All cause mortality (time to death) Class IC (Flecainide, Propafenone, Moricizine) vs. rate (Saksena et al 2011)		Not provided		Not provided			HR 0.936 [95% CI 0.584,1.501]	
Mortality in patients with moderate heart failure (Freudenberger, 2007)		29/134		25/107			Log rank P= 0.72; (rate vs. rhythm) See below*	
Mortality in patients with severe heart failure (Freudenberger, 2007)		33/74		30/81			Log Rank p= 0.39; (rate vs. rhythm)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
						See below*		
Mortality in patients with moderate *and* severe heart failure (Freudenberger, 2007)		62/208		55/188		RR 1.02 (0.75, 1.38)*		
Composite end point including death, disabling stroke, disabling anoxic encephalopathy, major bleeding(time to first cardiovascular hospital stay or death) (Saksena et al 2011)		Not provided		Not provided		HR 1.336 [95% CI 1.226, 1.456]		
Composite end point including death, disabling stroke, disabling anoxic encephalopathy, major bleeding(time to first cardiovascular hospital stay or death) amiodarone vs. rate (Saksena et al 2011)		Not provided		Not provided		HR 1.183 [95% CI 1.026,1.364]		
Composite end point including death, disabling stroke, disabling anoxic encephalopathy, major bleeding(time to first cardiovascular hospital stay or death) sotalol vs. rate (Saksena et al 2011)		Not provided		Not provided		HR 1.318 [95% CI 1.127,1.541]		
Composite end point including death, disabling stroke, disabling anoxic encephalopathy, major bleeding(time to first cardiovascular hospital stay or death) Class IC (Flecainide, Propafenone, Moricizine) vs. rate (Saksena et al 2011)		Not provided		Not provided		HR 1.222 [95% CI 0.961,1.555]		
Composite end point including death, disabling stroke, disabling anoxic		445/2033		416/2027		Log rank p value 0.33		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
encephalopathy, major bleeding at 5 years (Wyse et a 2002)							RR 1.07 [0.95, 1.20] - incidence	
Ischaemic stroke (Wyse et al 2002)			80/2033 (7.1%)		77/2027 (5.5%)		Log rank p value 0.79 RR 1.04 [0.76, 1.41]- incidence	
Bleeding			125/2033 (6.1%)		136/2027 (6.7%)		Log rank p value 0.44 RR 0.92 [0.72, 1.16]- incidence	
Hospitalization after base line (Wyse et al 2002)			1374/2033 (80.1%)		1220/2027 (73.1)		Log rank p value<0.001 RR 1.12 [1.07, 1.18] - incidence	
Congestive heart failure (Wyse et al 2002)			42/2033 (2.7%)		37/2027 (2.1%)		Log rank p value 0.58 RR 1.13 [0.73, 1.75] - incidence	
Time to first CVH* (Saksena et al 2011) (*CVH – cardiovascular hospitalisation)			Not provided		Not provided		HR 1.360 [95% CI 1.240, 1.491]	
Time to first CVH amiodarone vs. rate (Saksena et al 2011)			Not provided		Not provided		HR 1.196 [95% CI 1.026, 1.395]	
Time to first CVH sotalol vs. rate (Saksena et al 2011)			Not provided		Not provided		HR 1.364 [95% CI 1.155, 1.611]	
Time to first CVH Class IC (Flecainide, Propafenone, Moricizine) vs. rate (Saksena et al 2011)			Not provided		Not provided		HR 1.243 [95% CI 0.963, 1.604]	
Time to first CVH (Saksena et al 2011)			Not provided		Not provided		HR 1.360 [95% CI 1.240, 1.491]	
Hospitalization after base line (Wyse et al 2002)			1374/2033 (80.1%)		1220/2027 (73.1)		Log rank p value<0.001	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
							RR 1.12 [1.07, 1.18] - incidence	
Congestive heart failure (Wyse et al 2002)			42/2033 (2.7%)		37/2027 (2.1%)		Log rank p value 0.58 RR 1.13 [0.73, 1.75] - incidence	
Time to first CVH* (Saksena et al 2011) (*CVH – cardiovascular hospitalisation)			Not provided		Not provided		HR 1.360 [95% CI 1.240, 1.491]	
Time to first CVH amiodarone vs. rate (Saksena et al 2011)			Not provided		Not provided		HR 1.196 [95% CI 1.026, 1.395]	
Time to first CVH sotalol vs. rate (Saksena et al 2011)			Not provided		Not provided		HR 1.364 [95% CI 1.155, 1.611]	
Time to first CVH Class IC (Flecainide, Propafenone, Moricizine) vs. rate (Saksena et al 2011)			Not provided		Not provided		HR 1.243 [95% CI 0.963, 1.604]	
Time to first CVH (Saksena et al 2011)			Not provided		Not provided		HR 1.360 [95% CI 1.240, 1.491]	

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.9 Rate control strategies

Table 60: Khand 2003[521]

Study	Khand 2003{KHAND2003}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in United Kingdom; Setting: NR
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People with heart failure and AF
Subgroup analysis within study	Not applicable
Inclusion criteria	NR
Exclusion criteria	HR at rest <60 beats/min; systolic BP <90mmHg,; sick sinus syndrome or complete heart block; current treatment with a beta-blocker or HR lowering calcium channel antagonist or >200mg amiodarone; recent major cardiovascular event or procedure; asthma or reversible obstructive airways disease; serum creatinine >250micromol/l or significant hepatic disease, ; uncorrected significant valvular heart disease or any life-threatening non-cardiac disease.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): cardedilol 68.6 (9.4); placebo 68.4 (9.8). Gender (M:F): 29M/ 16F. Ethnicity:
Further population details	1. Age:
Extra comments	Persistent AF (>1 month) and heart failure who were receiving digoxin and diuretics.
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Rate control drugs - Digoxin. Phase 1: open label digoxin (as previously prescribed); double-blind carvedilol placebo. Phase 2: double-blind digoxin; double-blind carvedilol placebo. Duration 6 months. Concurrent medication/care: NR (n=20) Intervention 2: Rate control drugs - Beta blockers. Phase 1 (4 months): open label digoxin (as previously prescribed); double-blind carvedilol (starting dose 3.125mg bid, increased at 2 week intervals to the target dose of 25mg bid (up titration period of 2 months) or, for patients weighing >85kg, 50mg bid. Phase 2(6 months): double blind digoxin placebo; double-blind carvedilol (continued from phase 1). Duration 6 months. Concurrent medication/care:

Study	Khand 2003{KHAND2003}
	NR
Funding	Study funded by industry (Roche Pharmaceuticals)
RESULTS (NUMBERS ANALYSED): DIGOXIN versus BETA BLOCKERS Protocol outcome 1: Rate control - heart rate (time or amount of people) at latest follow-up - Actual outcome for People with heart failure and AF: HR at 6 months at 6 months; Group 1: mean 75.5 (SD 10.6); n=20, Group 2: mean 88.8 (SD 18.7); n=16 Protocol outcome 2: Left ventricular function - number of people/ejection fraction as % at latest follow-up - Actual outcome for People with heart failure and AF: LVEF (%) at 6 months; Group 1: mean 27.2 % (SD 11.7); n=21, Group 2: mean 21.6 % (SD 11); n=20	
Protocol outcomes not reported by the study	Mortality (long-term) at latest follow-up; stroke or thromboembolic complications at latest follow-up; Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up; Time to response at time reported; Rate of discontinuation of drug due to side effects at time reported; Quality of life at latest follow-up

Table 61: Mulder 2012[679]

Study	Mulder 2012{MULDER2012}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=738)
Countries and setting	Conducted in Multiple countries; Setting: unclear
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People with heart failure and AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Define

Study	**Mulder 2012{MULDER2012}**
Exclusion criteria	Define
Age, gender and ethnicity	Age - Mean (SD): nebivolol group: 77 (5); placebo: 77 (5). Gender (M:F): Define. Ethnicity:
Further population details	1. Age:
Extra comments	all patients were >70 years and had heart failure
Indirectness of population	No indirectness
Interventions	(n=361) Intervention 1: Rate control drugs - Beta blockers. Medication was titrated over a 16 week period from a starting dose of 1.25mg daily to a target of 10mg daily. During the first 4 months of follow-up patients were closely monitored as medication was carefully titrated. Target dose of nebivolol was 10mg or the maximum tolerated dose for the individual patient. For the duration of the maintenance phase it was advised to maintain the same individual dose of the study drug until the end of the follow-up period. During the titration phase, patients were required to attend study visits at 1-2 week intervals. In this phase they were seen at least 5 times. The maximum period of drug titration was 16 weeks and the minimum 4 weeks.. Duration 21 months. Concurrent medication/care: unclear (n=377) Intervention 2: Placebo. Identical placebo tablets. Duration 21 months. Concurrent medication/care: unclear
Funding	Study funded by industry (Menarini Richerche SpA, Italy. Funding for additional statistical analyses to the Clinical trials and Evaluation Unit in London.)
RESULTS (NUMBERS ANALYSED): BETA BLOCKERS versus PLACEBO Protocol outcome 1: Mortality (long-term) at latest follow-up - Actual outcome for People with heart failure and AF: All-cause mortality at 21 months; Group 1: 67/361, Group 2: 72/377 Protocol outcome 2: Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up - Actual outcome for People with heart failure and AF: Heart failure hospitalisation at 21 months; Group 1: 72/361, Group 2: 58/377	
Protocol outcomes not reported by the study	Rate control - heart rate (time or amount of people) at latest follow-up; stroke or thromboembolic complications at latest follow-up; Left ventricular function - number of people/ejection fraction as % at latest follow-up; Time to response at time reported; Rate of discontinuation of drug due to side effects at time reported; Quality of life at latest follow-up

Table 62: Tse 2001[867]

Study	Tse 2001{TSE2001B}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in Hong Kong (China)
Line of therapy	2nd line
Duration of study	Intervention time: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: chronic AF
Stratum	Persistent/permanent AF
Subgroup analysis within study	Not applicable
Inclusion criteria	not stated
Exclusion criteria	intolerance of amiodarone or digoxin or contraindication to their therapy; amiodarone therapy in the past 6 months; class III or IV heart failure; clinically significant valvular heart disease; unstable angina or recent MI in the past 6 months; implanted pacemaker
Age, gender and ethnicity	Age - Mean (SD): 63 (9). Gender (M:F): 13 M/ 3F. Ethnicity: Chinese
Further population details	1. Age:
Extra comments	all patients had previously failed an attempt to restore and maintain sinus rhythm
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Rate control drugs - Amiodarone. dose/quantity, brand name, extra details. Duration 24 weeks. Concurrent medication/care: warfarin (n=7) Intervention 2: Rate control drugs - Digoxin. 0.25mg daily or -.125mg daily if bodyweight <50kg or serum creatinine >200mmol/l. Duration 24 weeks. Concurrent medication/care: warfarin
Funding	Academic or government funding (Committee on Research Conference Grant)

Study	Tse 2001{TSE2001B}
RESULTS (NUMBERS ANALYSED): DIGOXIN versus AMIODARONE Protocol outcome 1: Quality of life at latest follow-up - Actual outcome for Persistent/permanent AF: SF-36 Role: physical at 24 weeks - Actual outcome for Persistent/permanent AF: SF-36 Bodily pain at 24 weeks - Actual outcome for Persistent/permanent AF: SF-36 Physical functioning at 24 weeks - Actual outcome for Persistent/permanent AF: SF-36 General health at 24 weeks - Actual outcome for Persistent/permanent AF: SF-36 Social functioning at 24 weeks - Actual outcome for Persistent/permanent AF: SF-36 Vitality at 24 weeks - Actual outcome for Persistent/permanent AF: SF-36 Mental health at 24 weeks - Actual outcome for Persistent/permanent AF: SF-36 Role: emotional at 24 weeks; - Actual outcome for Persistent/permanent AF: % reduction in VR during ambulatory exercise at 24 weeks; Group 1: mean 27 (SD 13); n=7, Group 2: mean 25 (SD 12); n=9 - Actual outcome for Persistent/permanent AF: % reduction in VR during peak exercise at 24 weeks; Group 1: mean 13 (SD 12); n=7, Group 2: mean 12 (SD 10); n=8	
Protocol outcomes not reported by the study	Rate control - heart rate (time or amount of people) at latest follow-up; stroke or thromboembolic complications at latest follow-up; Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up; Left ventricular function - number of people/ejection fraction as % at latest follow-up; Time to response at time reported; Rate of discontinuation of drug due to side effects at time reported; Mortality (long-term) at latest follow-up

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.10 Rhythm control strategies

G.10.1 Restoration of sinus rhythm

Table 63: Bertaglia 2001[90]

Study	Bertaglia 2001{BERTAGLIA2001}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Italy; Setting: secondary care cardiology department
Line of therapy	1st line
Duration of study	Intervention time: 30 days
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	AF >72 hours
Exclusion criteria	Intracellular calcium lowering drugs (verapamil, diltiazem, dihydropyridines or beta-blockers excluding sotalol); mean ventricular rate <60bpm; previous side effects of verapamil; LVEF<40%
Recruitment/selection of patients	not stated

Age, gender and ethnicity	Age - Mean (SD): 65.9 (9.0) verapamil and 65.3 (9.7) amiodarone. Gender (M:F): 64% male. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Electrical cardioversion+Ca channel blocker. amiodarone + verapamil + electrical cardioversion (initially external but could go on to internal if external ineffective). Duration 30 days. Concurrent medication/care: Oral anticoagulation for at least 4 weeks before and 4 weeks after external cardioversion (n=50) Intervention 2: Electrical cardioversion+amiodarone. Amiodarone + electrical cardioversion (initially external but could go on to internal if external ineffective). Duration 30 days. Concurrent medication/care: Oral anticoagulation for at least 4 weeks before and 4 weeks after external cardioversion
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION WITH ANTIARRHYTHMIC DRUG THERAPY versus ELECTRICAL CARDIOVERSION WIHT ANTIARRHYTHMIC DRUG THERAPY Protocol outcome 1: Recurrence of AF at Longest endpoint - Actual outcome: AF relapses at 30 days after cardioversion; Group 1: 21/39, Group 2: 18/42	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Restoration of sinus rhythm at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

Table 64: Bianconi 1993[98]

Study	**Bianconi 1993{BIANCONI1993}**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=35)

Study	Bianconi 1993{BIANCONI1993}
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Intervention time: At time of cardioversion only
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Scheduled for electrical cardioversion of chronic (>4 weeks) atrial fibrillation
Exclusion criteria	Bifascicular block, ventricular rate <60bpm, non-paced sinus node dysfunction, uncontrolled hyperthyroidism, major hepatic or renal dysfunction, severe cardiac or respiratory insufficiency
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 64.3 (12.5) propafenone and 68.5 (11.3) placebo. Gender (M:F): 51% male. Ethnicity: not stated
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Electrical cardioversion+propafenone - Electrical cardioversion + propafenone. External cardioversion + propafenone 750mg/day for preceding 48 hours. Duration Immediate only. Concurrent medication/care: Anticoagulated with warfarin or acenocoumarin for at least 3 weeks (n=19) Intervention 2: Electrical cardioversion - Electrical cardioversion alone. External cardioversion. Duration Immediate only. Concurrent medication/care: Anticoagulated with warfarin or acenocoumarin for at least 3 weeks
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSON + PROPAFENONE versus ELECTRICAL CARDIOVERSION ALONE Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at Immediately after treatment; Group 1: 11/15, Group 2: 14/19	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 65: Bianconi 1996[97]

Study	Bianconi 1996{BIANCONI1996}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention time: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 12 lead ECG, 24 hour ambulatory ECG (Holter) recording
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic (>1 month) AF scheduled for cardioversion
Exclusion criteria	Bifascicular block, mean daytime ventricular rate <80bpm in patients not on digitalis or other drugs depressing AV node conduction, sinus node dysfunction, uncontrolled hyperthyroidism, major hepatic or renal dysfunction, clinical signs of cardiac or respiratory insufficiency
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 67.3 (11.2) propafenone and 63.8 (10.7) placebo. Gender (M:F): 54% male. Ethnicity: Not stated
Indirectness of population	No indirectness
Interventions	(n=49) Intervention 1: Electrical cardioversion+propafenone - Electrical cardioversion + propafenone. Propafenone 750mg/day for 48 hours before cardioversion. Duration 48 hours. Concurrent medication/care: Full anticoagulation with warfarin or acenocoumarin for at least 3 weeks (n=51) Intervention 2: Electrical cardioversion + placebo. Placebo for 48 hours. Duration 48 hours. Concurrent medication/care: Full anticoagulation with warfarin or acenocoumarin for at least 3 weeks
Funding	Funding not stated

Study	Bianconi 1996{BIANCONI1996}
RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSON + PROPAFENONE versus ELECTRICAL CARDIOVERSION + PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at 48 hours; Group 1: 36/49, Group 2: 27/51	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 66: Capucci 2000[171]

Study	Capucci 2000{CAPUCCI2000}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=61)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 2 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients in a stable circulatory condition; first documented episode of persistent AF > 2 weeks duration; referred for cardioversion
Exclusion criteria	Age >75 years, left atrial diameter >55mm, thyrotoxicosis, pregnancy, acute myocarditis or pericarditis, acute MI, uncompensated heart failure, diastolic BP >115mmHg, history of pulmonary hypertension, unstable hepatic or renal function, amiodarone in last 12 months, resting rate <90bpm, sick sinus syndrome, bundle branch block, QT prolongation (corrected QT >0.45s)

Study	Capucci 2000{CAPUCCI2000}
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 59 (15) amiodarone and 58 (10) diltiazem. Gender (M:F): 49% male. Ethnicity: Not stated
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Electrical cardioversion+amiodarone. 400mg/day 1 month before and 200mg/day for 2 months after cardioversion. Duration 2 months after cardioversion. Concurrent medication/care: "Usual anticoagulation guidelines were followed" (n=30) Intervention 2: Electrical cardioversion+Ca channel blocker. Diltiazem - dose adjusted to reduce resting heart rate below 80bpm; starting dose 60mg three times daily to maximum of 360mg/day; 1 month before and 2 months after cardioversion. Duration 2 months after cardioversion. Concurrent medication/care: "Usual anticoagulant guidelines were followed"
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+AMIODARONE versus ELECTRICAL CARDIOVERSION+CA CHANNEL BLOCKER Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at Immediate; Group 1: 20/23, Group 2: 19/29 Protocol outcome 2: Recurrence of AF at Longest endpoint - Actual outcome: Recurrence of AF at 2 months; Group 1: 6/20, Group 2: 10/19	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

Table 67: Channer 2004[182]

Study	Channer 2004{CHANNER2004}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=172)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>18 years, AF >72 hours
Exclusion criteria	AF due to acute reversible condition, LVEF <20%, mitral regurgitation worse than mild, mitral stenosis, aortic stenosis, severe tricuspid regurgitation, pulmonary artery systolic pressure >40mmHg, female <50 years, previous long term therapy with or intolerance to amiodarone, previous/active thyroid disease, abnormal LFTs, FEV1 <1L, any medical condition that would make survival >1 year unlikely, contraindication to anticoagulation.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 68 (8) placebo, 65 (10) short term amiodarone, 66 (10) long term amiodarone. Gender (M:F): 76% male. Ethnicity: Not stated
Indirectness of population	No indirectness
Interventions	(n=123) Intervention 1: Electrical cardioversion+amiodarone. a) Short term amiodarone: 400mg twice daily for 2 weeks before and 200mg once daily for 8 weeks after electrical cardioversion, or b) long term amiodarone: 400mg twice daily for 2 weeks before and 200mg once daily for 52 weeks after electrical cardioversion. Duration 52 weeks. Concurrent medication/care: Anticoagulated with warfarin to INR >2.0 for a minimum of 2 weeks before randomisation Comments: Overall, 4 patients withdrawn for protocol violations and 7 withdrew before electrical cardioversion but not stated which groups (n=38) Intervention 2: Electrical cardioversion + placebo. Electrical cardioversion + placebo. Duration 52 weeks. Concurrent medication/care: Anticoagulated with warfarin to INR >2.0 for a minimum of 2 weeks before randomisation Comments: 38 completers

Study	Channer 2004{CHANNER2004}
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+AMIODARONE versus ELECTRICAL CARDIOVERSION + PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at Immediately after cardioversion; Group 1: 70/97, Group 2: 30/38 Protocol outcome 2: Maintenance of sinus rhythm at Longest endpoint - Actual outcome: Maintenance of sinus rhythm at 1 year; Group 1: 50/96, Group 2: 2/30	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 68: Climent 2004[218]

Study	Climent 2004{CLIMENT2004}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=54)
Countries and setting	Conducted in Spain; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Intervention + follow up: Intervention (single dose) + 1 month follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ECG
Stratum	Overall

Study	Climent 2004{CLIMENT2004}
Subgroup analysis within study	Not applicable
Inclusion criteria	Referred for cardioversion of persistent AF (>1 week)
Exclusion criteria	LVEF <0.40, 2nd or 3rd degree AV block, bifascicular block, sick sinus syndrome, permanent cardiac pacemaker, on oral flecainide, amiodarone, sotalol or quinidine
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 66.0 (10.3) flecainide, 65.1 (9.0) placebo. Gender (M:F): 50% male. Ethnicity: Not stated
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Electrical cardioversion+flecainide - Electrical cardioversion + flecainide. 2mg/kg in 100mL glucose 5% . Duration Single dose. Concurrent medication/care: 4 weeks correct anticoagulation with acenocoumarol to INR 2.0-3.0 (n=28) Intervention 2: Electrical cardioversion + placebo. 100mL glucose 5%. Duration Single dose. Concurrent medication/care: 4 weeks correct anticoagulation with acenocoumarol to INR 2.0-3.0
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION + FLECAINIDE versus ELECTRICAL CARDIOVERSION + PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at Immediate; Group 1: 19/26, Group 2: 23/28 Protocol outcome 2: Recurrence of AF at Longest endpoint - Actual outcome: Relapse of AF at 1 month; Group 1: 10/19, Group 2: 12/23	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

Table 69: De Simone 1999[267]

Study	De simone 1999{DESIMONE1999}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=107)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Persistent or chronic AF referred for electrical cardioversion
Exclusion criteria	History of sick sinus syndrome or trifascicular block, mean daytime ventricular rate 60bpm and/or 3s pause during 24 hour ECG, history of sustained VT, cardiac arrest or congenital QT syndrome, AF due to reversible causes, MI or revascularisation in last 6 months, thromboembolic events, left atrial thrombus, major hepatic or renal dysfunction, severe cardiac or respiratory insufficiency with LVEF <35%, implanted pacing device
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Group I 63.7 (10), group II 62.9 (10.5), group III 63.8 (11.4). Gender (M:F): 60% male. Ethnicity: Not stated
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Electrical cardioversion+propafenone - Electrical cardioversion + propafenone. 900mg/day from 3 days before electrical cardioversion to 3 months. Duration 3 months. Concurrent medication/care: Oral anticoagulation with warfarin sodium to INR 2.5 to 3.5 for 3 weeks before electrical cardioversion (n=73) Intervention 2: Electrical cardioversion+Ca channel blocker. Group II: verapamil 240mg/day for 3 days before electrical cardioversion to 3 months after; group III: verapamil 240mg/day for 3 days before electrical cardioversion to 3 days after. Duration 3 months. Concurrent medication/care: 900mg/day from 3 days before electrical cardioversion to 3 months after Comments: Group II: 38 + group III: 35

Study	De simone 1999{DESIMONE1999}
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSON + PROPAFENONE versus ELECTRICAL CARDIOVERSION+CA CHANNEL BLOCKER Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at Immediately after cardioversion; Group 1: 33/33, Group 2: 64/64 Protocol outcome 2: Recurrence of AF at Longest endpoint - Actual outcome: Recurrence of AF at 3 months; Group 1: 13/33, Group 2: 10/64	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

Table 70: Galperin 2001[367]

Study	Galperin 2001{GALPERIN2001}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=95)
Countries and setting	Conducted in Argentina
Line of therapy	1st line
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic AF lasting from 2 months to >10 years.

Study	Galperin 2001{GALPERIN2001}
Exclusion criteria	>75 years old; paroxysmal AF; acute MI in last 6 months; PR interval <0.24s; second or third degree Av block; in ECG recordings obtained before AF occurrence unless a permanent pacemaker was implanted; spontaneous HR <50bpm; history of sinus node disease without implanted pacemaker; QTc interval of <0.5s; thyroid disease; pregnancy; impossibility to follow-up for any reason; comorbidities conditioning the short-term prognosis; therapy with class I or class III antiarrhythmic drugs (at least 4 months without amiodarone); previous therapy with amiodarone with a history of severe adverse effects attributable to the drug; chronic atrial flutter; LA diameter >60mm; severe mitral stenosis; contraindications for anticoagulation.
Age, gender and ethnicity	Age - Range: 25-75 years. Gender (M:F): 69M; 26F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Amiodarone. 600mg daily orally. Duration at least 4 weeks. Concurrent medication/care: NR (n=48) Intervention 2: Placebo. 600mg daily orally. Duration at least 4 weeks. Concurrent medication/care: NR
Funding	Study funded by industry (GEMA and the Fundacion de Investigaciones Cardiologicas Einthoven)
RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of rhythm at 27.28 days; Group 1: 16/47, Group 2: 0/48	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 71: Hemels 2006[432]

Study	Hemels 2006{HEMELS2006}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=144)
Countries and setting	Conducted in Netherlands; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Persistent AF (non-self-terminating arrhythmia requiring ECV to obtain SR) without contraindications to oral anticoagulants
Exclusion criteria	This episode of AF >1year, , previous unsuccessful ECV, maximum 1 ECV in last year allowed, unstable angina, MI or cardiac surgery <4 weeks, current infection or thyroid disturbance, atrial flutter, concurrent untreated medical condition, unlikely to comply with protocol, class III or IV NYHA heart failure, current or previous treatment with amiodarone, pacemaker
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 65 (11) digoxin, 65 (8) verapamil. Gender (M:F): 62% male. Ethnicity: Not stated
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=74) Intervention 1: Electrical cardioversion+Ca channel blocker. Verapamil 120-360mg daily. Duration 18 months. Concurrent medication/care: Phenprocoumon or acenocoumarol to target INR 2.5-3.5 (n=70) Intervention 2: Electrical cardioversion+digoxin. Digoxin 0.125-0.25mg daily, after loading, depending on age, heart rate and renal function. Duration 18 months. Concurrent medication/care: Phenprocoumon or acenocoumarol to target INR 2.5-3.5
Funding	Other (Charitable + industry)
RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+CA CHANNEL BLOCKER versus ELECTRICAL CARDIOVERSION+DIGOXIN	

Study	Hemels 2006{HEMELS2006}
Protocol outcome 1: Recurrence of AF at Longest endpoint - Actual outcome: Permanent AF at 18 months; Group 1: 21/74, Group 2: 25/70	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Restoration of sinus rhythm at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

Table 72: Kanoupakis 2004[507]

Study	Kanoupakis 2004{KANOUPAKIS2004}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=145)
Countries and setting	Conducted in Greece; Setting: Not stated
Line of therapy	Unclear
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Persistent AF lasting >7 days; age <80 years; ventricular rate at rest >60bpm; SBP >90mmHg; left atrial diameter <50mm.
Exclusion criteria	LVEF <40%; concomitant treatment with class I or III antiarrhythmic drugs; recorded amiodarone use during the preceding 6 months and contraindications for beta blockade, such as conduction disturbances, asthma, or severe COPD
Recruitment/selection of patients	Not stated

Study	Kanoupakis 2004{KANOUPAKIS2004}
Age, gender and ethnicity	Age - Mean (SD): Beta-blocker group: 66 (9); amiodarone group: 64 (8); Placebo group: 61 (10). Gender (M:F): Beta-blocker group: M/F 29/19 Amiodarone group: M/F 28/20 Placebo group: M/F 27/19. Ethnicity: Not stated
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Electrical cardioversion+amiodarone. 600mg/day for the first 2 weeks (after entry to the study), which was reduced to a subsequent dose of 200mg/day up to the end of the study.. Duration 4 weeks. Concurrent medication/care: All patients were properly anticoagulated by oral treatment with acenocoumarol to INR 2.5 to 3.5 for at least 4 weeks (n=50) Intervention 2: Electrical cardioversion+B-blocker. Carvedilol starting dose of 6.25mg twice daily, which was titrated up to 25mg twice daily depending on patient tolerance. Duration 4 weeks. Concurrent medication/care: All patients were properly anticoagulated by oral treatment with acenocoumarol to INR 2.5 to 3.5 for at least 4 weeks before ECV (n=47) Intervention 3: Electrical cardioversion - Electrical cardioversion alone. ECV with no antiarrhythmic drugs. Duration 4 weeks. Concurrent medication/care: All patients were properly anticoagulated by oral treatment with acenocoumarol to INR 2.5 to 3.5 for at least 4 weeks
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+AMIODARONE versus ELECTRICAL CARDIOVERSION ALONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome: Restoration of sinus rhythm at Immediately after cardioversion; Group 1: 42/45, Group 2: 33/45

Protocol outcome 2: Recurrence of AF at Longest endpoint
- Actual outcome: Relapse of AF at 4 weeks; Group 1: 7/42, Group 2: 13/33

RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+B-BLOCKER versus ELECTRICAL CARDIOVERSION ALONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome: Restoration of sinus rhythm at Immediately after electrical cardioversion; Group 1: 43/47, Group 2: 33/45

Study	Kanoupakis 2004{KANOUPAKIS2004}
Protocol outcome 2: Recurrence of AF at Longest endpoint - Actual outcome: Relapse of AF at 4 weeks; Group 1: 12/43, Group 2: 13/33	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

Table 73: Kingma 1992[526]

Study	Kingma 1992{KINGMA1992}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in Netherlands
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 hour
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	AF/flutter lasting <6 months with a ventricular rate >100bpm at rest and no signs of heart failure
Exclusion criteria	Previously documented or suspected conduction disturbances of more than first degree AV block; concomitant therapy with class II antiarrhythmic drugs, WPW syndrome; sick sinus syndrome; acute MI; hyperthyroidism; cardiac surgery before the study; left atrial enlargement with AF/ AFl lasting >2 days without appropriate anticoagulant therapy; electrolyte imbalance; body weight >100kg.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 59 (14). Gender (M:F): 67 M/ 23 F. Ethnicity:
Further population details	None

Study	Kingma 1992{KINGMA1992}
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Flecainide. Flecainide acetate was administered IV at a dose of 2mg/kg body weight. Duration 10 minutes. Concurrent medication/care: Concomitant treatment: digoxin (7); beta-blocker (10); calcium antagonist(4) (n=25) Intervention 2: Propafenone. Propafenone hydrochloride IV at a dose of 2mg/kg body weight.. Duration 10 minutes. Concurrent medication/care: Concomitant treatment: digoxin (4); beta-blocker (3); calcium antagonist(1) (n=20) Intervention 3: Calcium channel blockers. Verapamil was administered as a fast IV bolus injection of 10mg. Duration 1 minute. Concurrent medication/care: Concomitant treatment: digoxin (4); beta-blocker (3); calcium antagonist(0)
Funding	Study funded by industry (3M Pharmaceuticas, St Paul, Minnesota)
RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PROPAFENONE Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of rhythm at 1 hour; Group 1: 32/37, Group 2: 11/20 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome: Time to reversion at 1hour; Group 1: mean 21 (SD 17); n=37, Group 2: mean 16 (SD 10); n=20 RESULTS (NUMBERS ANALYSED): FLECAINIDE versus CALCIUM CHANNEL BLOCKERS Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of rhythm at 1 hour; Group 1: 32/37, Group 2: 1/20 RESULTS (NUMBERS ANALYSED): CALCIUM CHANNEL BLOCKERS versus PROPAFENONE Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of rhythm at 1 hour; Group 1: 1/20, Group 2: 11/20	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at

Study	Kingma 1992{KINGMA1992}
	Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 74: Kochiadakis 1999[535]

Study	Kochiadakis 1999{KOCHIADAKIS1999A}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=67)
Countries and setting	Conducted in Greece; Setting:
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	AF lasting >48 hours who came to the ED or were treated in the clinic.
Exclusion criteria	Recent MI; heart surgery within the last 6 months; unstable angina; acute myocarditis; acute pericarditis; severe uncontrolled heart failure; cardiogenic shock.
Recruitment/selection of patients	Consecutive patients.
Age, gender and ethnicity	Age - Mean (SD): 64 (9). Gender (M:F): 32M; 35F. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Amiodarone. 300mg IV for 1 hour and then 20mg/kg for 24 hours. At the same time, patients were given 600mg/day orally divided into 3 doses for 1 week and thereafter 400mg/day for 3 weeks.. Duration 3 weeks. Concurrent medication/care: Digoxin was given to all patients who had not previously received it. (n=34) Intervention 2: Placebo. Patients in the placebo group received identical amount of saline the first day, 3 placebo tablets per day for 1 week and 2 per day for 3 weeks. Duration 3 weeks. Concurrent medication/care: Digoxin

Study	Kochiadakis 1999{KOCHIADAKIS1999A}
	was given to all patients who had not previously received it.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of rhythm at 3 weeks; Group 1: 16/33, Group 2: 0/34	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 75: Kochiadakis 1999[533]

Study	Kochiadakis 1999{KOCHIADAKIS1999}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=101)
Countries and setting	Conducted in Greece; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention time: 35 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Chronic AF
Exclusion criteria	Recent MI; heart surgery within the last 6 months; acute pericarditis; severe uncontrolled heart failure (ejection

Study	Kochiadakis 1999{KOCHIADAKIS1999}
	fraction <30%); cardiogenic shock; significant COPD; thyroid disease; unstable angina; acute myocarditis; PE; pneumonia; liver or kidney failure; electrolyte disturbances; pregnancy or lactation; age <18 years; sick sinus syndrome; a history of second or third degree AV block or the taking of any other antiarrhythmic drug apart from digoxin within a period less than 5 half-lives of the drug in question before the study.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Amiodarone group: 64 (9); Propafenone group: 64 (10); Placebo group: 63 (9). Gender (M:F): Amiodarone group: M/F: 16/18; Propafenone group: M/F: 16/16; Placebo group: M/F: 16/19. Ethnicity:
Further population details	
Indirectness of population	Serious indirectness: Some patients had already undergone successful cardioversion (pharmacological and electrical)
Interventions	(n=34) Intervention 1: Amiodarone. 300mg IV for 1 hour and then 20mg/kg over 24 hours. At the same time, they were given 600mg/day in 3 doses, orally for one week. Thereafter they received 400mg per day for 3 weeks.. Duration 35 days. Concurrent medication/care: Digoxin 0.5mg IV initially, followed by 0.25mg at 2h and 0.25mg every 6h thereafter was administered for 24h to all patients who had not previously received it. (n=32) Intervention 2: Propafenone. Began with 2mg/kg IV over 15 minutes, followed by 10mg/kg over 24 hours and then 450mg/day, orally, for one month. Duration 35 days. Concurrent medication/care: Digoxin 0.5mg IV initially, followed by 0.25mg at 2h and 0.25mg every 6h thereafter was administered for 24h to all patients who had not previously received it. (n=35) Intervention 3: Placebo. Patients received an identical amount of saline on the first day, and then oral placebo for one month. Duration 35 days. Concurrent medication/care: Digoxin 0.5mg IV initially, followed by 0.25mg at 2h and 0.25mg every 6h thereafter was administered for 24h to all patients who had not previously received it.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome: Restoration of rhythm at 35 days; Group 1: 16/34, Group 2: 0/0

RESULTS (NUMBERS ANALYSED): PROPAFENONE versus AMIODARONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint

Study	Kochiadakis 1999{KOCHIADAKIS1999}
- Actual outcome: Restoration of rhythm at 35 days; Group 1: 13/32, Group 2: 16/34 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome: Time to restoration at 35 days; Group 1: mean 20 (SD 2); n=32, Group 2: mean 23 (SD 1.4); n=34 RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of rhythm at 35 days; Group 1: 13/32, Group 2: 0/0	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 76: Le Heuzey 2010[579]

Study	Le heuzey 2010{LEHEUZEY2010}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=504)
Countries and setting	Conducted in Multiple countries; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 21 or over, AF >72 hours, cardioversion and antiarrhythmic treatment indicated, on oral anticoagulants
Exclusion criteria	Previous chronic treatment with amiodarone, hypo- or hyper-thyroidism, contraindications to amiodarone, corrected

Study	Le heuzey 2010{LEHEUZEY2010}
	QT 500ms or more, paroxysmal AF, atrial flutter, severe congestive heart failure, NYHA class III or IV, severe bradycardia, high degree AV block, contraindicated concomitant treatment (class I or III antiarrhythmic drugs, drugs causing torsade de pointes, potent CYP3A4 inhibitors, substrates of CYP3A4 with narrow therapeutic margin)
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 64 (10.7). Gender (M:F): 71% male. Ethnicity: 83.9% Caucasian; 15.3% Asian
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=255) Intervention 1: Electrical cardioversion+amiodarone. 600mg qd for 28 days then 200mg qd thereafter. Electrical cardioversion was to be performed between days 10 and 28 if the patient had not converted spontaneously to SR. Duration Median 7 months; maximum 13.8 months. Concurrent medication/care: At baseline the majority of patients were treated with oral anticoagulants (95.6%), beta-blockers (62.5%) and ACE inhibitors/ angiotensin II receptor antagonists (51.6%), with a similar distribution in both treatment groups. About 20.6% of patients were receiving digitalis. (n=249) Intervention 2: Electrical cardioversion+dronedarone. 400mg bid. Duration Median 7 months; maximum 13.8 months. Concurrent medication/care: At baseline the majority of patients were treated with oral anticoagulants (95.6%), beta-blockers (62.5%) and ACE inhibitors/ angiotensin II receptor antagonists (51.6%), with a similar distribution in both treatment groups. About 20.6% of patients were receiving digitalis.
Funding	Study funded by industry (Sanofi-Aventis)

RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+AMIODARONE versus ELECTRICAL CARDIOVERSION+DRONEDARONE

Protocol outcome 1: Mortality - long-term at Longest endpoint
- Actual outcome: Death at 12 months; Group 1: 5/255, Group 2: 2/249

Protocol outcome 2: Restoration of sinus rhythm at Longest endpoint
- Actual outcome: Restoration of sinus rhythm at Immediately after electrical cardioversion; Group 1: 131/153, Group 2: 166/200

Protocol outcome 3: Patients developing heart failure at Longest endpoint
- Actual outcome: Heart failure at 12 months; Group 1: 19/255, Group 2: 16/249

Study	Le heuzey 2010{LEHEUZEY2010}
Protocol outcome 4: Recurrence of AF at Longest endpoint - Actual outcome: AF recurrence at 12 months; Group 1: 62/214, Group 2: 91/195	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

Table 77: Manios 2003[637]

Study	Manios 2003{MANIOS2003}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=111)
Countries and setting	Conducted in Greece; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 6 weeks after electrical cardioversion
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: AF repeatedly documented on ECG without intervening SR
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	AF >3 months
Exclusion criteria	>75 years, previous cardiac surgery or implantation of anti-arrhythmia device, left atrial diameter >50mm, amiodarone in previous 3 months
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 64 (8) ECV + diltiazem group, 66 (7) ECV + amiodarone group, 62 (11) ECV only group. Gender (M:F): 54% male. Ethnicity: Not stated
Further population details	None
Indirectness of population	No indirectness

Study	Manios 2003{MANIOS2003}
Interventions	(n=36) Intervention 1: Electrical cardioversion+amiodarone. 2 weeks of 600mg/day then 200mg/day to 6 weeks after electrical cardioversion (ECV 6 weeks after starting drug). Duration 12 weeks in all. Concurrent medication/care: Oral acenocoumarol to INR 2.5 to 3.5 for at least 4 weeks before electrical cardioversion (n=38) Intervention 2: Electrical cardioversion+Ca channel blocker. Diltiazem 270mg-360mg daily in 3 divided doses. Duration 12 weeks in all. Concurrent medication/care: Oral acenocoumarol to INR 2.5 to 3.5 for at least 4 weeks before electrical cardioversion (n=37) Intervention 3: Electrical cardioversion - Electrical cardioversion alone. No antiarrhythmic drug. Duration 12 weeks in all. Concurrent medication/care: Oral acenocoumarol to INR 2.5 to 3.5 for at least 4 weeks before electrical cardioversion
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+AMIODARONE versus ELECTRICAL CARDIOVERSION+CA CHANNEL BLOCKER

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome: Restoration of sinus rhythm at Immediately after electrical cardioversion; Group 1: 30/30, Group 2: 28/33

Protocol outcome 2: Recurrence of AF at Longest endpoint
- Actual outcome: Relapse of AF at 6 weeks after electrical cardioversion; Group 1: 9/34, Group 2: 16/30

RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+AMIODARONE versus ELECTRICAL CARDIOVERSION ALONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome: Restoration of sinus rhythm at Immediately after electrical cardioversion; Group 1: 30/30, Group 2: 29/35

Protocol outcome 2: Recurrence of AF at Longest endpoint
- Actual outcome: Relapse of AF at 6 weeks after electrical cardioversion; Group 1: 9/34, Group 2: 15/30

RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+CA CHANNEL BLOCKER versus ELECTRICAL CARDIOVERSION ALONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome: Restoration of sinus rhythm at Immediately after electrical cardioversion; Group 1: 28/33, Group 2: 29/35

Study	Manios 2003{MANIOS2003}
Protocol outcome 2: Recurrence of AF at Longest endpoint - Actual outcome: Relapse of AF at 6 weeks after electrical cardioversion; Group 1: 16/30, Group 2: 15/30	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

Table 78: Nergardh 2007[690]

Study	Nergardh 2007{NERGARDH2007}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=168)
Countries and setting	Conducted in Sweden; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Repeated ECGs and 24 hour Holter monitoring
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic persistent AF up to 1 year duration, no history of earlier DC cardioversion
Exclusion criteria	Contraindications to beta-blockers (AV block II/III, sick sinus syndrome, asthma), poorly controlled congestive heart failure, untreated thyroid dysfunction, cardiac surgery in previous 2 months, absolute indications for beta-blockers e.g. known coronary artery disease, treatment with class I or III anti-arrhythmics or calcium channel blockers
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 68.2 (10.1) metoporlol and 66.5 (12.2) placebo. Gender (M:F): 71% male. Ethnicity: Not stated
Further population details	

Study	Nergardh 2007{NERGARDH2007}
Indirectness of population	No indirectness
Interventions	(n=83) Intervention 1: Electrical cardioversion+B-blocker. metoprolol CR 100mg tablets, initial dose 50mg once daily, increased in 50mg steps to target of 200mg once daily. Duration 6 months. Concurrent medication/care: Anticoagulation not stated (n=85) Intervention 2: Electrical cardioversion + placebo. Placebo. Duration 6 months. Concurrent medication/care: Anticoagulation not stated
Funding	Other (Charitable + industry)
RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+B-BLOCKER versus ELECTRICAL CARDIOVERSION + PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at Immediately after electrical cardioversion; Group 1: 75/79, Group 2: 75/81 outcome Protocol outcome 2: Stroke or thromboembolic events at Longest endpoint - Actual outcome: Stroke at 24 weeks; Group 1: 1/83, Group 2: 0/85 Protocol outcome 3: Maintenance of sinus rhythm at Longest endpoint - Actual outcome: Maintenance of sinus rhythm at 24 weeks; Group 1: 38/83, Group 2: 22/85 Protocol outcome 4: Recurrence of AF at Longest endpoint - Actual outcome: Relapse of AF at 6 weeks; Group 1: 41/75, Group 2: 40/75	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; health-related quality of life at Longest endpoint

Table 79: Singh 2005[818]

Study	Singh 2005{SINGH2005}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=665)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Other: 28 days (used for this question; actual study follow-up was longer
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Persistent AF
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	AF for at least 72 hours on ECG; still had AF at randomisation; receiving anticoagulants.
Exclusion criteria	Atrial flutter; paroxysmal AF; NYHA class III or IV heart failure; a calculated creatinine clearance <60ml per minute; intolerance of beta blockers; history of long QT syndrome. Originally patients who had AF for more than 12 months were excluded. Subsequently this restriction was eliminated.
Age, gender and ethnicity	Age - Mean (SD): 67.1 (9.3). Gender (M:F): 98.9% M. Ethnicity: 89.3% white
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=267) Intervention 1: Amiodarone. 800mg per day for the first 14 days then 600mg for the next 14 days. Duration 28 days. Concurrent medication/care: NR Comments: Regimen for the first 28 days of a longer study. Only results at 28 days are reported for the restoration of rhythm question. (n=261) Intervention 2: Beta-blockers - Sotalol. 80mg bd for the first week and 160mg twice daily thereafter.. Duration 28 days. Concurrent medication/care: NR Comments: Regimen for the first 28 days of a longer study. Only results at 28 days are reported for the restoration of rhythm question. (n=137) Intervention 3: Placebo. No further information. Duration 28 days. Concurrent medication/care: NR Comments: Regimen for the first 28 days of a longer study. Only results at 28 days are reported for the restoration of rhythm question.

Study	Singh 2005{SINGH2005}
Funding	Study funded by industry (Co-operative studies program of the Department of Veterans Affairs of Research and Development (Washington DC) and by unrestricted grants in aid from Berlex Laboratories and Wyeth-Ayerst Laboratories)
RESULTS (NUMBERS ANALYSED): AMIODARONE versus SOTALOL Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of rhythm at 28 days; Group 1: 70/258, Group 2: 59/244 RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of rhythm at 28 days; Group 1: 70/258, Group 2: 1/132 RESULTS (NUMBERS ANALYSED): SOTALOL versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of rhythm at 28 days; Group 1: 59/244, Group 2: 1/132	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 80: Villani 2000[890]

Study	Villani 2000{VILLANI2000}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line

Study	Villani 2000{VILLANI2000}
Duration of study	Intervention + follow up: Pre-treated with drugs 1 month, ECV, 1 month follow up
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients in a stable circulatory condition with chronic persistent AF (>2 weeks duration) referred for first cardioversion
Exclusion criteria	Age >75 years, left atrial diameter >55mm, thyrotoxicosis, pregnancy, acute myocarditis or pericarditis, acute MI, unstable severe heart failure NYHA III or IV, diastolic BP >115mmHg, history of pulmonary hypertension, unstable hepatic or renal function, amiodarone in last 12 months, resting heart rate without medication <90bpm, sick sinus syndrome, bundle branch block, corrected QT>0.45s
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 58 (7) amiodarone, 59 (3) diltiazem, 56 (5) digoxin. Gender (M:F): 67% male. Ethnicity: Not stated
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Electrical cardioversion+amiodarone. Amiodarone 400mg/day for 1 month before electrical cardioversion. Duration 1 month before electrical cardioversion. Concurrent medication/care: Oral anticoagulation with warfarin for at least 4 weeks before and after electrical cardioversion (n=46) Intervention 2: Electrical cardioversion+Ca channel blocker. Diltiazem 60mg 3 times daily, increased by 30mg 3 times daily until maximum dose 360mg daily, to reduce resting heart rate to <80bpm. Duration 1 month before electrical cardioversion. Concurrent medication/care: Oral anticoagulation with warfarin for at least 4 weeks before and after electrical cardioversion (n=30) Intervention 3: Electrical cardioversion+digoxin. Digoxin 0.25mg/day. Duration 1 month before electrical cardioversion. Concurrent medication/care: Oral anticoagulation with warfarin for at least 4 weeks before and after electrical cardioversion
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+AMIODARONE versus ELECTRICAL CARDIOVERSION+CA CHANNEL BLOCKER

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint

Study	Villani 2000{VILLANI2000}
- Actual outcome: Restoration of sinus rhythm at Immediately after electrical cardioversion; Group 1: 30/33, Group 2: 33/43 Protocol outcome 2: Recurrence of AF at Longest endpoint - Actual outcome: Relapse to AF at 1 month; Group 1: 8/29, Group 2: 17/31 RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+AMIODARONE versus ELECTRICAL CARDIOVERSION+DIGOXIN Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at Immediately after electrical cardioversion; Group 1: 30/33, Group 2: 19/29 Protocol outcome 2: Recurrence of AF at Longest endpoint - Actual outcome: Relapse to AF at 1 month; Group 1: 8/29, Group 2: 12/16 RESULTS (NUMBERS ANALYSED): ELECTRICAL CARDIOVERSION+CA CHANNEL BLOCKER versus ELECTRICAL CARDIOVERSION+DIGOXIN Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at Immediately after electrical cardioversion; Group 1: 33/43, Group 2: 19/29 Protocol outcome 2: Recurrence of AF at Longest endpoint - Actual outcome: Relapse to AF at 1 month; Group 1: 17/31, Group 2: 12/16	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard

deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.11 Maintenance of sinus rhythm

Table 81: Lafuente-Lafuente 2012 [563]

Study	Affirm first antiarrhythmic drug sub study investigators 2003{AFFIRM2003}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=222)
Countries and setting	Conducted in Canada, USA
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were at least 65 years of age or who had other risk factors for stroke or death could be enrolled in this study. The overriding criteria for enrolment were that (in the clinical judgment of the investigators) atrial fibrillation was likely to be recurrent; atrial fibrillation was likely to cause illness or death; long-term treatment for atrial fibrillation was warranted; anticoagulant therapy was not contraindicated; the patient was eligible to undergo trials of at least two drugs in both treatment strategies; and treatment with either strategy could be initiated immediately after randomisation
Exclusion criteria	NR
Age, gender and ethnicity	Age - Mean (SD): Amiodarone group: 67.9 (8.5) Sotalol group: 70.4 (8.9). Gender (M:F): Amiodarone group: M= 86/131 Sotalol group: M=79/125 . Ethnicity:
Further population details	None
Extra comments	This sub study was a second randomisation of patients assigned to the rhythm control arm of AFFIRM.
Indirectness of population	No indirectness
Interventions	(n=131) Intervention 1: Amiodarone. 10g over ≥ 1 week. Minimum dose 200mg/ day; maximum dose 400mg/day..

Study	Affirm first antiarrhythmic drug sub study investigators 2003{AFFIRM2003}
	Duration 1 year. Concurrent medication/care: Unclear (n=125) Intervention 2: Beta-blockers - Sotalol. 160mg/day. Minimum maintenance dose= 240mg/day.. Duration 1 year. Concurrent medication/care: Unclear
Funding	Academic or government funding (NHLBI, National Institutes of Health, Bethesda, Maryland)
RESULTS (NUMBERS ANALYSED): AMIODARONE versus SOTALOL Protocol outcome 1: Mortality - long-term at Longest endpoint - Actual outcome: Mortality at 1 year; Group 1: 15/131, Group 2: 24/125 Protocol outcome 2: Recurrence time at Longest endpoint - Actual outcome: Recurrence rate at 1 year; Group 1: 15/123, Group 2: 22/115	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Recurrence rate- proportion of time in AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Drug withdrawal due to side effects at Longest endpoint; Time to first relapse at Time to event; Quality of life at Longest endpoint

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.12 Left atrial ablation

G.12.1 Catheter ablation

Table 81: Chen 2012 [188]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
CHEN2012[188] Chen HS, Wen JM, Wu SN et al. Catheter ablation for paroxysmal and persistent atrial fibrillation. Cochrane Database Syst Rev. 2012; 4:CD007101.	Cochrane systematic review	N=7 RCTs N=767 Catheter ablation n=365 Medical treatment n=382 Lost to follow-up: N=6 (0.36% catheter ablation group, and 0.27% medical therapies group)	Patients with paroxysmal and persistent AF. AF was defined as a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. Episodes of AF lasting less than or equal to 7 days were defined as paroxysmal AF, while sustained episodes lasting more than 7 days were defined as persistent AF. The definitions were according to the ACC/AHA/ESC	Catheter ablation was defined as to ablation local myocardial cell by inducing catheters and radio frequent currents so as to inhibit the re-entrant cycle or reduce the focal zone and cure the tachycardia (Ma 2006). Any type of catheter ablation, including pulmonary vein electrical isolation, superior vena cava isolation, left atrium posterior wall ablation, crista terminalis ablation, coronary sinus ostium	Medical therapies N=3 RCTS patients did not discontinue anti-arrhythmics before ablation procedure (Calo 2006; Fassini 2005; Rajappan 2009) N=4 RCTs did not describe medical therapies (Liu02 2006; Marrouche 2007; Oral	One month to one year	Health related quality of life, Wazni 2005	SF=36. General health, physical functioning, bodily pain, social functioning favoured catheter ablation ($p<0.001$, $p=0.001$, $p=0.004$ and $p=0.004$ respectively) Forleo 2009 SF-36 mean change in quality of life scores were greater in the catheter ablation group compared to	None	Allocation concealment N=4 computer N=4 not described Randomisation N=3 computerised randomisation N=4 not described N=7 blinding not described

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			Guidelines for the Management of Patients With AF in 2001(Ryden 2001). Chronic AF were included in persistent AF, but those patients diagnosed with permanent AF, which was failed by cardioversion or had been foregone, were excluded. Studies using more specific diagnostic criteria were included.	ablation, inter-atrial septum ablation and 'ligament of Marshall ablation', were included. Catheter ablation for atrial flutter were excluded. N=2 RCTs circumferential pulmonary vein ablation (CPVA) N=1 RCT cavo-tricuspind and left inferior pulmonary vein (PV)-mitral isthmus ablation plus CPVA N=3 pulmonary vein isolation (PVI) N=1 double atrium ablation	2003; Rajappan 2009) N=1 RCTs, class I anti-arrhythmics, amiodarone, and sotalol was discontinued for one day and restarted the following day after ablation (Arentz 2007). N=1 anti-arrhythmics except amiodarone were discontinued for three to five half-lives before ablation. An anticoagulation (heparin) were applied before ablation to a			medical therapy (p<0.05) Jais 2008 Physical and mental scores. Physical and mental component summary scores of the catheter ablation group were significantly higher than those of medical treatment group (p=0.01).		
							Mortality, Stabile 2006	(n=137) Catheter ablation 1/16 Medical therapies 2/69		
							Death of thrombo-embolic events, Stabile 2006	n=137 Catheter ablation 1/68 Medical		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
					target of international normalised ration (INR) of 2 to 3			therapies 0/69		
							Fatal and non-fatal embolic complication, Krittayaphong 2003; Stabile 2006	N=167 Catheter ablation 2/83 Medical treatment 2/84 RR 1.01 (95%CI 0.18 to 5.68)		
							Recurrence of AF, 7 RCTs (Forleo 2009; Jais 2008; Krittayaphong 2003; Oral 2006; Pappone 2006; Stabile 2006; Wazni 2005)	n=767 Catheter ablation 79/379 Medical therapies 288/381 RR 0.27 (95%CI 0.18 to 0.41) with significant heterogeneity		

Table 82: Cosedis 2012 [239]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Cosedis 2012[239] MANTRA-PAF Trial	RCT Multicentre	Catheter ablation N=146 Anti-arrhythmics N=148	Patients with symptomatic paroxysmal AF who were considered to be candidates for rhythm control were screened. Inclusion: At least two episodes of symptomatic AF within preceding 6 months but no episode of AF that was longer than 7 days. Exclusion: age of more than 70 years, previous or on-going treatment with class IC or class III antiarrhythmic drugs, contraindication to both class IC and class III	Radiofrequency catheter ablation. Percutaneous transvenous radiofrequency catheter ablation performed by encircling the left and right sided pulmonary veins with a 3.5mm catheter with an irrigated tip or an 8 mm solid tip catheter. A supplementary linear ablation was placed along the roof of the left atrium between the two encircled areas. Ablation lines in the mitral and tricuspid isthmuses were optional. Antiarrhythmic medication	Class IC agent (flecainide at a dose of 200 mg per day or propafenone at a dose of 600 mg per day). If contraindicated, a class III agent (either amiodarone at a dose of 200 mg per day or sotalol at a dose of 160 mg per day). During treatment with class IC agents, supplementary use of a beta-blocker, a calcium channel blocker. Or	Holter monitor recording were scheduled at 3, 6, 12, 18 and 24 months with a	Free from any AF at 24 months	CA:124/146 85% ADT: 105/148 71% P=0.004	Supported by unrestricted grants from the Danish heart Foundation and Biosense Webster and by a grant from the Finnish Foundation for Cardiovascular Research.	Block randomisation with the use of an automated telephone randomisation system, after stratification according to centre, sex, and hypertension status. Analysis was blinded to randomisation and treatment. No significant differences at baseline.
							Free from symptomatic AF at 24 months	CA:93% ADT: 84% P=0.01		
							Mean (SD) SF-36 for physical component	Baseline CA: 44.3 (8.9) ADT: 45.2 (8.9) 12 months CA:50.2(8.5) ADT: 47.5 (9.7) 24 months CA: 50.0 (8.8) ADT:47.9 (8.9)		
							Mean (SD) SF-36 for mental	Baseline CA: 45.2 (11.7) ADT: 46.1		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			agents, previous ablation for AF, a left atrial diameter of more than 50 mm, a left ventricular ejection fraction of less than 40%, contraindication to OAC therapy, moderate to severe mitral valve disease, severe heart failure, expected surgery for structural heart disease, and secondary AF.	allowed during the initial 3 months after the ablation. Thereafter, supplementary antiarrhythmic drug therapy was discouraged. Patients with recurrent AF after the blanking period were offered a second ablation procedure. 2 ablations: n=58 3 ablations: n=8 4 ablations: n=3 At 24 months patients receiving ADT: n=13	digoxin was recommended. Combination of class I C and class III agents were not allowed. An aggressive rhythm control strategy, with use of direct current cardioversion and trial of all clinically appropriate antiarrhythmic drugs, was recommended for any patient with recurrent AF. If failed, supplementary ablation of AF was offered. Supplementar		component	(11.2) 12 months CA:50.8 (9.3) ADT: 50.1 (8.5) 24 months CA: 51.1 (9.2) ADT:50.9 (8.0)		Only episodes of AF longer than 1 minute were included in the analysis.
							Burden of AF (defined as % of time in AF on each Holter recording)	24 months (90^{th} percentile): CA: 9% ADT: 18% P=0.007		
							Number of patients without AF in 7 day Holter – monitor recordings	Baseline CA:61 ADT:66 12 months CA:120 ADT:106 24 months CA:124 ADT:105		
							All cause mortality	CA: 3 ADT:4		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of fundin g	Comments
					y radiofrequenc y ablation performed in 54 patients		Stroke	CA: 1 ADT: 0		
							Hospitalis ation for heart failure	CA: 0 ADT:2		
							Median time to recurrenc e, days	CA:25 ADT:27 HR for ablation vs drug: 0.79 [0.57-1.09]		

Table 83: Macdonald 2011[630]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
MACDONALD 2011[630] MacDonald MR, Connelly DT, Hawkins NM et al. Radiofreque ncy ablation	RCT	N=44 randomised N=19 medical therapies N=22 Catheter ablation	Medical treatment n=19 N (%)/mean (SD) Age 64.4 (8.3) Male 15 (79) Previous HF hospitalisation 15 (79) AF Duration mths	Radiofrequency ablation Oral amiodarone was started before discharge and continued for	Medical therapies Rate control All patients had been receiving optimal heart	6 mths (some patients had a second procedur e and were	SF-36 Physical Change at end of study mean (SD)	Medical treatment n=18 -1 (4.4) Ablation (n=20) +4 (9.5)	Chief Scientific Office, Scotland	Allocatio n conceal ment: sealed envelop ed Randomi sation:
							SF-36 Mental Change at end	Medical treatment		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart.* 2011; 97(9):740-747.		Analysed/completers N=18 medical therapies N=20 catheter ablation Men and women aged 18-80 yrs. with New York Heart Association functional class II-IV symptoms despite optimal heart failure treatment for at least three mths, ejection fraction < 35%, persistent AF and no contraindication to cardiovascul	64 (47.6) Past medical history: Diabetes 4 (21) Hypertension 11 (58) COPD 3 (16) Angina 1 (5) CABG 7 (37) CHD 10 (53) Cerebrovascular disease 2 (11) Medical treatment: Digoxin 9 (47) Aldosterone antagonist 3 (16) Beta-blocker 18 (95) ACE or ARB 18 (95) Catheter ablation n=22 N (%)/ mean (SD) Age 62.3 (6.7) Male 17 (77) Previous HF hospitalisation 17	three mths	failure treatment for three mths. If mean heart rate was > 80 bpm over a 24 hr period then digoxin was added to treatment	followed up three mths after)	of study mean (SD)	n=18 +5.9 (8.5) Ablation (n=20) +0.4 (9.5)		computer generated
							Maintenance of sinus rhythm	Medical treatment 0/18 Ablation 10/20		
							Hospitalisation (cardiovascular)	Medical treatment 1/20 Ablation 0/18		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		ar MRI Exclusion criteria: paroxysmal AF; QRS duration > 150 ms (or QRS 120-150 with evidence of mechanical cardiac dysnchrony) and contraindication to oral anticoagulant drugs; primary valvular disease or acute myocarditis as the cause of heart failure; coronary revascularisation within the	(77) AF Duration mths 44 (36.5) Past medical history: Diabetes 7 (32) Hypertension 14 (64) COPD 6 (27) Angina 4 (18) CABG 6 (27) CHD 11 (50) Cerebrovascular disease 2 (9) Medical treatment: Digoxin 12 (55) Aldosterone antagonist 10 (45) Beta-blocker 18 (82) ACE or ARB 21 (95)							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		preceding 6 mths; pregnancy and expected cardiac transplantation within 6 mths								

Table 84: Packer 2013[720]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Packer 2013[720]	Design: RCT Enrolment: 245 patients with symptomatic paroxysmal AF and previously failed therapy with ≥1 membrane active anti-arrhythmic drug Randomisation: Not described	n = 245 Drop-outs: 3/82 drug treated patients lost to follow up Crossover: Patients on drug therapy allowed to cross over to ablation	Inclusion criteria: >2 episodes of paroxysmal AF in prior 2 months; previously failed therapy with ≥1 membrane active anti-arrhythmic drug Exclusion criteria: left atrium ≥5.0cm; LVEF <40%; NYHA class III or IV congestive heart failure; coronary heart disease warranting intervention; stroke or TIA in previous 6 months; previous left atrial ablation or surgery for AF; prosthetic heart valve; amiodarone in previous 3 months; >2 cardioversions in 2 years; implantable rhythm device Demographics and baseline characteristics:	Cryoballoon ablation followed by 90 day "blanking period" during which time patients could be treated with arrhythmic drug therapy with flecainide, propafenone or sotalol and	Anti-arrhythmic drug therapy with flecainide, propafenone or sotalol (if patient had not previously experienced failure with these drugs); 90 day dose	1, 3, 6, 9 and 12 months	The primary efficacy outcome was freedom from chronic treatment failure (absence of any detectable AF after blanking period; use of non-study anti-arrhythmic drug; any	Medtronic Inc.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	Allocation concealment: Not described Blinding: open trial unclear if endpoints blinded Sample size calculation: not stated ITT analysis: Available case analysis done.	if met protocol-defined effectiveness failure endpoints (65/82 crossed over)	See table below Drug therapy: Anticoagulation with warfarin to INR 2.0 to 3.0 for 3 months after ablation; then discontinued at investigator's discretion according to clinical guidelines	one repeat cryoablation was allowed (31/163 had repeat cryoablation)	optimisation period; if necessary a change to one of the other of the 3 drugs was allowed		non-protocol intervention for AF (i.e. radiofrequency ablation). Co-primary safety endpoints: proportion of ITT ablated patients with >1 cryoablation procedure-related event (CPE = serious AE: access site complications; cardiac damage including MI; embolic complications including stroke; arrhythmias, persistent phrenic nerve palsy; pulmonary vein stenosis; death) and	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
							ITT freedom from major AF events (non-procedure related serious AE including cardiovascular death; hospitalisation for AF recurrence or ablation; atypical atrial flutter ablation; systemic embolization; CHF; non-stroke haemorrhagic events; MI; stroke; anti-arrhythmic drug initiation, adjustment or complications requiring hospitalisation).	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Results:								
						p value		
Freedom from chronic treatment failure at 12 months (includes criterion for no AF)			114/163 (69.9%)		6/82 (7.3%)	p<0.001		
On antiarrhythmic drugs at 1 year			26%		not stated	not stated		
On warfarin at 1 year			24%		not stated	not stated		
Symptomatic AF at 12 months			19.0%		not stated	not stated		
Serious CPE (defined above)			5/163 (3.1%)		0	not stated		
Major AF events (defined above)			5/163 (3.1%)		7/82 (8.5%)	non-inferior		
CPE or MAFE			6.1%		8.5%	p<0.001		
Stroke			4/163 (2.5%) patients		1/82 (1.2%; crossover patient)	not stated		
TIA			3/163 (1.8%) patients		1/82 (1.2%; crossover patient)	not stated		
Mortality, n (%) 1 year			1/163 (0.6%)		0/82 (0%)	not stated		
Major bleeding (haemorrhage requiring transfusion)			3/163 (1.8%)		1/82 (1.2%)	not stated		

Table 85: Pappone 2011[723]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
PAPPONE 2011 Pappone C, Vicedomini G, Augello G et al. Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. Circ Arrhythm Electrophysiol. 2011; 4(6):808-814.	RCT	N=398	Patients with paroxysmal AF	Pulmonary vein ablation N=99	Anti-arrhythmic drugs Monotherapy or a combination of 3 drugs (flecainide, sotalol and amiodarone)	4 yrs.	Recurrence of AF (after single ablation)	Ablation 17/99 Medical therapies 12/99	San Raffaele University Hospital	No details of randomisation or allocation concealment No details of blinding
							SF-36 physical	Ablation 52.3 SD9 n=99 Medical therapies 44.1 SD7 n=87		
							SF-36 mental	Ablation 52.9 SD9 n=99 Medical therapies 42.5 SD10 n=87		

Table 86: Pokushalov et al 2013[748]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
POKUSHALOV 2013A [748]	RCT	N=154	Numbers: AAD: 59/18;re-ablation:56/21 Age: AAD: 56 ± 7; re-ablation: 57 ± 7 Inclusion criteria: Patients with a history of symptomatic PAF eligible for AAD therapy or re-ablation after a previous failed initial RF ablation procedure involving only PVI were eligible for this study. Exclusion criteria: Patients with persistent AF or atrial flutter, inability to tolerate any AAD, amiodarone therapy within 3 months before the ablation procedure,	Re-ablation (n=77) Re-isolation of the PVs was performed by identifying the breakthrough site on the mapping catheter (NaviStar ThermoCool, Biosense-Webster Inc., Diamond Bar, CA). RF energy was delivered at 43°C, 35 W, 0.5 cm away from the PV ostia at the anterior wall, and was reduced to 43°C, 30 W, 1 cm away from the PV ostia at the posterior wall, with a saline irrigation rate of 17 mL/min. Each lesion was ablated continuously until the local potential amplitude decreased by >80% or RF energy deliveries exceeded 40 s.	Antiarrhythmic drug therapy (AAD) n= 77 Recurrent episodes were pharmacologically managed by conventional AAD therapy (propafenone, flecainide, and/or sotalol as first-line drugs in patients without structural heart disease or amiodarone as a single drug or in combination in patients with structural heart disease or in case of first-line drug failure) according to AF	3 years	AF-free	Re-ablation: 50/77 AAD: 35/77	Not stated	In the AAD group, 43 patients (56%) with recurrent AF crossed over to undergo re-ablation (second ablation). In re-ablation group, 21 of the patients with AF recurrences required treatment with AAD

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of fundin g	Comments
			congestive heart failure, LV ejection fraction < 35% or left atrial diameter > 60 mm were excluded from the study.	The endpoint of ablation was complete PVI; this was confirmed when Lasso catheter mapping showed the disappearance of all PV potentials or the dissociation of PV potentials from LA activity. Only in patients with induced left atrial flutter, additional RF ablation lines were created by connecting the left inferior PV to the mitral annulus (mitral isthmus) and the roof of the LA between the two superior PVs.	management guidelines					

Table 87: Wilber 2010[908]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
WILBER2010[908] Wilber DJ, Pappone C, Neuzil P et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA.* 2010; 303(4):333-340.	RCT	N=167 Catheter ablation n=106 Included in primary analysis n=103 Antiarrhythmic drugs n=61 Included in primary analyses n=56 Inclusion: At least 3 symptomatic AF episodes (≥ 1 episode by electrocardiogram) within 6 mths before randomisation, and not responding to at least one	Catheter ablation: Age mean yrs. 55.5 Male % 73 Patient history: AF duration, median (IQR) yrs. 5.4 (4.3-57.3) Hypertension 51 Diabetes 10 Structural heart disease 10 Cerebrovascular accident/TIA 2 Prior thromboembolic events 2 NYHA class I 81 Class II 12 LVEF, mean (SD) % 62.3 (60.4 to 64.3) Prior anti-arrythmic drug failures Sotalol 36 Dofetelide 3 Propafenone 53	Catheter ablation	Antiarrhythmic drug therapy (ADT) Received a not previously administered medication (dofetilide, flecainide, propafenone, sotalol or quinidine) Amiodarone was not allowed	3 mths	SF-36 mental Mean change (95%CI)	**Catheter ablation** n=90 8.5 (5.9 to 11.1) **ADT** N=39 6.9 (2.6 to 11.2) P <0.001	Biosense Webster	Allocation concealment: sealed envelopes Randomisation: computerised
							SF-36 physical Mean change (95%CI)	**Catheter ablation** n=90 6.9 (5.2 to 8.6) **ADT** n=39 0.4 (-1.7 to 2.6) p<0.001		
							Recurrent of AF	**Catheter ablation** 38/103 **ADT** 46/56		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		antiarrhythmic drug (class I, class III, or atrioventricular nodal blocker) Exclusion: Patients with AF more than 30 days in duration, age younger than 18 yrs., an ejection fraction of less than 40%, previous ablation for AF, documented left atrial thrombus, amiodarone therapy in previous 6 mths, New York Heart Association class III,	Flecainide 33 Amiodarone 7 Baseline QoL scores, mean (95%CI) Mental component summary 44.5 (42.2 to 46.7) Physical component summary 46.1 (44.4 to 47.8) Symptom frequency score 20.7 (18.9 to 22.6) Symptom severity score 17.1 (15.5 to 18.7) Anti-arrhythmic therapy n=61 Age mean 56.1 yrs. Male % 62 Patient history: AF duration, median (IQR) yrs. 6.2 (4.6 to 7.9)							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of fundin g	Comments
		myocardial infarction within the previous 2 mths, coronary artery bypass graft procedure in the previous 6 mths, thromboem bolic event in the previous 12 mths, severe pulmonary disease, a prior valvular cardiac surgical procedure, presence of an implanted cardioverter - defibrillator, contraindica tion to antiarrhyth	Hypertension 30 Diabetes 7 Structural heart disease9 Cerebrovascular accident/TIA 3 Prior thromboembolic events 2 NYHA Class I 50 Class II 8 LVEF, mean (SD) % 62.7 (60.7 to 64.7) Prior anti-arrhythmic drug failures Sotalol 22 Dofetelide 1 Propafenone 30 Flecainide 13 Amiodarone 6 Baseline QoL scores, mean (95%CI) Mental component summary 44.0 Physical component							

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of fundin g	Comments
		mic or anticoagulati on medications, life expectancy of less than 12 mths, and left atrial size of at least 50 mm in the parasternal long axis view	summary 47.6 Symptom frequency score 18.6 Symptom severity score 16.0							

G.12.2 Surgical ablation

Table 88: Abreu 2005[10]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Abreu Filho CAC, Lisboa LAF, Dallan LAO, Spina GS, Grinberg M, Scanavacca M, Sosa EA,	Design: RCT Enrolment: 70 consecutive patients with permanent AF pre-existing for more than 1 year	n = 70 Drop-outs: None Crossover: N/A	Inclusion criteria: Patients with permanent AF pre-existing for more than 1 year and rheumatic MV disease Exclusion criteria: Not stated Demographics and baseline characteristics:	MV surgery associated with a modified Maze III procedure using saline irrigated	MV surgery alone	12 months; mean follow-up in Group A was 13.8 months ±	Mortality; Rhythm status; Thrombo-embolic events.	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ramires JA, Oliveira SA. Effectiveness of the maze procedure using cooled-tip radiofrequency ablation in patients with permanent atrial fibrillation and rheumatic mitral valve disease. *Circulation.* 2005; 112(9 Suppl):I20-I25.	and rheumatic MV disease Randomisation: Method of randomisation not described Allocation concealment: Not described Blinding: Not discussed. Sample size calculation: Not provided ITT analysis: Yes. 12 month follow up occurred in all surviving patients		Operative data only provided Drug therapy: All patients received prophylactic amiodarone postoperatively. This anti-arrhythmic medication was administered IV in hospital at a dose between 900 mg to 1200 mg/day. After discharge from intensive care the drug was administered orally, starting at 200 mg/day and then adjusted according to the heart rte. All patients were maintained on anticoagulant therapy during the first 3-6 months of follow-up. This was maintained if atrial fibrillation ensued.	cooled tip radio-frequency ablation (SICTRA)		3.4 months and in Group B it was 11.5 + 7.3 months This paper also reports early and mid-term study results at 3 and 6 months		

Results:

	Group A N=42	Group B N=28	P value
Mortality (in hospital), n(%)	1 (2.3)	0	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Survival after 12 months, n(%)		39/41 patients (95.1)		26/28 (92.8)		>0.99		
Thromboembolic event		0		0		1.00		
Sinus rhythm at 3 month, n(%)		26/41 (63.4)		7/25 (28)				
Sinus rhythm at 6 month, n(%)		31/41 (76)		8/25 (32)				
Sinus rhythm at 1 year, n(%)		31/39 (79.5)		7/26 (26.9)		0.001		

Table 89: Akpinar 2003[24]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Akpinar B, Guden M, Sagbas E, Sanisoglu I, Ozbek U, Caynak B, Bayindir O. Combined radiofrequency modified maze and mitral valve procedure through a port access approach: early and mid-term	Design: RCT Enrolment: Patients with AF presenting at Florence Nightingale Hospital, Istanbul, Turkey undergoing port access mitral valve surgery Randomisation: Method of randomisation not described Allocation	n = 67 Drop-outs: None Crossover: N/A	Inclusion criteria: Patients with persistent AF for more than 6 months and undergoing minimally invasive port access valve surgery Exclusion criteria: Patients with severe chest wall deformities (pectus excavatum), significant coronary artery disease, aortic valve insufficiency, lung adhesions and with iliac artery disease. Demographics and baseline characteristics: See table below Drug therapy: All patients received prophylactic amiodarone postoperatively. Anti arrhythmic medication was administered for 3 months in Group A	Port access mitral valve surgery + modified RF Maze	Port access mitral valve surgery	Median follow-up was 10 months This paper reports early and mid-term study results	Mortality; Rhythm status; Functional capacity; Thrombo-embolic events;	Not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
results. *European Journal of Cardio-Thoracic Surgery.* 2003; 24(2):223-230. (Guideline ref …)	concealment: Not described Blinding: Not discussed. Sample size calculation: Not provided ITT analysis: Yes. There were not patients lost to follow-up		(surgery + modified RF Maze). Patients in Group B (surgery only) received cordarone for 12 months.					

Results:

	Group A (surgery + modified RF Maze) N=33	Group B (surgery) N= 34	P value
Mortality (30 days)	1 (3%)	1 (2.9%)	>0.05
Cardiac mortality (late)	0	1 (2.9%)	Not reported
Non cardiac mortality (late)	1 (3 %)	1 (2.9%)	Not reported
Thromboembolic event	0	2 (6%)	0.08
Improvement in NYHA	2.81 ± 0.60	3.19 ±0.69	0.023
Sinus rhythm at 6 months, n(%)	26/31 (83.9)	3/32 (9.4)	
Sinus rhythm at 1 year, n(%)	28/31 (90.3)	3/32 (9.4)	
Sinus rhythm at >1 year, n(%)	10/31 (32.3)	1/32 (3.1)	

Table 90: Albrecht 2009[28]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Albrecht A, Kalil RAK, Schuch L, Abrahao R, Sant'Anna JR, de Lima G, Nesralla IA. Randomized study of surgical isolation of the pulmonary veins for correction of permanent atrial fibrillation associated with mitral valve disease. *Journal of Thoracic and Cardiovascular Surgery.* 2009; 138(2):454-459.	Design: RCT Enrolment: 60 consecutive patients, Porto Alegre, Brazil Randomisation: Method of randomisation not described Allocation concealment: A sealed envelope was opened by the surgeon immediately before the beginning of the operation to indicate the procedure to be performed Blinding: Not described Sample size	n = 60 Drop-outs: None Crossover: None	Inclusion criteria: Patients with permanent AF and fulfilling clinical and hemodynamic criteria for elective mitral valvular correction Exclusion criteria: AF of less than 6 months duration, age under 18 or over 79 years, left ventricular ejection fraction below 20%, on-going pregnancy at the time of surgery, reoperations, presence of intra-pericardial adhesions, reference from a cardiologist to any AF correction technique, and patient non-acceptance of the Free Informed Consent Form. Drug therapy: Not described except for patients requiring post-op cardioversion who were treated with amiodarone.	Mitral valve surgery plus modified Maze (Cox maze III) or surgical isolation of the pulmonary veins (SPVI)	Mitral valve surgery only	Mean follow-up of 35 ± 20 months	Mortality; Sinus rhythm; NYHA	Brazilian Ministry of Education; Agency CAPES/Program PROSUP and Research foundation of Rio Grande do Sul.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
(Guideline ref ID…)	calculation: Not described ITT analysis: Yes							

Results				
Characteristics	**SPVI (n=20)**	**Maze (n=20)**	**Control (n=20)**	**P value**
Time (mos)	39.18 ± 19.3	31.35 ± 19.3	36.1 16.9	.468
Mortality, early, n (%)	1/20 (5)	1/20 (5)	0	.153
Mortality, late, n (%)	0	2/19 (10.5)	0	
Sinus rhythm, n (%)	17/19 (90)	14/17 (85)	6/20 (30)	
Freedom from thromboembolic events at 60 months (Kaplan Meir curve), n (5)	18/20 (90)	18/20 (92)	12/20 (60)	
NYHA				
I (%)	85	80	65	.346
II (%)	10	5	25	
III (%)	5	15	10	
Recurrence of AF according to technique				

Group	Permanent AF, recurrence (first event)	Patients/mo	Permanent AF, incidence (per 100 pt-mo)	RR (95% CI)	P value
Control (n=20)	14	366.00	3.83	1	---
Maze (n=20)	4	536.06	0.76	.195 (0.07-0.56)	.002

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
SPVI (n=20)	2	749.50	0.26	.070 (0.02-0.27)			,.001	
SPVI vs. maze	---	---	---	.358 (0.08-1.67)			.215	

Table 91: Blomstrom-Lundqvist 2007[101]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Blomstrom-Lundqvist C, Johansson B, Berglin E, Nilsson L, Jensen SM, Thelin S, Holmgren A, Edvardsson N, Kallner G, Blomstrom P. A randomized double-blind study of epicardial left atrial cryoablation for permanent atrial fibrillation in patients	Design: RCT Enrolment: Patients aged 18-80 years with permanent AF for at least 3 months and mitral valve disease requiring MV surgery Randomisation: Block randomization stratified by hospital (4 centres) Allocation concealment: Not described	n = 69 Drop-outs: 2 Crossover: N/A	Inclusion criteria: Patients aged 18-80 years with permanent AF for at least 3 months and mitral valve disease requiring MV surgery Exclusion criteria: Heart failure in NYHA function class IV, previous cardiac surgery other than CABG surgery, planned MVS combined with other surgical procedures other than CABG, and tricuspid valvuloplasty, conditions that would impose an increased risk for prolonged surgical procedure, permanent pacemaker secondary to AV block, hyperthyroidism, geographical reasons, or unwillingness to participate. Demographics and baseline characteristics: See table below	Surgery + epicardial left atrial cryoablation	Surgery alone	During surgery, prior to discharge and at 1, 2, 3, 6 and 12 months	The primary endpoint was regained sinus rhythm without documented episodes of AF recurrence at 6 months after surgery. The secondary endpoints were maintained SR after 12 months without recurrences of AF during the preceding 6 months, quality of life,	The Swedish Heart-Lung Foundation

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
undergoing mitral valve surgery: the SWEDish Multicentre Atrial Fibrillation study (SWEDMAF). *European Heart Journal.* 2007; 28(23):2902-2908. (Guideline ref …)	Blinding: Patients, personnel and all physicians (excluding the operating team) were blinded to the allocated surgery, which was recorded separately from the patient's surgical notes. Sample size calculation: Estimated minimum number of patients required to show a difference of 40% with a statistical power of 90% was 60 patients (30 in each arm). ITT analysis: ACA for primary endpoints and ITT for adverse		Drug therapy: Prophylactic antiarrhythmic drugs (sotalol, flecainide, propafenone, disopyramide or amiodarone as the last resort), were administered to patients with post-op AF that required cardioversion and were continued for the first 3 months after surgery and then withdrawn in the absence of AF recurrence. Warfarin was advised from the day of surgery for at least 3 months or longer if patients had mechanical valve prosthesis or recurrence of AF.				morbidity and the incidence of predefined adverse events.	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	events							

Results	Surgery + epicardial left atrial cryoablation N=30 reached endpoint (2 deaths, 2 unable to complete surgery) N=34 for adverse events	Surgery alone N=35	P value
Mortality, in hospital, n(%)	1/34 (2.9) Death due to peri-operative heart failure	0	
Late mortality, n (%)	1/33 (3.1)	0	
Sinus rhythm at 6 months, n (%)	22/30 (73.3)	16/35 (45.7)	P=0.024
Sinus rhythm at 12 months, n (%)	22/30 (73.3)	15/35 (42.9)	
TIA, n (%)	1/34 (2.9)	0	
MI & VT, n (%)	1/34 (2.9)	0	
Congestive heart failure, pleural effusion, n (%)	1/34 (2.9)	0	
Late complications:			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
TIA/stroke, n (%)		4/34 (11.8)		2/35 (5.7)				
Congestive heart failure, n (%)		1/34 (2.9)		3/35 (9.0)				
MI, n (%)		0		1/35 (2.9)				
Bleeding – ocular, n (%)		0		1/35 (2.9)				
Antiarrhythmic, n (%)		8/30 (26.7)		11/35 (31.4)		0.787		
Beta-blocking agents, n (%)		14/30 (46.7)		19/35 (54.3)		0.540		
Verapamil or diltiazen, n (%)		1/30 (3.3)		1/35 (2.9)		1.000		
Digitalis, n (%)		8/30 (26.7)		4/35 (11.4)		0.199		
ACE inhibitors or ARB, n (%)		19/30 (63.3)		22/35 (62.9)		0.968		
Diuretics, n (%)		21/30 (70.0)		17/35 (48.6)		0.081		
Warfarin, n (%)		18/30 (60.0)		27/35 (77.1)		0.135		
Aspirin, other anticoagulants, n (%)		8/30 (26.7)		2/35 (5.7)		0.020		

Table 92: Budera 2012[143]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Budera[143] Petr Budera, Zbyněk Straka, Pavel Osmančík, et al. Comparison of cardiac surgery with left atrial surgical ablation vs. cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation: final results of the PRAGUE-12 randomized	Design: RCT Enrolment: 224 patients with AF scheduled for valve and/or coronary surgery Randomisation: Not described Allocation concealment: Not described Blinding: open trial but primary endpoint blinded Sample size calculation: According to available publications, the authors assumed that the SR restoration rate 1 year after surgery would be 70% in	n = 224 Drop-outs: Overall complete-ness of clinical follow-up (patients who died were included) was 97.8% at 1 month, 94.6% at 3 months, 95.1% at 6 months, and 91.4% at 1 year Crossover: N/A	Inclusion criteria: indication for cardiac surgery (CABG, valve replacement or repair, others, or combinations) and AF (paroxysmal, persistent, or long-standing persistent) documented at least twice in the previous 6 months before surgery, a signed informed consent, and an age >18 years Exclusion criteria: emergency surgery Demographics and baseline characteristics: See table below Drug therapy: Patient medication was maintained until the day of surgery except for anticoagulation or antiplatelet therapy, which was either discontinued 5 days prior to surgery or switched to heparin. Post-operative care was identical for both groups. Unless contraindicated, all patients received anti-arrhythmic drugs (AADs) post-operatively on the day of surgery; amiodarone was the first choice, with propafenone or sotalol as the second choice. All patients were put on warfarin with a target international normalized ratio of 2–2.5. Other medication, including beta-blockers, was adjusted routinely, according to the patient's comorbidities. It	CABG and/or valve surgery plus left atrial surgical ablation (pulmonary vein (PV) ablation (left-sided and right-sided PV pairs separately), left atrial appendage (LAA) surgical resection, and three other lesions—interconnecting lesion between PV pairs, connecting lesion from PV to mitral annulus, and a lesion from the left upper PV to the rim of the LAA)	CABG and/or valve surgery (no ablation)	1 month, 3 months, 6 months, and 1 year	The primary safety outcome was the combined endpoint of death/ myocardial infarction/ stroke/renal failure at 30 days. The primary efficacy outcome was sinus rhythm. Secondary outcomes: all-cause 1-year mortality; stroke; pacemaker implantation	The study was partially funded, including the Open Access publication charges for this article, by the Charles University Research projects MSM0021620817 and UNCE 204010/2012

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
multicentre study. European Heart Journal (2012) 33, 2644–2652	the ablation group and 30% in the control group. A power analysis revealed that a minimum of 100 patients per group were required to assure at least 90% power for detecting the anticipated between-group differences in SR prevalence at 1-year and 5-year follow-ups and to compensate for the expected drop-out rate. ITT analysis: Available case analysis done.		was recommended that AADs be discontinued 3 months after surgery if the patient appears to be AF-free. Unless otherwise contraindicated, warfarin was recommended to be discontinued 6 months after surgery (i.e. 3 months after discontinuation of AADs) if patients remained in stable SR					

Results:

			p value
Mortality, n (%) 30 days	9/116 (7.8%)	9/102 (8.8%)	0.809
Mortality, n (%) 1 year	18/111 (16.2%)	16/92 (17.4%)	0.800

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sinus rhythm end of operation, n(%) (ITT)		69/117 (59%)		79/105 (75.2%)				
Sinus rhythm at discharge, n(%)(ITT)		59/111 (53.2%)		30/100 (30%)				
Sinus rhythm at day 30, n(%)(ITT)		57/107 (53.3%)		34/95 (35.8%)				
Sinus rhythm at day 90, n(%)(ITT)		64/101 (63.4%)		34/84 (40.5%)				
Sinus rhythm at day 180, n(%)(ITT)		63/97 (64.9%)		34/84 (40.5%)				
Sinus rhythm at day 360, n(%)(ITT) of which number without AADs: and number without warfarin:		65/93 (69.9%) 36 (64.2%) 23 (41%)		30/76 (39.5%) 20 (74%) 11 (40.7%)				
Stroke (30 days)		2/116 (1.7%)		4/102 (3.9%)				
Stroke (1 year)		3/111 (2.7%)		4/92 (4.3%)				
Bleeding (1 year)		11/111 (9.9%)		9/92 (9.8%)				
Medication: Discharge, n (%) Beta-blockers Anti-arrhythmics Digitalis		(n = 111) 64 (58%) 91 (82%) 9 (8%)		(n = 100) 67 (67%) 76 (76%) 7 (7%)		p value: 0.162 0.285 0.761		
Day 30, n (%) Beta-blockers Anti-arrhythmics Digitalis		(n = 107) 74 (69%) 80 (75%) 10 (9%)		(n = 93) 69 (74%) 62 (67%) 6 (7%)		 0.431 0.207 0.451		
Year 1, n (%) Beta-blockers Anti-arrhythmics Digitalis		(n = 93) 67 (72%) 29 (31%) 10 (11%)		(n = 76) 59 (78%) 17 (22%) 12 (16%)		 0.406 0.200 0.333		

Table 93: Chevalier 2009[200]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chevalier P, Leizorovicz A, Maureira P, Carteaux JP, Corbineau H, Caus T, DeBreyne B, Mabot P, Dechillou C, Deharo JC, Barry S, Touboul P, Villemot JP, Obadia JF. Left atrial radiofrequency ablation during mitral valve surgery: a prospective randomized multicentre study (SAFIR). Archives of Cardiovascular Diseases. 2009; 102(11):769-	Design: RCT Enrolment: Patients > 18 years at each of four university hospital centres in France, who were admitted for mitral valve disease requiring surgery that was associated with persistent AF evolving for more than six months were eligible. Randomisation: Centralized randomization Allocation concealment: Not described Blinding: Described as a double blind study as the follow up	n = 43 Drop-outs: None Crossover: N/A	Patients > 18 years at each of four university hospital centres in France, who were admitted for mitral valve disease requiring surgery that was associated with persistent AF evolving for more than six months were eligible. Demographics and baseline characteristics: See table below Drug therapy: At 12 months the numbers of class I, II, and III anti-arrhythmic drugs were similar in the two groups	MV surgery plus radio frequency ablation (RAF)	MV surgery alone	3 months and one year	Mortality; Rhythm status; thrombo-embolic event	Ministere Francais de la Sante and promoted by the hospices civils de Lyon.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
775. (Guideline ref …)	was blinded. Sample size calculation: According to sample size calculations the number of patients required was estimated to be at least 23 patients per group. To account for patients lost to follow-up an enrolment of 30 patients per group was considered sufficient. Enrolment was slower than anticipated and was therefore extended to two years, but ceased in September 2005 due to lack of funding. ITT analysis: Yes. 12 month follow up occurred in all		(control vs RFA: 1 vs 2, 11 vs 7 and 6 vs 7 respectively).					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
	surviving patients							

Results		MV surgery plus RFA N= 21	MV surgery alone N=22	P value
Mortality, early		1/21	0/22	Not reported
Thromboembolic event		3/21	0/22	Not reported
Sinus rhythm at discharge, n(%)		16/21 (72.73)	1/22 (4.76)	0.005
Sinus rhythm at 3 months, n(%)		18/21 (85.71)	5/22 (23.81)	0.0126
Sinus rhythm at 12 months, n(%)		12/20 (60)	1/22 (4)	0.004
Mean hospital stay (days)		16	16	0.5

G.12.3 Surgical ablation compared to catheter ablation

Table 94: Boersma 2012 [103]

Study	Boersma 2012{BOERSMA2012}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in Netherlands, Spain; Setting: St Antonius Hospital, Netherlands and the Hospital Clinic in Barcelona, Spain.
Line of therapy	2nd line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 7 day Holter performed to establish pre-existing type and burden of AF.
Stratum	Overall

Study	Boersma 2012{BOERSMA2012}
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 30 and 70 years, and mentally able and willing to give informed consent. Included patients who were considered less amenable to CA on basis of LA diameter of 40-44mm with hypertension, LA diameter more or equal to 45mm or failure of prior catheter ablation for AF.
Exclusion criteria	Long standing AF of greater than 1 year, cardiac catheter ablation or a surgical cardiac procedure in the last 3 months, previous stroke or TIA, LA thrombus, LA size>65mm, left ventricular ejection fraction <45%, mitral or aortic value regurgitation above grade 2, moderate to severe mitral or aortic stenosis, active infection or sepsis, pregnancy, unstable angina, myocardial infarction within the previous 3 months, AF secondary to electrolyte imbalance, thyroid disease, other reversible or non-cardiovascular causes for AF, history of blood clotting abnormalities, known sensitivity to heparin or warfarin, life expectancy of less than 12 months. Involvement in another study, pleural adhesions, prior thoracotomy, prior cardiac surgery and elevated hemidiaphragm.
Recruitment/selection of patients	Consecutive patients with drug refractory AF referred for invasive treatment were screened for eligibility.
Age, gender and ethnicity	Age - Mean (SD): 56 (8). Gender (M:F): 100/24. Ethnicity:
Further population details	1. Duration of AF: Short term (All patients had AF for less than 12 months). 2. Left atrial size: Large size (excluded if 65 mm.).
Extra comments	Symptomatic paroxysmal and/or persistent AF for at least 12 months that was refractory to or intolerant of at least one anti-arrhythmic drug.
Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: Catheter ablation - radiofrequency ablation. Wide area linar antrum ablation with documented PV isolation with decapolar circular mapping catheter as the end point. Local anaesthesia with lidocaine, and during the ablation, conscious sedation with diazepam combined with fentanyl at the discretion of the operator. Trans-septal access achieved. Different techniques described for each centre. Vitamin K antagonists discontinued to lower INR to 2-2.5 (St Antonius Hospital) or to <2 with 3 days of bridging LMWH (Hospital clinic). During procedure - Intravenous heparin given to reach an activated clotting time of more than 250 seconds.. Duration Operation time only. Concurrent medication/care: ALL patients treated under either aspirin or Vitamin K antagonist treatment (depending on CHADS score). INR target to <2.5 but >2 for patients with persistent AF. All patients treated with vitamin K antagonists in the first 3 months after the procedure, continued at discretion of treating cardiologist (n=61) Intervention 2: Surgical ablation - PVI. Video assisted thoracoscopy under general anaesthesia. PVI performed from the epicardial side with a bipolar RF ablation clamp. At least 2 overlapping applications around each of the ipsilateral veins were made and isolation confirmed by absence of PV potentials and exit block during pacing. Different techniques described for each centre. The LA appendage was removed by stapling and then cutting the blind end of

Study	Boersma 2012{BOERSMA2012}
	the appendage. . Duration Operation time only. Concurrent medication/care: ALL patients treated under either aspirin or Vitamin K antagonist treatment (depending on CHADS score). INR target to <2.5 but >2 for patients with persistent AF. All patients treated with vitamin K antagonists in the first 3 months after the procedure, continued at discretion of treating cardiologist
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED): CATHETER ABLATION versus SURGICAL ABLATION Protocol outcome 1: All cause mortality at 30 days - Actual outcome: All cause mortality at One month; Group 1: 1/63, Group 2: 0/61 Protocol outcome 2: Stoke or thromboembolic complications at Latest endpoint - Actual outcome: Stoke or thromboembolic complications at 12 months; Group 1: 3/63, Group 2: 1/61 Protocol outcome 3: Maintenance of sinus rhythm at Latest endpoint - Actual outcome: Freedom from left atrial arrhythmia lasting more than 30 seconds without antiarrhythmic drugs at 12 months; Group 1: 23/63, Group 2: 40/61 Protocol outcome 4: Major bleeding including intracranial bleeding at Latest endpoint - Actual outcome: Major bleeding at 12 months; Group 1: 0/63, Group 2: 1/61	
Protocol outcomes not reported by the study	Rehospitalisation (cardiovascular) at Latest endpoint; Necessity for concomitant anti-arrhythmic drug therapy at Latest endpoint; All cause mortality at Latest endpoint; Quality of life at Latest endpoint

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.13 Pace and ablate

Table 95: Brignole 1999[131]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Brignole M, Gianfranchi L, Menozzi C et al. Prospective, randomized study of atrioventricular ablation and mode-switching, dual chamber pacemaker implantation versus medical therapy in drug-resistant paroxysmal atrial fibrillation. The PAF study. *Europace.* 1999; 1(1):15-19.	RCT multicentre	Randomised N=43 Completers n=39 Patients with intolerable, recurrent paroxysmal AF (≥3 episodes/last 6 mths), not controlled with ≥3 antiarrhythmic drugs)	Not reported	Abl + pace AV junction ablation and implantation of a DDDR mode-switching pacemaker Anti-arrhythmic drugs stopped	Drugs Anti-arrhythmic drugs shown to have the best efficacy	6 months	Living with Heart Failure SCORE 0 TO 105. Higher the score the worst	Abl + Pm N=21 mean 20 (sd16) Drugs n=18 mean 43 (sd22)		[including risk of bias assessments, per outcome as necessary]
							NYHA class	Abl + Pm n=21 Mean 1.9 (sd0.7) Drugs n=18 mean 2.3 (sd 0.8)		

Table 96: Brignole 1997 (same study as Brignole 1999)[130]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Brignole M, Gianfranchi L, Menozzi C et al. Assessment of atrioventricular junction ablation and DDDR mode-switching pacemaker versus pharmacological treatment in patients with severely symptomatic paroxysmal atrial fibrillation: a randomized controlled study. *Circulation.* 1997; 96(8):2617-2624.	RCT Multicentre	N=45 (randomised) N=39 completed Abl plus Pm n=21 Drugs n=18 Patients with paroxysmal AF and (i) tachyarrhythmia episodes that caused severe symptoms that were intolerable (ii) failure of 3 or more antiarrhythmic drugs (including amiodarone)	Abl + Pm age 66 (SD 10), male 45%, only AF 68% Drug age 64 (SD 10), male 48%, only AF 76%	Abl + Pm Complete, persistent AV block plus dual-chamber rate-responsive pacemaker equipped with a single algorithm, which is able to identify pathological atrial rhythms and to differentiate them from physiological variations in sinus rate, irrespective of their frequency	Drug treatment Month 6 No. of patients Amiodarone 2 Sotalol 10 Propafenone 3 Flecainide 4 Quinidine 1 Digitalis 5 Verapamil/diltiazem 2	6 mths	Hospitalisation or electrical cardioversion Ejection fraction	Abl + Pm 1/21 Drugs (6/18 Abl + Pm 57 (sd12) N=19 Drugs 58 (sd10) n=16	Not specified	Blocked randomisation. Computer generated sequences hidden from participants until allocation no blinding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		(iii) 3 or more episodes of paroxysmal tachyarrhythmia during previous 6 mths (iv) duration of tachyarrhythmic episodes > 1 yr. and (v) age > 50 yrs.								

Table 97: Brignole 1994[132]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Brignole M, Gianfranchi L, Menozzi C et al. Influence of atrioventricular junction radiofrequency ablation in patients with	RCT	N=23 Consecutive patients affected by chronic (> 3 mths) AF or flutter, with	Abl + PM Age mean 64 (sd10), men 6/12, atrial fibrillation 10/12, acute heart failure 2/12	Abl + PM complete, persistent AV block. Pacemaker was programmed in VVI mode at a basic rate of 70 beats/min and at	PM VVIR pacemaker programmed at the lowest rate available	15 days	NYHA classification	ABl + PM mean 2.0 (sd0.6) N=12 PM	None specified	Randomisation no details, allocation concealment no details, no blinding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
chronic atrial fibrillation and flutter on quality of life and cardiac performance. *Am J Cardiol.* 1994; 74(3):242-246.		resting heart rate >100 beats/min on 3 consecutive standard ECGs performed on different days. A variety of drug treatments had failed to control the symptoms or restore sinus rhythm. No changes in cardiovascular therapy were made on enrolment or during the study period except for the suspension of	PM mean age 70 (sd6), men 6/11, AF 7/11, acute heart failure 2/11	an activity upper-sensor rate of 130 beats/min Drug therapy discontinued	Plus anti-arrhythmic drug therapy			n=11 mean 2.4 (sd0.7)		
							Specific Activity Scale	Abl + PM n=12 Mean 1.7 (sd0.5) PM n=11 2.1 (sd0.7)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		antiarrhythmic drugs after the ablation procedure								

Table 98: Marshall 1999[648]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Marshall HJ, Harris ZI, Griffith MJ et al. Prospective randomized study of ablation and pacing versus medical therapy for paroxysmal atrial fibrillation: effects of pacing mode and mode-switch algorithm. *Circulation.* 1999; 99(12):1587-	RCT and Crossover (DDDR/MS and VVIR)	N=56 (data analysed) N=19 drugs N=37 Abl + Pace N=37 DDR/MS N=29 VVIR N=37 DDR/ Inclusion criteria: (i) Electrocardiographically documented paroxysmal atrial fibrillation at	Drugs Mean age 60.3 yrs. (SD9.8), male 63.2%, no. episodes per month 3.6 (SD3.8) Ablation Age 65.2 yrs. (SD7.5), male sex 48.6%, No. of episodes per month 3.4 (SD4.2)	Abl+Pace DDDR/MS pacemaker implanted Sub-randomised to slow mode switch or "fast" mode switch pulse generators Antiarrhythmic drugs were discontinued 2 to 3 days before ablation and pacing	Drugs No. of patients Amiodarone 3 Sotalol 8 Flecainide 9 Propafenone 9 Quinidine 4 Disopyramide 11 Digoxin 4 Others 6	6 wks. DDDR or VVIR 18 wks. Drugs (3 visits, mean scores reported)	The Psychological General Well Being Questionnaire (PGWB) [score out of 110, higher score greater well-being]	Abp + pace (DDDR/MS) n=37 Mean 77.4 (SD21.6) Abl + Pace (VVIR) n=29 Mean 72.4 (SD21.0) Drugs n=19	British Heart Foundation	Randomisation and allocation concealment no details, no blinding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
1592.		least 6 mths previously. (ii) Symptoms occurring at least monthly or intolerable drug side effects (iii) At least 2 different attempts at drug therapy to maintain sinus rhythm or control ventricular rate during AF						mean 68.5 (SD13.6)		
							The McMaster Health Index (MHI) (MHI) [score out of 20, higher the score the greater the ability]	Abl + Pace (DDDR/MS) n=37 mean 16.1 (SD3.2) Abl + Pace (VVIR) n=29 mean 15.6 (SD3.2) Drugs n=19 mean 15.7 (SD3.0)		

Table 99: Weerasooriya 2003[902]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Weerasooriya R, Davis M, Powell A et al. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). *J Am Coll Cardiol.* 2003; 41(10):1697-1702	RCT multicentre	N=99 N=17 withdrawals N=47 Drugs N=34 Abl + Pm Patients (i) aged > 40 yrs. (ii) symptomatic permanent AF (> 12 mths or with failed cardioversion or medication therapy) with uncontrolled ventricular rate in which a good rate could be achieved by	Abl + Pm mean age 68 (sd8.5), male 69% Drugs mean age 67.9 (sd9), male 72%	Abl + Pm AV junction ablation plus programmed VVIR pacemaker with rate-response functions optimised for each patient. The minimum pacing was 80 to 90 beats/min for one month after ablation, with reprogramming to a lower rate thereafter Ceased ventricular rate-controlling drugs following the procedure	Drugs Drugs were prescribed to achieve satisfactory control of ventricular rate. Included digoxin, metoprolol, atenolol, verapamil, and diltiazem alone or combination	12 mths	Assessment of Quality of Life Questionnaire (AQoL) 1.0 best quality of life 0 worst possible quality of life	Abl + Pm n=34 mean 0.75 (sd0.18) Drugs n=47 mean 0.66 (sd0.18)	None specified	[including risk of bias assessments, per outcome as necessary]
							Sickness Impact Profile Higher score better the quality of life	Abl + Pm n=34 mean 8.89 (sd8.32) Drugs n=47 6.76 (sd4.63)		
							Mortality	Abl + Pace 2/49 Drugs 1/50		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		drugs during the three month screening period (iv) ability to perform a treadmill test					Outcome 4			

G.13.1 Ablate and Pace versus Pharmacological therapies (Heart failure)

Table 100: Brignole 1998[134]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Brignole M, Menozzi C, Gianfranchi L et al. Assessment of atrioventricular junction ablation and VVIR pacemaker versus pharmacologic al treatment in patients with heart failure	RCT multic entre	N=66 randomised N=54 completers Abl + Pace n=28 Drugs n=26	Consecutive patients affected by chronic AF (lasting > 6 mths) who met all of the following criteria (i) clinically manifest heart failure responsible for episodes of congestive heart failure or pulmonary	Complete persistent AV block plus single chamber rate-responsive pacemaker. Programmed to the VVIR mode, lower rate 80 bpm an upper rate of 120 bpm. Beta-blockers,	Drug treatment Plus calcium-antagonists, sotalol and amiodarone Antithrombotic therapy	12 month	Living with Heart Failure Questionnaire	Abl + Pm n=28 mean 32 (sd20) Drugs n=26 mean 37 (sd18)	Not specified	Central, blocked randomisation Allocation if sequence computer generated and the intervention assignments were hidden from
							NYHA class	Abl + Pm		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
and chronic atrial fibrillation: a randomized, controlled study. *Circulation.* 1998; 98(10):953-960.			oedema or persistent severe symptoms (ii) evidence of structural heart disease (iii) heart rate > 90 bpm on 3 standard ECGs recorded at rest during stable clinical conditions on different days Abl + pace age 72 (SD 9), male sex 56%, atrial fibrillation only 29/32 Drugs Age 72 (SD 9), male sex 38%, atrial fibrillation only 29/34	amiodarone and calcium antagonists Antithrombotic therapy				n=28 mean 2.4 (sd0.5) Drugs n=26 Mean 2.5 (sd0.8)		participants until the time of allocation no blinding
							Specific Activity Scale Class1 to IV (IV worse)	Abl + Pm n=28 mean 2.3 (sd0.8) Drugs n=26 mean 2.6 (sd0.9)		
							Mortality	Abl + Pm 3/32 Drugs 4/34		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Hospitalisation (cause not specified)	Abl + Pm 9/32 Drugs 13/34		
							Ejection fraction	Abl+ Pm 44 (sd11) n=26 Drugs 41 (sd12) n=24		

G.13.2 Ablate and Pace versus Pace and Rate Control

Table 101: Levy 2001[358]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Levy T, Walker S, Mason M et al. Importance of rate control or rate regulation for improving exercise capacity and quality of life in patients with permanent atrial fibrillation and normal left ventricular function: a randomised controlled study. *Heart.* 2001; 85(2):171-178.	RCT	N=36 Abl + Pm n=18 Pm + Drugs n=18 Permanent AF (> 6 mths).Symptomatic fast ventricular response rate to their AF that could not be controlled by drugs Fully ambulant	Abl + Pm mean age 68 (sd8), male: female 11:7 Pm + Drugs mean age 69 (sd7), male:female 11:7	His junction ablation + pacemaker (Abl + Pm). The pacemaker was programmed to VVIR base rate 60 bpm, upper rate 85% of age predicted (220 minus age) Drugs discontinued	(Pm + drugs) VVIR pacemaker programmed to VVI base rate 70 bpm Plus atrioventricular modifying medication. First choice drugs were verapamil or diltiazem, with the addition of digoxin if required. Beta blockers could be substituted or added.	12 mths	Modified Karolinska Questionnaire total score 0 asymptomatic and 140 very symptomatic	Abl + Pm n=16 mean 20 (sd18) Pm + drugs n=16 mean 22 (sd17)	None specified	Randomisation inadequate, allocation concealment unclear, no blinding
							Nottingham Health Profile total score 0 to 600 higher score greater the limitation	Abl + Pm n=16 mean 80 (sd 116) Pm + Drugs n=16 mean 52 (sd 63)		
							Outcome 3			
							Outcome 4			

G.13.3 Ablate and Pace versus pulmonary vein isolation (PVI)

Table 102: Khan 2008[519]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Khan MN, Jais P, Cummings J et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med.* 2008; 359(17):1778-1785.	RCT multic entre	N=81 randomised N=41 pulmonary vein isolation (Iso) N=40 AV node ablation plus pacing (Abl+Pm) Patients with symptomatic AF and symptoms of NYHA class II or III heart failure, despite the use of antiarrhythmic drugs.	Iso Mean age 60 (sd8), male 95%, paroxysmal AF 49%, persistent or long standing AF 51%, Minnesota Living with Heart Failure score mean 89 (sd12) Abl + Pm Mean age 61 (sd8), male 88%, paroxysmal AF 54%, persistent or long standing AF 46%, Minnesota Living with Heart Failure score mean 89 (sd11)	Complete AV junction block plus biventricular pacing. The type and settings of the device and the atrioventricular and venoventricular timing were chosen by the physician	Pulmonary vein isolation Antiarrhythmic medication was discontinued after 2 mths	6 mths	Freedom from AF	Abl + Pm 0/40 Iso 36/41	Ministry of Education, Youth and Sports and St Jude Medical Educational Grant	Computer generated randomisation Allocation concealment unclear No blinding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
		Patients were included if they had ejection fraction of 40% or less; had a medication regimen of beta-blockers and angiotensin-converting-enzyme-inhibitors and, in patients with NYHA class III heart failure, spironolactone, were able to complete a 6-minute walk test and were 18 yrs. or over								

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV=

electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

G.14 Acute

G.14.1 Rate

Table 103: Demircan 2005[272]

Study	Demircan 2005{DEMIRCAN2005}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Turkey; Setting: Emergency department
Line of therapy	Not applicable
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	ventricular rate ≥ 120/minute; systolic blood pressure ≥ 95mmHg
Exclusion criteria	history of allergic reactions to diltiazem and metoprolo, congestive heart failure (New York Heart Association Class IV), systolic blood pressure <95mmHg, sick sinus syndrome, atrioventricular block (2nd or 3rd degree), pre-excitation syndromes, ventricular rate >220/min, QRS >0.08s, unstable angina pectoris, acute MI, hyperthyroidism, temperature >38.0˚C, Hb <11.0g/dl, bronchial asthma, COPD, diabetes mellitus, peripheral vascular disease, pregnancy, history of use of diltiazem, verapamil, digoxin, B-blockers, theophylline or beta mimetics within the last 5 days.
Age, gender and ethnicity	Age - Mean (SD): diltiazem group: 62.1 (12.9); metoprolol group: 60.2 (range 31-82). SD not given for both groups.. Gender (M:F): --Define--. Ethnicity: NR
Further population details	1. Age:
Extra comments	atrial fibrillation

Study	Demircan 2005{DEMIRCAN2005}
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Rate control drugs - Beta blockers. IV metoprolol 0.15mg/kg (maximum 10 mg) over 2 minutes.. Duration 2 minutes. Concurrent medication/care: none (n=20) Intervention 2: Rate control drugs - Calcium limiting antagonists. IV diltiazem 0.25mg/kg (maximum 25mg). Duration 2 minutes. Concurrent medication/care: none
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): BETA BLOCKERS versus CALCIUM LIMITING ANTAGONISTS Protocol outcome 1: Rate control - heart rate (time or amount of people) at latest follow-up - Actual outcome for Unstable with acute AF: mean (SD) % decrease in VR at 2 minutes after administration of treatment ; Group 1: mean 17.5 (SD 11.6); n=20, Group 2: mean 25.6 (SD 12); n=20 - Actual outcome for Unstable with acute AF: mean (SD) % decrease in VR at 5 minutes after administration of treatment; Group 1: mean 20.4 (SD 11.8); n=20, Group 2: mean 30.7 (SD 9.7); n=20 - Actual outcome for Unstable with acute AF: mean (SD) % decrease in VR at 10 minutes after administration of treatment; Group 1: mean 24.3 (SD 11.6); n=20, Group 2: mean 33.6 (SD 8.4); n=20 - Actual outcome for Unstable with acute AF: mean (SD) % decrease in VR at 15 minutes after administration of treatment; Group 1: mean 25.9 (SD 11.5); n=20, Group 2: mean 34.5 (SD 8); n=20 - Actual outcome for Unstable with acute AF: mean (SD) % decrease in VR at 20 minutes after administration of treatment; Group 1: mean 28.9 (SD 10.9); n=20, Group 2: mean 35.9 (SD 6.6); n=20	
Protocol outcomes not reported by the study	Mortality (long-term) at latest follow-up; stroke or thromboembolic complications at latest follow-up; Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up; Left ventricular function - number of people/ejection fraction as % at latest follow-up; Time to response at time reported; Rate of discontinuation of drug due to side effects at time reported; Quality of life at latest follow-up

Table 104: Hofmann 2006[450]

Study	Hofmann 2006{HOFMANN2006}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Austria; Setting: hospital
Line of therapy	Not applicable
Duration of study	Intervention time: one hour
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People with AF
Subgroup analysis within study	Not applicable
Inclusion criteria	AF and a mean ventricular rate >135bpm
Exclusion criteria	age <18 years, baseline systolic BP <100mmHg, known thyroid function disorder, serum potassium <3.5mmol/l, pre-treatment with any antiarrhythmic drug with class I or class III properties, history of torsade de pointes arrhythmia, documented permanent AT and a QTc interval of above 440ms measured in the qualifying ECG. In addition, patients with organised tachyarrhythmia's such as atrial flutter were excluded.
Age, gender and ethnicity	Age - Mean (SD): amiodarone group: 68.3 (13); digoxin group: 69.3 (13). Gender (M:F): amiodarone group: M:28/100; digoxin group: M: 28/100. Ethnicity:
Further population details	1. Age:
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Rate control drugs - Amiodarone. 450mg amiodarone IV as a single bolus. If the ventricular rate exceeded 100bpm after 30 min, another 300mg was added. Duration 1 hour. Concurrent medication/care: 'no other antiarrhythmic agent or drug that might influence conduction through the AV node was allowed'. (n=50) Intervention 2: Rate control drugs - Digoxin. 0.6mg IV as a single bolus. If ventricular rate exceeded 100bpm after 30 min, another 0.4mg was added.. Duration 1 hour. Concurrent medication/care: 'no other antiarrhythmic agent or drug that might influence conduction through the AV node was allowed'.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): AMIODARONE versus DIGOXIN	

Study	Hofmann 2006{HOFMANN2006}
Protocol outcome 1: Rate control - heart rate (time or amount of people) at latest follow-up - Actual outcome for People with AF: Mean ventricular rate at 1 hour; Group 1: mean 94.2 (SD 22); n=50, Group 2: mean 105.3 (SD 22); n=50	
Protocol outcomes not reported by the study	Mortality (long-term) at latest follow-up; stroke or thromboembolic complications at latest follow-up; Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up; Left ventricular function - number of people/ejection fraction as % at latest follow-up; Time to response at time reported; Rate of discontinuation of drug due to side effects at time reported; Quality of life at latest follow-up

Table 105: Jordaens 1997[495]

Study	Jordaens 1997{JORDAENS1997}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=39)
Countries and setting	Conducted in Belgium
Line of therapy	1st line
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Acute AF
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Symptomatic AF of recent onset (<1 week) as judged from clinical history or documented with ECG. VR >100bpm
Exclusion criteria	Treatment with cardiac glycosides within the last week or if antiarrhythmic drugs had already been used in the last 72h. Atrial flutter. Previous use of amiodarone, acute MI, recent CABG. Haemodynamic or respiratory instability.
Age, gender and ethnicity	Age: 64 (17) Gender (M:F): 23:16 --Define--. Ethnicity: unclear
Further population details	None
Indirectness of population	None
Interventions	(n=19) Intervention 1: Rate control drugs - Digoxin. The digoxin ampoules contained 0.50mg of digoxin in a volume of 2ml. A total amount of 1.25mg digoxin was given. It was intended to give the full dosage even if sinus rhythm

Study	Jordaens 1997{JORDAENS1997}
	occurred. The initial dose of digoxin was infused over 10 min, the subsequent 0.25mg doses over 5 min. . Duration 12 hours. Concurrent medication/care: verapamil was allowed if there was no lessening in the rapidity of HR. Other pharmacological antiarrhythmic treatment was allowed after the initial 12h. (n=20) Intervention 2: Placebo. dose/quantity, brand name, extra details. Duration 12 hours. Concurrent medication/care: gf
Funding	Equipment / drugs provided by industry
RESULTS (NUMBERS ANALYSED): DIGOXIN versus PLACEBO Protocol outcome 1: Rate control - heart rate (time or amount of people) at latest follow-up - Actual outcome for Unstable with acute AF: HR at 10 minutes; Group 1: mean 123 beats per min (SD 27); n=19, Group 2: mean 133 beats per min (SD 28); n=20 - Actual outcome for Unstable with acute AF: HR at 30 minutes at 30 minutes; Group 1: mean 118 (SD 23); n=19, Group 2: mean 139 (SD 33); n=20	
Protocol outcomes not reported by the study	Mortality (long-term) at latest follow-up; stroke or thromboembolic complications at latest follow-up; Re-hospitalisation with a primary diagnosis of AF or heart failure at latest follow-up; Left ventricular function - number of people/ejection fraction as % at latest follow-up; Time to response at time reported; Rate of discontinuation of drug due to side effects at time reported; Quality of life at latest follow-up

G.14.2 Restoration of rhythm

Table 106: Azpitarte 1997[63]

Study	Azpitarte 1997{AZPITARTE1997}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=55)
Countries and setting	Conducted in Spain; Setting: Emergency department
Line of therapy	1st line
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Propafenone group: 60 (12); Placebo group: 57 (14)
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Acute AF
Exclusion criteria	Taking antiarrhythmic medication; previous embolic event; mean VR<70 bpm; symptomatic ischaemic heart disease, dilated or hypertrophic cardiomyopathy, severe hypertension; AF with ventricular pre-excitation; hepatic or renal dysfunction; severe pulmonary disease; intra-ventricular conduction defects; documented sick sinus syndrome; haemodynamic instability. Special care was taken to exclude left sided heart failure because of the potentially adverse effects of propafenone in this clinical setting.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Gender (M:F): Propafenone group: M=14, F=15; Placebo group: M=7, F=19. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=29) Intervention 1: Propafenone. Oral propafenone was given in a titrated dose according to the weight of the patient: a tablet of 450mg for patients weighing between 50-64kg, one of 600mg for those between 65-85kg, and one of 750mg for those weighing 85kg or more.. Duration single dose. Concurrent medication/care: NR (n=26) Intervention 2: Placebo. Placebo tablets of identical appearance to propafenone. Duration single dose. Concurrent medication/care: NR
Funding	Study funded by industry (Laboratorios Knoll, Madrid, Spain)

Study	Azpitarte 1997{AZPITARTE1997}
RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Conversion to sinus rhythm at 2 hours; Group 1: 12/29, Group 2: 2/25	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 107: Baldi 1990[71]

Study	Baldi 1990{BALDI1990}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Italy; Setting: unclear
Line of therapy	1st line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	AF of recent onset (not more than 3 days) and a ventricular rate over 100 bpm at rest.

Study	Baldi 1990{BALDI1990}
Exclusion criteria	Recent MI (<1 month), heart failure, valvular heart disease, SBP<100mmHg, concomitant antiarrhythmic therapy and/or digitalis.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 51.52 (14.48). Gender (M:F): 33M; 5F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Flecainide. 2mg/kg body weight IV at a dosage of 10mg/min; for patients <75kg, up to a maximum dosage of 150mg.. Duration unclear. Concurrent medication/care: NR (n=18) Intervention 2: Digoxin. dosage of 0.5mg IV in 10 minutes, 4 hours later another dose of 0.5mg IV and finally 2 oral doses of 0.25mg after 8 and 16 hours.. Duration unclear. Concurrent medication/care: NR
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): FLECAINIDE versus DIGOXIN Protocol outcome 1: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: conversion time at 4 to 1020 minutes; Group 1: mean 80.4 minutes (SD 222.5); n=20	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Restoration of sinus rhythm at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 108: Balla 2011[72]

Study	Balla 2011{BALLA2011}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in Albania; Setting: Emergency department.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	AF diagnosed by European Society of Cardiology guidelines.
Exclusion criteria	Uncontrolled congestive heart failure; acute MI within 7 days; previous ECG documentation of AV block or sick sinus syndrome; antiarrhythmic therapy at time of admission; prior thromboembolic episodes or stroke; impaired hepatic/ renal function; advanced obstructive bronchopulmonary disease; pregnancy.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Fleciainide group: 57.9 (9.5); amiodarone group: 58.9 (10.4); propafenone group: 57.4 (9.8); placebo group: 58.6 (10.7). Gender (M:F): M: 101/ F: 64. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Flecainide. 3mg/kg (single oral dose). Duration single dose. Concurrent medication/care: 'no other rate control drugs were used' (n=40) Intervention 2: Amiodarone. 30mg/kg (single oral dose). Duration single dose. Concurrent medication/care: 'no other rate control drugs were used' (n=40) Intervention 3: Propafenone. 8.5mg/kg (single oral dose). Duration single dose. Concurrent medication/care: 'no other rate control drugs were used' (n=40) Intervention 4: Placebo. No further details. Duration single dose. Concurrent medication/care: ;no other rate

Study	Balla 2011{BALLA2011}
	control drugs were used'
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): FLECAINIDE versus AMIODARONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion rate at 24 hours; Group 1: 35/40, Group 2: 34/40

RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PROPAFENONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion rate at 24 hours; Group 1: 35/40, Group 2: 34/40

RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion rate at 24 hours; Group 1: 35/40, Group 2: 7/40

RESULTS (NUMBERS ANALYSED): AMIODARONE versus PROPAFENONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion rate at 24 hours; Group 1: 34/40, Group 2: 34/40

RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion rate at 24 hours; Group 1: 34/40, Group 2: 7/40

RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion rate at 24 hours; Group 1: 34/40, Group 2: 7/40

Study	Balla 2011{BALLA2011}
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table: 109: Bellandi 1995[83]

Study	Bellandi 1995{BELLANDI1995}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=182)
Countries and setting	Conducted in Italy; Setting: unclear
Line of therapy	1st line
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Recent-onset AF
Exclusion criteria	Angina or clinical signs of heart failure; spontaneous low MVR (<70bpm) and previous treatment with digoxin, beta-blockers, calcium channel blockers or other antiarrhythmic drugs.
Age, gender and ethnicity	Age - Mean (SD): 61.18 (13). Gender (M:F): 94 M; 88F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=98) Intervention 1: Propafenone. 2mg/kg for 3 minutes followed by infusion of 10mg/kg/24h. Duration 24 hours. Concurrent medication/care: NR (n=84) Intervention 2: Placebo. 0.9% saline solution 500ml/ 24 hr. Duration 24 hours. Concurrent medication/care: NR

Study	Bellandi 1995{BELLANDI1995}
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Conversion into sinus rhythm at 24 hours; Group 1: 89/98, Group 2: 27/84 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: Time for conversion at 24 hours; Group 1: mean 2.51 hours (SD 2.77); n=98, Group 2: mean 17.15 hours (SD 5.78); n=84	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 110: Bellone 2012[85]

Study	Bellone 2012{BELLONE2012}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=247)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Follow up (post intervention): 60 days
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years; AF <48 hours

Study	Bellone 2012{BELLONE2012}
Exclusion criteria	AF >48 hours; haemodynamic instability; valve disease; acute coronary syndrome; electrolyte disturbances; sepsis; fever; hypothermia; untreated hyperthyroidism; daily antiarrhythmic drugs; CHADS2 score 2 or more; unclear duration of symptoms
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 67 (14) propafenone; 68 (13) electrical cardioversion. Gender (M:F): 53% male. Ethnicity: not stated
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=126) Intervention 1: Propafenone. IV 2mg/kg over 10 minutes. Duration Single dose. Concurrent medication/care: 32% on beta-blockers, 28% long-acting nitrates, 25% ACE inhibitors, 34% aspirin, 44% calcium antagonist (n=121) Intervention 2: Electrical cardioversion - Electrical cardioversion alone. External synchronised cardioversion. Duration Single dose. Concurrent medication/care: 35% on beta-blockers, 27% long-acting nitrates, 21% ACE inhibitors, 41% aspirin, 37% calcium antagonist
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): PROPAFENONE versus ELECTRICAL CARDIOVERSION ALONE Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Successful cardioversion at Within 6 hours of intervention; Group 1: 93/126, Group 2: 108/121 Protocol outcome 2: Recurrence of AF at Longest endpoint - Actual outcome: Patients in AF at 60 days; Group 1: 21/74, Group 2: 24/91	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; health-related quality of life at Longest endpoint

Table 111: Blanc 1999[99]

Study	Blanc 1999{BLANC1999}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=86)
Countries and setting	Conducted in France; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention + follow up: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age between 25 and 80 years old; AF lasting for <2 weeks.
Exclusion criteria	NYHA class II or more before AF, hypotension (<90mmHg), bradyarrhythmia (<45bpm), dysthyroidism, second or third degree AV block without pacemaker, 3mmol/L<kalaemia<5.5mmol/L, stroke or MI in the last 3 months, severe obstructive bronchopathy, known hepatic or renal failure, and treatment with any antiarrhythmic drug at inclusion or one that had been discontinued for <5 half-lives.
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Propafenone group: 61 (12); Placebo group: 64 (12). Gender (M:F): Propafenone group: M=8, F=35; Placebo group: M=8, F=35. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Propafenone. 600mg for the first 24 hours (orally). Duration single dose. Concurrent medication/care: Heparin was administered IV at admission to all patients (n=43) Intervention 2: Amiodarone. 30mg/kg (usually 10 to 12 pills over 2 to 3 minutes). Duration single dose. Concurrent medication/care: Heparin was administered IV at admission to all patients
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): PROPAFENONE versus AMIODARONE Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint	

Study	Blanc 1999{BLANC1999}
- Actual outcome: Restoration of sinus rhythm at 24 hours; Group 1: 1/43, Group 2: 7/43	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 112: Boriani 1997[113]

Study	Boriani 1997{BORIANI1997}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=240)
Countries and setting	Conducted in Italy; Setting: Hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention): 8 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	recent-onset AF
Exclusion criteria	Age >80 years; heart failure> NYHA class II, recent MI; bundle branch block; sick sinus syndrome; severe hypoxia; thyroid dysfunction; previous antiarrhythmic treatment
Age, gender and ethnicity	Age - Mean (SD): Propafenone group: 59 (12); Placebo group: 58 (13). Gender (M:F): Propafenone group: M=70;, F=49; Placebo group: M=67, F=54. Ethnicity: Not reported
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=119) Intervention 1: Propafenone. 300mg in 2 tablets as a single oral dose. Duration single dose. Concurrent medication/care: NR

Study	Boriani 1997{BORIANI1997}
	(n=121) Intervention 2: Placebo. no further details. Duration NR. Concurrent medication/care: NR
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Conversion to sinus rhythm at 8 hours; Group 1: 90/119, Group 2: 45/121	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 113: Camm 2011[161]

Study	Camm 2011{CAMM2011}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=254)
Countries and setting	Conducted in multiple countries; Setting: Unclear
Line of therapy	1st line
Duration of study	Intervention + follow up: 90 minutes
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18-85 years; symptomatic recent-onset AF (duration 3-48 hours), who were eligible for cardioversion, haemodynamically stable and taking adequate anticoagulation therapy.

Study	Camm 2011{CAMM2011}
Exclusion criteria	Uncorrected QT interval >440ms; familial long QT syndrome; previous torsades de pointes; ventricular fibrillation; sustained ventricular tachycardia; symptomatic bradycardia; known sick sinus syndrome; VR <50 bpm; QRS interval >140ms; pacemaker; atrial flutter; atrial thrombus; unstable congestive heart failure; NYHA functional class IV heart failure or heart failure requiring inotropes; MI; acute coronary syndrome; cardiac surgery within 30 days prior to enrolment; cerebrovascular accident within 3 months prior to enrolment; AV block; valvular stenosis; hypertrophic obstructive cardiomyopathy; restrictive cardiomyopathy; constrictive pericarditis; end-stage disease states; previously failed electrical cardioversion; secondary causes of AF; uncorrected electrolyte imbalance; digoxin toxicity; contraindications to amiodarone; previous exposure to vernakalent.
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Mean (SD): Vernakalent group: 63.1 (10.81); Amiodarone group: 62.2 (11.63). Gender (M:F): Vernakalent group: 75/116 male, Amiodarone group: 71/116. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=116) Intervention 1: Vernakalent. 10 minute infusion of 3mg/kg vernakalent in one infusion line, followed by a 15 minute observation period and an additional 10 minute infusion of 2mg/kg vernakalent if still in AF. To maintain blinding, a 60 minute infusion of placebo (5% dextrose in water) was administered in a second infusion line, followed by a maintenance infusion of placebo for an additional 60 minutes. Duration 90 minutes. Concurrent medication/care: Patients were not permitted to receive class I or III antiarrhythmic drugs from 24h pre-dose to 24h after the start of infusion and IV/oral amiodarone with 30 or 90 days pre-dose, respectively. (n=116) Intervention 2: Amiodarone. Patients randomised to amiodarone received a 60 minute infusion of 5mg/kg amiodarone in one infusion line, followed by a maintenance infusion of 50mg amiodarone over an additional 60 minutes (equivalent to approximately 15mg/kg over 24h). To maintain blinding, these patients received a 10 minute infusion of placebo (normal saline) in a second infusion line, followed by a 15 minute observation period and a second 10 minute infusion of placebo if still in AF. Duration 90 minutes. Concurrent medication/care: Patients were not permitted to receive class I or III antiarrhythmic drugs from 24h pre-dose to 24h after the start of infusion and IV/oral amiodarone with 30 or 90 days pre-dose, respectively.
Funding	Study funded by industry (Cardiome Pharma Corp)
RESULTS (NUMBERS ANALYSED): VERNAKALENT versus AMIODARONE	

Study	Camm 2011{CAMM2011}
Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Conversion from AF to sinus rhythm at 90 minutes; Group 1: 60/116, Group 2: 6/116	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 114: Capucci 1992[168]

Study	Capucci 1992{CAPUCCI1992}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=62)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Recent-onset AF (defined as an arrhythmia of ≤7 day's duration. The main criteria to define the time of onset of the arrhythmia included either ECG documentation during hospitalisation of an abrupt, well-defined onset of palpitations, with subsequent ECG evidence of AF on admission to the hospital.
Exclusion criteria	Age >75 years; NYHA functional class >2 or symptoms of heart failure on physical examination; mean ventricular rate (calculated over 15 RR cycles) during AF of <70 bpm; previous MI or angina pectoris; valvular heart disease or cardiomyopathy; ECG evidence of ventricular pre-excitation or compete bundle branch block; previous ECG evidence of second to third degree AV or bifscicular block; known sick sinus syndrome; hypokalaemia; renal or hepatic insufficiency; severe hypoxia or metabolic disturbances or known thyroid dysfunctions. Patients were also excluded if they were currently receiving digitalis or antiarrhythmic agents, or had taken of these drugs ≤8 hours before entry to

Study	Capucci 1992{CAPUCCI1992}
	the study.
Age, gender and ethnicity	Age - Mean (SD): Flecainide: 58 (12); Amiodarone: 59 (10); Placebo: 57 (11). Gender (M:F): M/F Flecainide: 14/8; Amiodarone: 10/9; Placebo: 11/10. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Amiodarone. IV amiodarone (5mg/kg in 20ml of saline solution infused during 5 minutes, followed by 1.8g in 500ml of saline solution administered IV for 24 hours.. Duration 24 hours. Concurrent medication/care: none (n=22) Intervention 2: Flecainide. Oral flecainide (3 tablet of 100mg as a single oral dose), plus 500ml of saline solution administered IV for 24 hours.. Duration 24 hours. Concurrent medication/care: none (n=21) Intervention 3: Placebo. 3 tablets as a single oral dose, plus 500ml of saline solution administered IV for 24 hours. Duration 24 hours. Concurrent medication/care: none
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion to sinus rhythm at 8 hours; Group 1: 7/19, Group 2: 10/21

RESULTS (NUMBERS ANALYSED): FLECAINIDE versus AMIODARONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion to sinus rhythm at 8 hours; Group 1: 20/20, Group 2: 7/19

RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion to sinus rhythm at 8 hours; Group 1: 20/22, Group 2: 10/21

Study	Capucci 1992{CAPUCCI1992}
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 115: Capucci 1994[167]

Study	Capucci 1994{CAPUCCI1994A}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=181)
Countries and setting	Conducted in Italy; Setting: unclear
Line of therapy	1st line
Duration of study	Intervention + follow up: 8 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Recent-onset AF was defined as an arrhythmia of ≤7 days duration. The time of onset of the arrhythmia was documented either electrocardiographically during hospitalisation or by an abrupt, well-defined historical onset of palpitations with subsequent ECG evidence of AF.
Exclusion criteria	age >75 years, NYHA functional class >II, signs of heart failure, mean VR during AF of <70bpm, recent (<6 months) MMI, unstable angina pectoris, ECG evidence (present or past) or ventricular pre-excitation or of complete bundle branch block, previous ECG evidence of 2 to 3 degree AV block or of bifascicular block, sick sinus syndrome, hypokalaemia, renal or hepatic insufficiency and severe hypoxia or severe metabolic disturbances or known thyroid dysfunction. Patients were also excluded if they were chronically taking digitalis or antiarrhythmic agents or had taken 1 or these drugs in the 8 hours preceding entry into the study.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Other: Mean. flecainide group: 60; propafenone group: 59; placebo group: 58. Gender (M:F): women (%):

Study	Capucci 1994{CAPUCCI1994A}
	flecainide group: 50; propafenone group: 48; placebo group: 48. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: Propafenone. 2 tablets, 300mg as a single oral dose. Duration single dose. Concurrent medication/care: NR Comments: saline solution was intravenously administered to all patients throughout the study period. (n=58) Intervention 2: Flecainide. 3 tablets, 100mg as a single oral dose. Duration single dose. Concurrent medication/care: NR Comments: saline solution was intravenously administered to all patients throughout the study period. (n=62) Intervention 3: Placebo. 3 tablets as a single oral dose. Duration single dose. Concurrent medication/care: NR Comments: saline solution was intravenously administered to all patients throughout the study period.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion rate at 8 hours; Group 1: 44/61, Group 2: 24/62

Protocol outcome 2: Time to restoration for acute AF at Time reported
- Actual outcome for Unstable with acute AF: Mean conversion time at 8 hours; Group 1: mean 165 (SD 119); n=61, Group 2: mean 215 (SD 133); n=62

RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PROPAFENONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Conversion rate at 8 hours; Group 1: 45/58, Group 2: 44/61

Protocol outcome 2: Time to restoration for acute AF at Time reported
- Actual outcome for Unstable with acute AF: Mean conversion time at 8 hours; Group 1: mean 158 (SD 109); n=58, Group 2: mean 165 (SD 119); n=61

RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PLACEBO

Study	Capucci 1994{CAPUCCI1994A}
Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Conversion rate at 8 hours; Group 1: 45/58, Group 2: 24/62 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: Mean conversion time at 8 hours; Group 1: mean 158 (SD 109); n=58, Group 2: mean 215 (SD 133); n=62	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 116: Capucci 1999[170]

Study	Capucci 1999{CAPUCCI1999}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=176)
Countries and setting	Conducted in Unknown multicentre; Setting: 13 cardiac centres
Line of therapy	1st line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	AF <48 hour duration; age >18 and <75 years; mean ventricular rate >70 bpm; NYHA functional class <II
Exclusion criteria	overt heart failure; recent (<3 months) MI; unstable angina pectoris; ECG evidence (present or past) of ventricular pre-excitation, complete bundle branch block or bifascicular block; sick sinus syndrome; hypokalaemia; renal or hepatic insufficiency; severe hypoxia; severe metabolic disturbances; thyroid dysfunction; taking digitalis or any antiarrhythmic therapy during the last 24 hours.

Study	Capucci 1999{CAPUCCI1999}
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): 58 (11). Gender (M:F): NR. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=66) Intervention 1: Propafenone. >60mg: 600mg orally at the study entry followed by 300mg orally after 6 hours if AF persisted; <60kg the starting dose was 450mg. Duration maximum of 12 hours. Concurrent medication/care: NR (n=70) Intervention 2: Combinations of drugs - Propafenone and other. Propafenone: >60mg: 600mg orally at the study entry followed by 300mg orally after 6 hours if AF persisted; <60kg the starting dose was 450mg.Digoxin: >60mg, digitalis 0.5mg IV at study entry and 0.25mg IV after4 hours, 0.125mg IV after 8 hours and 0.125mg IV after 12 hours (total maximum dose 1mg/12 hours); <60kg, digitalis 0.5mg IV at entry, 0.125mg IV after 4 hours, 0.065mg IV after 8 hours and 0.065mg IV after 12 hours (total maximum dose 0.755mg/12 hours).. Duration maximum of 12 hours. Concurrent medication/care: NR Comments: propafenone +digoxin (n=40) Intervention 3: Placebo. Saline infusion and placebo tablets were administered following the same protocols for the other groups. Duration maximum of 12 hours. Concurrent medication/care: NR
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PROPAFENONE AND OTHER

Protocol outcome 1: Time to restoration for acute AF at Time reported
- Actual outcome for Unstable with acute AF: Mean conversion time at 12 hours; Group 1: mean 4 (SD 4.1); n=66

RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO

Protocol outcome 1: Time to restoration for acute AF at Time reported
- Actual outcome for Unstable with acute AF: Mean conversion time at 12 hours; Group 1: mean 4 hours (SD 4.1); n=66

RESULTS (NUMBERS ANALYSED): PROPAFENONE AND OTHER versus PLACEBO

Protocol outcome 1: Time to restoration for acute AF at Time reported

Study	Capucci 1999{CAPUCCI1999}
- Actual outcome for Unstable with acute AF: Mean conversion time at 12 hours; Group 1: mean 5 hours (SD 8.6); n=66	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Restoration of sinus rhythm at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 117: Chiladakis 2001[202]

Study	Chiladakis 2001{CHILADAKIS2001}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=46)
Countries and setting	Conducted in Greece; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention time: 6 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Prolonged and continuous paroxysms of AF of <12 h duration with a mean ventricular response >100bpm
Exclusion criteria	Acute MI; severe circulatory failure requiring inotropic agents; hypotension with a SBP of <90mmHg; electrocardiographic evidence of high degree AV block or ventricular pre-excitation; a history of sick sinus syndrome or known thyroid disease; pacemaker dependence; severe metabolic disturbances and women in pregnancy. Patients already receiving beta-blockers, calcium channel blockers, digitalis and antiarrhythmic drugs were also excluded.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Magnesium group: 61 (6); Diltiazem group: 64 (4). Gender (M:F): Magnesium group: 12M, 11F;

Study	Chiladakis 2001{CHILADAKIS2001}
	Diltiazem group: 13M, 10F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Magnesium. Magnesium sulphate was administered as a bolus of 2.5g over 15 minutes, followed by continuous infusion of 7.5g over 6 hours.. Duration 6 hours. Concurrent medication/care: Supplemental potassium was given in patients with hypokalaemia before entry into the study. Conjunctive therapy included heparin with a bolus of 5000IU, followed by an infusion of 1000IU/h further adjusted as required to keep the activated partial thromboplastin time at twice the upper normal limit. (n=23) Intervention 2: Calcium channel blockers. Diltiazem was given as a bolus of 25mg over 15 minutes, followed by continuous infusion of 12.5mg/h over 6 hours. Duration 6 hours. Concurrent medication/care: Supplemental potassium was given in patients with hypokalaemia before entry into the study. Conjunctive therapy included heparin with a bolus of 5000IU, followed by an infusion of 1000IU/h further adjusted as required to keep the activated partial thromboplastin time at twice the upper normal limit.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): MAGNESIUM versus CALCIUM CHANNEL BLOCKERS Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Restoration of sinus rhythm at 6 hours; Group 1: 13/23, Group 2: 5/23	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 118: Chu 2009[210]

Study	Chu 2009{CHU2009}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=48)
Countries and setting	Conducted in Australia; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18 years and older presenting with paroxysmal AF of less than 48 hours duration, plus a sustained ventricular rate of ≥100bpm.
Exclusion criteria	AF with a wide-complex ventricular response; acute pulmonary oedema; hypotension (SBP <90mmHg),electrocardiographic evidence of acute MI.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): Magnesium group: 46.9 (14.9); Placebo group: 58.4 (17.7). Gender (M:F): Magnesium group: M19, F5; Placebo group: M17, F7. Ethnicity:
Further population details	None
Indirectness of population	None
Interventions	(n=24) Intervention 1: Magnesium. 10 mmol magnesium sulphate (2.5g). The trial drug was loaded in 100ml of normal saline and infused over 15 minutes.. Duration 15 minutes. Concurrent medication/care: Other antiarrhythmic drugs were not prescribed, as directed by the study protocol within the 2 hours. However, other antiarrhythmic drugs were permissible within the 2 hours after commencing the trial drug if deemed necessary by the treating physician. (n=24) Intervention 2: Placebo. Normal saline 100ml infusion over 15 minutes. Duration 15 minutes. Concurrent medication/care: Other antiarrhythmic drugs were not prescribed, as directed by the study protocol within the 2 hours. However, other antiarrhythmic drugs were permissible within the 2 hours after commencing the trial drug if deemed necessary by the treating physician.
Funding	Funding not stated

Study	Chu 2009{CHU2009}
RESULTS (NUMBERS ANALYSED): MAGNESIUM versus PLACEBO Protocol outcome 1: health-related quality of life at Longest endpoint - Actual outcome for Unstable with acute AF: Conversion to sinus rhythm at 2 hours; Group 1: 2/24, Group 2: 6/24	
Protocol outcomes not reported by the study	Mortality - long-term at Longest endpoint; Restoration of sinus rhythm at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; Mortality - 30 days at 30 days

Table 119: Cybulski 2003[249]

Study	Cybulski 2003{CYBULSKI2003}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=160)
Countries and setting	Conducted in Poland; Setting: Hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention): 20 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	New-onset AF lasting <24 hours
Exclusion criteria	Age <18 years; premenopausal women not using birth control; NYHA class II or more before AF, anginal chest pain, hypotension (<90mmHg), bradyarrhythmia (<45bpm), dysthyroidism, second or third degree AV block without pacemaker, 3mmol/L<kalaemia<5.5mmol/L, stroke or MI in the last 3 months, severe obstructive bronchopathy, known hepatic or renal failure, amiodarone therapy or prolonged antiarrhythmic therapy with another agent,

Study	Cybulski 2003{CYBULSKI2003}
	haemodynamically significant valvular heart disease, contraindications to immediate rhythm reversion, WPW syndrome, mean HR during AF of <80bpm, insulin dependent diabetes mellitus, history of pro-arrhythmia following administration of drugs prolonging QT interval.
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): 61.5 (12.5). Gender (M:F): 89M, 71F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=106) Intervention 1: Amiodarone. Amiodarone hydrochloride (Cordarone, Sanofi Winthrop, Gentilly-Cedex, France) was given at an initial dose of 5mg/kg body weight in 50ml of saline (infusion rate 100ml/h) followed by a continuous infusion of amiodarone at a dose of 10mg/kg diluted in 1000ml of 10% glucose with 20IU of human rapid-action insulin with 80 mEq of KCl and 8m of magnesium sulphate (GIKM) at a rate of 51ml/h.. Duration up to 20 hours. Concurrent medication/care: NR (n=54) Intervention 2: Placebo. 1000ml GIKM alone. Duration up to 20 hours. Concurrent medication/care: NR
Funding	Academic or government funding (State Committee for Scientific Research)
RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 20 hours; Group 1: 88/106, Group 2: 24/54 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: Time to restoration at 20 hours; Group 1: mean 8.2 (SD 6.2); n=106, Group 2: mean 7.2 (SD 4.9); n=54	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 120: Donovan 1991[292]

Study	Donovan 1991{DONOVAN1991}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=102)
Countries and setting	Conducted in Australia; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Recent-onset AF (present for ≥30 minutes and ≤72 hours with a ventricular response ≥120bpm)
Exclusion criteria	Plasma potassium >5.5 or<3.5mmol/l, severe heart/ circulatory failure, pacemaker dependence, sick sinus syndrome, high degree Av block, recent antiarrhythmic therapy (including oral amiodarone within the previous 3 months). Patients receiving long term beta blockers or calcium channel blockers were not excluded. Digitalis intoxication, flecainide hypersensitivity, pregnancy and lactation, age <18 years, unable/unwilling to give informed consent.
Age, gender and ethnicity	Age - Mean (range): 60 (21-90). Gender (M:F): 72M, 30F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Flecainide. 2mg/kg IV, maximum dose 150mg. Duration 30 minutes. Concurrent medication/care: Digoxin IV (500µg) for all patients who had not previous taken digoxin (n=51) Intervention 2: Placebo. no further details. Duration 30 minutes. Concurrent medication/care: Digoxin IV (500µg) for all patients who had not previous taken digoxin
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PLACEBO	

Study	Donovan 1991{DONOVAN1991}
Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Reversion to sinus rhythm at 6 hours; Group 1: 34/51, Group 2: 18/18	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 121: Donovan 1992[293]

Study	Donovan 1992{DONOVAN1992}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=104)
Countries and setting	Conducted in Australia; Setting: intensive care unit.
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	recent-onset AF: present for ≥ 30 minutes and ≤ 72 hours with a ventricular response ≤120 beats/min.
Exclusion criteria	severe heart or circulatory failure; sick sinus syndrome; high degree AV block; bifacicular block or pacemaker dependence; recent antiarrhythmic drugs (within 5 drug elimination half-lives; incorrect hyper or hypokalaemia; digoxin intoxication; flecainide hypersensitivity; pregnancy or lactation; age <18 years; unwilling to give informed consent.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): 60 (21-90). Gender (M:F): Define. Ethnicity:
Further population details	None

Study	Donovan 1992{DONOVAN1992}
Extra comments	recent-onset AF: present for ≥ 30 minutes and ≤ 72 hours with a ventricular response ≤120 beats/min.
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Flecainide. 2mg/kg IV, maximum dose 150mg. Duration 30 minutes. Concurrent medication/care: Digoxin 500µg over 30 minutes IV to all patients who had not previously received digoxin. (n=51) Intervention 2: Placebo. no details. Duration 30 minutes. Concurrent medication/care: Digoxin 500µg over 30 minutes IV to all patients who had not previously received digoxin.
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 1 hour; Group 1: 34/51, Group 2: 18/51	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 122: Donovan 1995[294]

Study	Donovan 1995{DONOVAN1995}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=98)

Study	Donovan 1995{DONOVAN1995}
Countries and setting	Conducted in Australia
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Recent onset AF (≥30 minutes and ≤72 hours) with a ventricular response of ≥100bpm.
Exclusion criteria	significant left ventricular dysfunction (ejection fraction <0.35),severe circulatory failure requiring inotropic drugs, unstable angina with on-going pain, pacemaker dependence, sick sinus syndrome, high degree AV block, recent antiarrhythmic therapy (including amiodarone within the previous 3 months, overt thyroid disease, digitalis intoxication, flecainide or amiodarone sensitivity, pregnancy and lactation, age <18 years hypotension (<90mmHg), bradyarrhythmia (<45bpm), dysthyroidism, second or third degree AV block without pacemaker, 3.5mmol/L<kalaemia<5.5mmol/L, stroke or MI in the last 3 months, severe obstructive bronchopathy, known hepatic or renal failure
Recruitment/selection of patients	All patients referred to investigators during the trial who met the entry criteria were included.
Age, gender and ethnicity	Age - Mean (SD): Flecainide group: 59 (16); Amiodarone group: 56 (13); Placebo group: 59 (12). Gender (M:F): NR. Ethnicity:
Further population details	None
Extra comments	Patients taking long-term beta blockers or calcium channel blockers were included if these drugs were not being used as antiarrhythmic agents.
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Flecainide. 2mg/kg IV, maximum 150mg.. Duration 2 hours. Concurrent medication/care: NR (n=32) Intervention 2: Amiodarone. 7mg/kg IV. Duration 2 hours. Concurrent medication/care: NR (n=32) Intervention 3: Placebo. no further details. Duration 2 hours. Concurrent medication/care: NR
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PLACEBO	

Study	Donovan 1995{DONOVAN1995}
Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Reversion to stable sinus rhythm at 2 hours; Group 1: 20/34, Group 2: 7/32 RESULTS (NUMBERS ANALYSED: AMIODARONE versus FLECAINIDE Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Reversion to stable sinus rhythm at 2 hours; Group 1: 11/11, Group 2: 20/34 RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Reversion to stable sinus rhythm at 2 hours; Group 1: 11/32, Group 2: 7/32	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 123: Falk 1987[324]

Study	Falk 1987{FALK1987}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=36)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 18 hours
Method of assessment of guideline condition	Not reported
Stratum	Unstable with acute AF

Study	Falk 1987{FALK1987}
Subgroup analysis within study	Not applicable
Inclusion criteria	NR
Exclusion criteria	NR
Age, gender and ethnicity	NR
Further population details	None
Indirectness of population	None
Interventions	(n=18) Intervention 1: Digoxin. Digoxin solution in capsules given in doses of 0.6, 0.4, 0.2 and 0.2mg at 0, 4, 8 and 14 hours or until conversion to sinus rhythm, whichever occurred first.. Duration 18 hours. Concurrent medication/care: NR (n=18) Intervention 2: Placebo. Placebo solution in capsules given in doses of 0.6, 0.4, 0.2 and 0.2mg at 0, 4, 8 and 14 hours or until conversion to sinus rhythm, whichever occurred first.. Duration 18 hours. Concurrent medication/care: NR
Funding	Study funded by industry (Burroughs Wellcome Company, North Carolina)
RESULTS (NUMBERS ANALYSED): DIGOXIN versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 18 hours; Group 1: 9/18, Group 2: 8/18	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 124: Fresco 1996[349]

Study	Fresco 1996{FRESCO1996A}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=75)
Countries and setting	Conducted in Italy; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Paroxysmal AF of recent onset (<72 hours)
Exclusion criteria	Age >70 years; clinical heart failure; recent (<6 months) MI; WPW syndrome; AV block HR>70bpm; current treatment with antiarrhythmic agents or digitalis; hyperthyroidism.
Age, gender and ethnicity	Age - Range: 18-70. Gender (M:F): Propafenone group: 53.8%M; Placebo group: 82.4% M. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Propafenone. 2mg/kg IV in 15 minutes followed by 1mg/kg in 2 hours.. Duration 3 hours. Concurrent medication/care: NR (n=34) Intervention 2: Placebo. 2mg/kg IV in 15 minutes followed by 1mg/kg in 2 hours.. Duration 3 hours. Concurrent medication/care: NR
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Restoration of rhythm at 3 hours; Group 1: 24/41, Group 2: 10/34

Study	Fresco 1996{FRESCO1996A}
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 125: Galve 1996[368]

Study	Galve 1996{GALVE1996}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in Spain; Setting: Emergency department/wards/ coronary unit.
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Criteria defining the onset of the arrhythmia included a documented onset in patients admitted to the hospital or, or those cases seen in the emergency department, an abrupt, well defined onset of symptoms, such as palpitations, chest discomfort or dyspnoea, in patients with no previous history of recurrent arrhythmias.
Exclusion criteria	Any previous antiarrhythmic treatment (digoxin included); baseline SBP <100mmHg; baseline mean VR <120bpm; moderate or severe clinical or radiologic signs of CHF (mild cases were accepted); clinical or laboratory data indicative of severe impairment of LVF; obstructive hypertropic cardiomyopathy; renal insufficiency; goitre or thyroid dysfunction; high degree AV block; sick sinus syndrome; pulmonary fibrosis; hepatic dysfunction.
Age, gender and ethnicity	Age - Mean (SD): 61 (12). Gender (M:F): 55M; 45F. Ethnicity:
Further population details	None

Study	Galve 1996{GALVE1996}
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Amiodarone. 5mg/kg body weight over 30 minutes, diluted in 100ml of saline, followed by 1200mg diluted in 500ml of saline over 24 hours. Amiodarone was given by means of an infusion pump through either a peripheral vein or a central line. Patients were continuously monitored and received S/C calcium heparin at a dosage of 2500IU/10kg over 12 h. The IV infusion was stopped as soon as conversion to sinus rhythm was observed. Afterwards, patients were treated with oral digoxin alone and followed up for a 15 day period. Duration 24 hours. Concurrent medication/care: IV digoxin , 0.5mg initially, followed by 0.25mg at 2h and 0.25mg every 6h thereafter, to complete 24h while the ventricular rate was >100bpm. (n=50) Intervention 2: Placebo. 5mg/kg body weight over 30 minutes, diluted in 100ml of saline, followed by 1200mg diluted in 500ml of saline over 24 hours. Placebo was given by means of an infusion pump through either a peripheral vein or a central line. Patients were continuously monitored and received S/C calcium heparin at a dosage of 2500IU/10kg over 12 h. The IV infusion was stopped as soon as conversion to sinus rhythm was observed. Afterwards, patients were treated with oral digoxin alone and followed up for a 15 day period.. Duration 24 hours. Concurrent medication/care: IV digoxin , 0.5mg initially, followed by 0.25mg at 2h and 0.25mg every 6h thereafter, to complete 24h while the ventricular rate was >100bpm.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 24 hours; Group 1: 34/50, Group 2: 30/50	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 126: Ganau 1998[369]

Study	Ganau 1998{GANAU1998}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=156 (88M/68F))
Countries and setting	Conducted in Italy; Setting: Emergency department
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	VR more than 110bpm, AF symptoms (mainly palpitations) for less than 72 hours, age 18=8- years, SBP greater than 110mmHg, availability on admittance to the ED of ECG documentation of AF.
Exclusion criteria	refusal to give informed consent, clinical evidence of acute or chronic congestive heart failure, history of bronchial asthma or other severe respiratory disease, history of severe hepatic or renal disease, clinical hyperthyroidism, MI in the previous 3 months, bifascicular heart block or QRS width greater than 0.10s, known cardiac valve dysfunction, presence of a prosthetic cardiac valve, known sinoatrial node disease, digitalis therapy, anti-dysrhythmic therapy (including non-di-hydropiridinic calcium channel blockers, eta-blockers and digitalis) administered in the last 12h, chronic amiodarone therapy.
Recruitment/selection of patients	Consecutive patients.
Age, gender and ethnicity	Age - Range: 18-80 years. Gender (M:F): 88M/ 68F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=81) Intervention 1: Propafenone. bolus 2mg/kg IV. Duration 10 min. Concurrent medication/care: NR (n=75) Intervention 2: Placebo. 2mg/kg saline solution. Duration 10 min. Concurrent medication/care: NR
Funding	Funding not stated

Study	Ganau 1998{GANAU1998}
RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Conversion to sinus rhythm at 2 hours; Group 1: 57/81, Group 2: 13/75	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 127: Hassan 2007[426]

Study	Hassan 2007{HASSAN2007}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in USA; Setting: Emergency department
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Acute/ paroxysmal AF and a rapid ventricular rate (mean 100bpm or more over 10 minutes
Exclusion criteria	History of allergy or adverse reactions to diltiazem or esmolol, cardiogenic shock or heart failure requiring inotropic agents or intubation, pregnancy, lactation, SBP <80mmHg, respiratory failure requiring intubation, ST elevation MI, severe COPD or asthma, chronic/ persistent AF, and the inability or unwillingness to perform informed consent.
Age, gender and ethnicity	Age - Mean (SD): Diltiazem group: 62 (15); esmolol group: 65 (15). Gender (M:F): Diltiazem group: 11M, 13F; Esmolol group: 13M, 13F. Ethnicity:

Study	Hassan 2007{HASSAN2007}
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Calcium channel blockers. Diltaizem was administered as a bolus injection of 0.25mg/kg over 2 minutes. If the ventricular rate was still more than 100bpm, a second bolus of 0.35mg/kg was administered over 2 minutes. 15 minutes later, a maintenance infusion was started as follows: 5mg/h if the ventricular rate was < 90bpm, 10mg/h if the ventricular rate was 90 to 120 bpm, and 15mg/h if the ventricular rate was >120bpm.. Duration 2 minutes. Concurrent medication/care: Patients with paroxysmal AF who were being treated with oral antiarrhythmic drugs were included in the study, but no patient received a rhythm-control agent during the 24 hour study period. (n=26) Intervention 2: Beta-blockers - Esmolol. Esmolol was administered as a bolus of 0.5mg/kg followed by another bolus of 0.5mg/kg if the ventricular rate was still more than 100bpm. 15 minutes later, a maintenance infusion was started as follows: 0.1mg/kg/min if the ventricular rate was <90 bpm, 0.2mg/kg/min if the ventricular rate was 90 to 120 bpm andd 0.3mg/kg/min if the ventricular rate was >120bpm. As with diltiazem, the infusion rate was titrated every 15 minutes to maintain a ventricular rate of 80 to 100bpm.. Duration 2 minutes. Concurrent medication/care: Patients with paroxysmal AF who were being treated with oral antiarrhythmic drugs were included in the study, but no patient received a rhythm-control agent during the 24 hour study period.
Funding	Academic or government funding (Graduate Medical Education Committee of St John Hospital and Medical Center and University of Michigan Health System)
RESULTS (NUMBERS ANALYSED): CALCIUM CHANNEL BLOCKERS versus ESMOLOL Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome: Conversion to sinus rhythm at 24 hours; Group 1: 10/24, Group 2: 10/26	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 128: Hornestam 1997[468]

Study	Hornestam 1997{HORNESTAM1997}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=239)
Countries and setting	Conducted in Sweden; Setting: 13 Swedish hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up: 16 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	AF of at most 7 days duration; age >18 years
Exclusion criteria	On-going treatment with digitalis or antiarrhythmic drugs other than beta-blockers (including sotalol) or calcium channel blockers; sick sinus syndrome or a history of second or third degree AV block without an artificial pacemaker; WPW syndrome; HR<60 or >170bpm; on-going MI or MI at 4 weeks or less prior to entry to the study; haemodynamic instability; on-going angina pectoris.
Age, gender and ethnicity	Age - Mean (SD): 66.2 (13). Gender (M:F): Placebo group: 55F, 67M; Digoxin group: 55F, 62M. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=117) Intervention 1: Digoxin. The mean dose of digoxin administered at baseline and at 2 and 6h were 0.455mg (n=117), 0.308mg (n=93) and 0.318mg (n=65) respectively. The mean total dose of digoxin was 0.88±0.35mg (range 0-1.5). Four patients were given a fourth dose of the study drug (mean 0.28mg). The mean serum concentration of digoxin at 16h was 1.56±1.02µmol per litre. Duration 16 hours. Concurrent medication/care: NR (n=122) Intervention 2: Placebo. The dose of placebo was 0.96±0.37mg. Four patients were given a fourth dose of the study drug (mean 0.28mg). Duration 16 hours. Concurrent medication/care: NR
Funding	Academic or government funding (Swedish Society of Cardiology; Draco Lakemedel AB)

RESULTS (NUMBERS ANALYSED): DIGOXIN versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint

Study	Hornestam 1997{HORNESTAM1997}
- Actual outcome for Unstable with acute AF: Conversion to sinus rhythm at 16 hours; Group 1: 60/117, Group 2: 56/122 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: Time to restoration at 16 hours; Group 1: mean 4.7 (SD 4.2); n=117, Group 2: mean 5.8 (SD 4.9); n=122	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 129: Joseph 2000[496]

Study	Joseph 2000{JOSEPH2000}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Australia; Setting: Emergency department
Line of therapy	1st line
Duration of study	Intervention time: 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	AF onset within 24h; consent obtained; serum potassium >3.5mmol/L and <5.5mmol/L; serum creatinine <0.2mmol/L
Exclusion criteria	AF present within 7d and >24h; no consent; serum potassium <3.5mmol/L and >5.5mmol/L; serum creatinine >0.2mmmol/L; current beta-blocker treatment; digoxin or sotalol treatment in the last week; amiodarone treatment within 3 months; hypotension (MAP<70mmHg); previous adverse reaction to any of trial medications; known thyroid disease; asthma/bronchospasm with beta-blocker; wide-complex tachycardia; contraindication to anticoagulation; age<18 years; left ventricular dysfunction; pregnancy
Age, gender and ethnicity	Age - Other: Mean±SEM. digoxin group 64.9±2.0; amiodarone group 61.3±2.6; sotalol group 62.9±2.4.

Study	Joseph 2000{JOSEPH2000}
Further population details	None
Extra comments	New-onset AF (less than 24 hours duration) or atrial flutter with ventricular rate> 100bpm.
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Amiodarone. 5mg/kg IV over 30 minutes, then 400mg orally every 8 hours for 6 doses. Duration 48 hours. Concurrent medication/care: NR (n=36) Intervention 2: Digoxin. 500µg IV over 30 minutes followed by 250µg orally every 6 hours for 4 doses and then 250µg daily if any renal impairment as defined by serum creatinine concentration>120µmol/L.. Duration 48 hours. Concurrent medication/care: NR (n=40) Intervention 3: Beta blockers - Sotalol. 1.5mg/kg IV over 30 minutes, then 80mg orally every 8 hours for 6 doses.. Duration 48 hours. Concurrent medication/care: NR
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): AMIODARONE versus DIGOXIN

Protocol outcome 1: Time to restoration for acute AF at Time reported
- Actual outcome for Unstable with acute AF: time to reversion (h; mean±SEM) at 48 hours; Group 1: mean 18.1 hours (SD 2.9); n=39, Group 2: mean 26.9 hours (SD 3.4); n=36

Protocol outcome 2: Stroke or thromboembolic events at Longest endpoint
- Actual outcome for Unstable with acute AF: Stroke at 48 hours; Group 1: 0/0, Group 2: 1/0

RESULTS (NUMBERS ANALYSED): AMIODARONE versus SOTALOL

Protocol outcome 1: Time to restoration for acute AF at Time reported
- Actual outcome for Unstable with acute AF: time to reversion (h; mean±SEM) at 48 hours; Group 1: mean 18.1 hours (SD 2.9); n=39, Group 2: mean 13 hours (SD 2.5); n=40

Protocol outcome 2: Stroke or thromboembolic events at Longest endpoint
- Actual outcome for Unstable with acute AF: Stroke at 48 hours; Group 1: 0/39, Group 2: 0/40

RESULTS (NUMBERS ANALYSED): SOTALOL versus DIGOXIN

Study	Joseph 2000{JOSEPH2000}
Protocol outcome 1: Stroke or thromboembolic events at Longest endpoint - Actual outcome for Unstable with acute AF: time to reversion (h; mean±SEM) at 48 hours; Group 1: mean 13 hours (SD 2.5); n=40, Group 2: mean 26.9 hours (SD 3.4); n=36 - Actual outcome for Unstable with acute AF: Stroke at 48 hours; Group 1: 0/40, Group 2: 1/36	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Restoration of sinus rhythm at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 130: Kociadakis 1998[534]

Study	Kochiadakis 1998{KOCHIADAKIS1998}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=143)
Countries and setting	Conducted in Greece; Setting: Hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	AF lasting <48 hours
Exclusion criteria	Recent MI; heart surgery within the last 6 months; unstable angina; acute myocarditis; acute pericarditis; baseline SBP <100mmHg; hypertrophic obstructive cardiomyopathy; severe uncontrolled heart failure (EF <30%); cardiogenic shock; significant COPD; PE; pneumonia; liver/kidney failure; thyroid disease; electrolyte disturbances; digoxin intoxication; pregnancy/ lactation; age <18 years; sick sinus syndrome; history of second or third degree AV block; those who had taken an antiarrhythmic drug other than digoxin within less than 5 drug elimination half-lives prior to

Study	Kochiadakis 1998{KOCHIADAKIS1998}
	the study.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 63 (12). Gender (M:F): 77M; 66 F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Propafenone. 2mg/kg IV over 15 minutes followed by 10mg/kg over 24 hours. Duration 24hours. Concurrent medication/care: IV digoxin (0.5mg initial dose, followed by 0.25mg after 2 hours and 0.25mg 9.6 hours for 24 hours, or until the ventricular response was <100bpm) was administered to all patients who had not previously received it. (n=48) Intervention 2: Amiodarone. 300mg IV over 1 hour, followed by 20mg/kg over the next 24 hours. They also received simultaneously 1800mg/day orally in 3 divided doses. Duration 24 hours. Concurrent medication/care: IV digoxin (0.5mg initial dose, followed by 0.25mg after 2 hours and 0.25mg 9.6 hours for 24 hours, or until the ventricular response was <100bpm) was administered to all patients who had not previously received it. (n=49) Intervention 3: Placebo. Identical amount of saline. Duration 24 hours. Concurrent medication/care: IV digoxin (0.5mg initial dose, followed by 0.25mg after 2 hours and 0.25mg 9.6 hours for 24 hours, or until the ventricular response was <100bpm) was administered to all patients who had not previously received it.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): PROPAFENONE versus AMIODARONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Restoration of rhythm at 24 hours; Group 1: 36/44, Group 2: 40/47

Protocol outcome 2: Time to restoration for acute AF at Time reported
- Actual outcome for Unstable with acute AF: Mean time to conversion at 24 hours; Group 1: mean 2 (SD 3); n=44, Group 2: mean 7 (SD 5); n=47

RESULTS (NUMBERS ANALYSED): PROPAFENONE versus PLACEBO

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint

Study	Kochiadakis 1998{KOCHIADAKIS1998}
- Actual outcome for Unstable with acute AF: Restoration of rhythm at 24 hours; Group 1: 36/44, Group 2: 27/49 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: Mean time to conversion at 24 hours; Group 1: mean 2 (SD 3); n=44, Group 2: mean 13 (SD 8); n=49 RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 24 hours; Group 1: 40/47, Group 2: 27/49 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: Mean time to conversion at 24 hours; Group 1: mean 7 (SD 5); n=47, Group 2: mean 13 (SD 9); n=49	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 131: Martinez-Marcos 2000[651]

Study	Martinez-marcos 2000{MARTINEZMARCOS2000}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=150)
Countries and setting	Conducted in Spain; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable

Study	Martinez-marcos 2000{MARTINEZMARCOS2000}
Inclusion criteria	Acute AF (≥48 hours duration of symptoms). Criteria defining the onset of the arrhythmia included an abrupt, well-defined onset of symptoms, such as palpitations, chest discomfort or dyspnoea.
Exclusion criteria	Uncertain or >48 hours duration of symptoms; known LVEF <35%; usual NYHA functional class >II; current CXR with cardiothoracic ratio >0.6 if clinical or radiologic signs of CHF; baseline SBP <100mmHg; baseline mean ventricular rate <110bpm; unstable angina or MI within the preceding month; known sick sinus syndrome; high degree AV block; overt thyroid disease; antiarrhythmic therapy with the trail drugs within the previous 3 months; pulmonary fibrosis; hepatic dysfunction; renal insufficiency; pregnancy or lactation; age <18 years.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 60 (!3). Gender (M:F): 70M; 80F. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Flecainide. Bolus dose of 2mg/kg in 20 minutes. A second bolus dose of 1mg/kg in 20 minutes was administered if conversion to sinus rhythm was not achieved after 8 hours.. Duration one/two bolus doses of drug. Concurrent medication/care: NR (n=50) Intervention 2: Propafenone. Bolus dose of 2mg/kg in 20 minutes. A second bolus dose of 1mg/kg in 20 minutes was administered if conversion to sinus rhythm was not achieved after 8 hours.. Duration one/two bolus doses of drug. Concurrent medication/care: NR (n=50) Intervention 3: Amiodarone. Bolus of 5mg/kg in 20 minutes followed by a continuous infusion of 50mg/hour. Duration 12 hours. Concurrent medication/care: NR
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED): FLECAINIDE versus PROPAFENONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint
- Actual outcome for Unstable with acute AF: Restoration of rhythm at 12 hours; Group 1: 45/50, Group 2: 36/50

RESULTS (NUMBERS ANALYSED): PROPAFENONE versus AMIODARONE

Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint

Study	Martinez-marcos 2000{MARTINEZMARCOS2000}
- Actual outcome for Unstable with acute AF: Restoration of rhythm at 12 hours; Group 1: 36/50, Group 2: 32/50 RESULTS (NUMBERS ANALYSED): AMIODARONE versus FLECAINIDE Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 12 hours; Group 1: 32/50, Group 2: 45/50	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 132: Peuhkurinen 2000[733]

Study	Peuhkurinen 2000{PEUHKURINEN2000}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=72)
Countries and setting	Conducted in Finland; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >18 years; recent onset AF (<48 hours) continuing for >3 hours in the hospital; BR<50 and <150bpm;; haemodynamically stable; normal serum potassium.
Exclusion criteria	Known thyroid disease; history of acute MI, acute pulmonary oedema; known sick sinus syndrome; high degree AV block; anaemia; hypovolaemia; stroke; sepsis; severe renal/ hepatic disease. Women of child bearing potential were also excluded

Study	Peuhkurinen 2000{PEUHKURINEN2000}
Age, gender and ethnicity	Age - Mean (SD): Amiodarone group: 62 (12); Placebo group: 56 (13). Gender (M:F): Amiodarone group: 25M, 6F; Placebo group: 20M, 11F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Amiodarone. 30mg/kg orally. Duration single dose. Concurrent medication/care: All medication affecting cardiac rhythm or conduction (including beta blockers) was discontinued before randomisation, and patients taking sotalol or other class III antiarrhythmic drugs were excluded. (n=31) Intervention 2: Placebo. 30mg/kg orally. Duration single dose. Concurrent medication/care: All medication affecting cardiac rhythm or conduction (including beta blockers) was discontinued before randomisation, and patients taking sotalol or other class III antiarrhythmic drugs were excluded.
Funding	Study funded by industry (Sanofi Winthrop Company, Helsinki, Finland)
RESULTS (NUMBERS ANALYSED): AMIODARONE versus PLACEBO Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 24 hours; Group 1: 27/31, Group 2: 11/31	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Time to restoration for acute AF at Time reported; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

Table 133: Thomas 2004[856]

Study	Thomas 2004{THOMAS2004}
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=140)

Study	Thomas 2004{THOMAS2004}
Countries and setting	Conducted in Australia; Setting: Emergency department
Line of therapy	Mixed line
Duration of study	Intervention time: 12 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Unstable with acute AF
Subgroup analysis within study	Not applicable
Inclusion criteria	Recent onset AF
Exclusion criteria	Patients who had taken amiodarone or sotalol in the preceding month or who had previously had an adverse reaction to a trial drug were excluded. Patients who had previously experienced AF while taking amiodarone or sotalol were also excluded. Other exclusion criteria included: asthma or chronic airway limitation; signs or symptoms of heart failure; known or suspected pulmonary fibrosis; pregnancy; uncorrectable hypotension (<90mmHg); sick sinus syndrome; bradycardia (<50bpm); Qtc>450mg; active hepatitis; postoperative (<1 month); patients previously randomised to the trial.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Amiodarone group: 54.3 (15.9); Sotalol group: 57.7 (15.9); Digoxin group: 55.5 (16.5). Gender (M:F): Amiodarone group: 33% F; Sotalol group: 40% F; Digoxin group: 23% F. Ethnicity:
Further population details	None
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: Amiodarone. Administered at 10mg/kg in 30 minutes IV. Duration 30 minutes. Concurrent medication/care: NR Comments: In patients >75 years old, the dose was halved. (n=45) Intervention 2: Beta blockers - Sotalol. 1.5mg/kg IV. Duration 10 minutes. Concurrent medication/care: NR Comments: In patients >75 years old, the dose was halved. (n=43) Intervention 3: Digoxin. 500µg IV in 20 minutes followed by 250µg every 6 hours when the HR remained >100bpm. Duration 12 hours. Concurrent medication/care: NR
Funding	Academic or government funding (National Heart Foundation of Australia)

Study	Thomas 2004{THOMAS2004}
RESULTS (NUMBERS ANALYSED): AMIODARONE versus SOTALOL Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 12 hours; Group 1: 27/52, Group 2: 20/45 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: Time to reversion at 12 hours; Group 1: mean 4.5 (SD 4.1); n=52, Group 2: mean 4.4 (SD 4.5); n=45 RESULTS (NUMBERS ANALYSED): AMIODARONE versus DIGOXIN Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 12 hours; Group 1: 27/52, Group 2: 21/42 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: Time to reversion at 12 hours; Group 1: mean 4.5 (SD 4.1); n=52, Group 2: mean 4.9 (SD 3.7); n=43 RESULTS (NUMBERS ANALYSED): SOTALOL versus DIGOXIN Protocol outcome 1: Restoration of sinus rhythm at Longest endpoint - Actual outcome for Unstable with acute AF: Restoration of rhythm at 12 hours; Group 1: 20/45, Group 2: 21/42 Protocol outcome 2: Time to restoration for acute AF at Time reported - Actual outcome for Unstable with acute AF: Time to reversion at 12 hours; Group 1: mean 4.4 (SD 4.5); n=45, Group 2: mean 4.9 (SD 3.7); n=43	
Protocol outcomes not reported by the study	Mortality - 30 days at 30 days; Mortality - long-term at Longest endpoint; Stroke or thromboembolic events at Longest endpoint; Rehospitalisation with a primary diagnosis of AF at Longest endpoint; Patients developing heart failure at Longest endpoint; Maintenance of sinus rhythm at Longest endpoint; Recurrence of AF at Longest endpoint; health-related quality of life at Longest endpoint

AAD= antiarrhythmic drug; Abl= ablation; ACA= available case analysis; ACC= American college of cardiology; ACEi= angiotensin converting inhibitor; AF= atrial fibrillation; AHA= American heart association ASA=acetyl salicylic acid; ARB= angiotensin receptor blocker; AUC= area under the curve; AV= atrioventricular; CAD= coronary artery disease; ECG= electrocardiogram; ECV= electrical cardioversion; ESC= European society of cardiology; HR= hazard ratio/ heart rate; INR= international normalised ratio; IQR= inter quartile range; ITT= intention- to- treat; LAA= left

atrial appendage; LV= left ventricle; LVEF= left ventricular ejection fraction; MD= mean difference; M/F=male/female, MV=mitral valve; N=total number of people randomised,; NA= not applicable; NR= not reported; NRI= net reclassification index; NYHA= New York Heart Association; OAC= oral anticoagulation therapy; OR= odds ratio; PAD= peripheral arterial disease; PCI=percutaneous coronary intervention; PM= pacemaker; PVI= pulmonary vein isolation; QoL= quality of life; RCT= randomised controlled trial; RR=relative risk/ risk ratio; SD= standard deviation; SE= standard error; SF-36= Short Form (36) Health Survey; SR=sinus rhythm; TIA= transient ischaemic attack; TOE/TEE= transoesophageal echocardiography; VKA= vitamin K antagonist

Appendix H: Economic evidence tables

H.1 Diagnosis

See Appendix S

H.2 Referral

Table 134: Hendriks 2013[433]

J. Hendriks, F. Tomini, T. van Asselt, H. Crijns, and H. Vrijhoef. Cost-effectiveness of a specialized atrial fibrillation clinic vs. usual care in patients with atrial fibrillation. Europace 15 (8):1128-1135, 2013.				
Study details	**Population & interventions**	**Costs:**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (outcome: cost per QALY) **Study design:** Within trial analysis **Approach to analysis:** Costing of resources used for two arms of an RCT, with QALY estimated by overall survival and QoL measured at baseline and at 12 month follow up. **Perspective:** Netherlands provider perspective	**Population:** Adults referred for newly diagnosed AF **Cohort settings:** Start age: NR Male: NR **Intervention 1:** Specialist care provided in the AF clinic based on the chronic care model, consisting of nurse led outpatient care steered by decision support software based on the guidelines and supervised by a cardiologist	**Mean total costs per patient (SD):** Intervention 1: £1,949 (£4,662) €2301.85 (€5506.10) Intervention 2: £2,572 (£5,070) €3037.22 (€5987.07) Incremental (2−1): -£623(95% CI: -£1,569 to £661) -€735.38 (95% CI: -€1852.67 to €781.14) (p = NR) **Currency & cost year:**	**Mean QALYs per patient(SD):** Intervention 1: 0.603 (0.007) Intervention 2: 0.594 (0.0103) Incremental (2−1): 0.009 (95% CI: -0.007 to 0.024) (p = NR)	**ICER (Intervention 2 versus Intervention 1):** Probability Intervention 1 cost-effective (€20K): 99% **Analysis of uncertainty:** No deterministic analysis undertaken. Bootstrapping technique employed to assess impact of uncertainty on results. Authors report a 99% probability that nurse led care is cost effective using a €20,000 threshold.

Time horizon/Follow-up: 12 months **Treatment effect duration:** 12 months **Discounting:** Costs: NA; Outcomes: NA	**Intervention 2:** Usual care by a cardiologist in the outpatient clinic	2011 euros presented here as 2011 UK pounds[(e)] **Cost components incorporated:** Diagnostics (ECG, Holter monitoring, exercise test, chest x-ray, lab tests, thrombosis centre) ; outpatient care (consultation, telephone, emergency); drug therapy (acenocoumol, amiodarone, ascal, beta-blocker, digoxin, fenprocoumon, flecanide, sotalol, verapamil, other), interventions Hospital care (pharmaceutical and electrical cardioversion, other intervention); software; inpatient care.		

Data sources

Health outcomes: One economic analysis was conducted alongside the RCT study[439], however information regarding this evaluation has only been published as a conference abstract [434] and information was available only from the thesis by the author. [433,439] . **Quality-of-life weights:** data collected from patients using SF6D, HADS or AF knowledge scale questionnaires and translated to the SF36 using Linkert's method. No information was given on how this was mapped to utilities**. Cost sources:** hospital costs were estimated from one provider, drug costs obtained from the Dutch pharmacotherapeutic compass, no further sources were given.

Comments

Source of funding: Maastricht University Medical Centre, Stichting Hartsvrienden RESCAR, Bayer Health Care B.V. Boehringer-Ingelheim B.V., Europe ExPro, Stinchting Zorgvernieruwing Nederland. **Limitations:** Potential conflict of interest, Non UK setting. Various questionnaires used to estimate QoL which were translated to the SF36, no mapping of SF36 to EQ5D reported. Poor specification of intervention (potential for confounding factors), relied on one source for treatment effect and resource utilisation. Individual unit cost of inpatient care not reported for cross comparison to UK unit cost, other unit prices appear reasonable. Analysis not published in a peer review journal. **Other:** Information taken from thesis.

Overall applicability[f]: Partially applicable	Overall quality[g]: Potentially serious limitations

Abbreviations: CCA: cost–consequence analysis; CEA: cost-effectiveness analysis; CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 means worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; NA: not applicable; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Converted using 2011purchasing power parities[719]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

H.3 Education

There were no included studies for this review

H.4 Stroke risk tools

There were no included studies for this review

H.5 Anticoagulation

Table 135: Shah 2011

Shah, V and B. F. Gage. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation 123 (22):2562-2570, 2011.				
Study details	**Population & interventions**	**Costs (£UK)**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Decision Analytic Model **Approach to analysis:** Markov model with clinical events of	**Population:** People with AF with a high to moderate risk of stroke (mean $CHADS_2$ score of 2.1) **Cohort settings (mean):** Start age = 70 M =50% **Intervention 1:**	**Total costs (mean per patient):** Intvn 1: na Intvn 2: 30,038 ($44300) Intvn 3: 29,631 ($43700) Intvn 5: 23,054 ($34000)	**QALYs (mean per patient):** Intvn 1: nr Intvn 2: 8.54 Intvn 3: 8.64 Intvn 5: 8.32 Intvn 4: 8.40 Intvn 6: 8.17	Low dose dabigatran was dominated by high dose dabigatran, being more costly and less effective. Aspirin and clopidogrel as usual therapy was dominated by warfarin, being more costly and less effective. Dominated options were excluded from incremental analysis. **ICER (Intvn 3 vs Intvn 4):** £58,666 ($86520) per QALY gained

transient ischemic attack, mild/major stroke, second stroke, intracranial haemorrhage (± stroke), myocardial infarction, dyspepsia, major/minor bleed and death with health states of well, post TIA/mild stroke/major stroke/ICH and dead. **Perspective:**. USA insurer (Medicare) **Time horizon:** 20 years **Treatment effect duration:** 2 years of follow up in RE-LY trial extrapolated over horizon **Discounting:** Costs = 3%; Outcomes = 3%	No antithrombotic therapy **Intervention 2:** Low dose Dabigatran 110mg twice daily **Intervention 3:** High Dose Dabigatran 150 mg twice daily **Intervention 4:** Warfarin **Intervention 5:** Dual therapy aspirin (325mg) and clopidogrel (75mg) **Intervention 6:** Aspirin (325mg)	Intvn 4: 15,595 ($23000) Intvn 6: 13,561 ($20000) **Currency & cost year:** 2010 US dollars, presented here in UK pounds **Cost components incorporated (US$):** Annual prophylaxis of: Aspirin: 10; aspirin and clopidogrel: 1857; warfarin: 180; dabigatran: 3240; Cost of INR control pt visit: 26; Short term/long term moderate to severe neurological events: 14680/5400; minor neurological events: 9200/2470; ICH: 38500/5700; TIA: 7500; ischemic neurological event and ICH: 7200; major/minor bleed: 4400/69; cost of non-stroke or haemorrhagic death: 10000; MI: 17000		**ICER (Intvn 4 vs Intvn 6):** £8,844 ($13043) per QALY gained **Analysis of uncertainty:** Probabilistic sensitivity analysis was not performed. One way, two way and three way analysis was performed, however reporting of results focused on parameters that influenced cost effectiveness of dabigatran in particular and in relation to a threshold of $50000. Inspection of graphics for three way sensitivity analysis suggests that for pts with • $CHADS_2$ score of 0 aspirin is optimal for pts with a HEMORR2HAGES score of 0-2, and no antithrombotic is preferable for HEMORR2HAGES score 3+. • $CHADS_2$ score of 1, aspirin is optimal for pts with a HEMORR2HAGES score of 2+, and warfarin is preferable for pts with a HEMORR2HAGES score 0-1. If time in therapeutic range is >72.6% • $CHADS_2$ score of 2,warfain is optimal for pts with a HEMORR2HAGES score of 0-2 and dabigatran is preferable for pts with a HEMORR2HAGES score 2+; however this is sensitive to time spent in INR (whereby if this parameter is <57.1% dabigatran is optimal and >72.6%.warfarin is optimal). • $CHADS_2$ score of 3+,dabigatran is optimal for all scores of HEMORR2HAGES score. The exception is if time spent in INR >72.6% then warfarin is optimal across all HEMORR2HAGES scores
Data sources				
Health outcomes: RE-LY trial informed efficacy of dabigatran and warfarin. A traditional random effects analysis and network meta-analysis (including the ACTIVE W				

trial) informed bleeding risk of warfarin versus dual therapy **Quality-of-life weights:** Survey data (n=69) AF patients (Gage 1996) and other published sources. Method not specified. **Cost sources:** A combination of estimates derived by published studies, HCUPnet, Medicare remuneration and a survey of 4 pharmacies.
Comments
Source of funding: American Heart Association and Knowlton foundation. **Limitations:** RE-LY trail was the principle source for probabilities in the model, whereby warfarin was not blinded (potentially favouring dabigatran) and only had follow up of 2 years. Time in INR for the RE-LY trial was approximately 64% **Other:** Authors note compliance and lapses in dabigatran not fully explored (noting the 12-17 half-life of dabigatran, a lapse with this drug could be more problematic than lapse in warfarin therapy).
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 136: Kensal 2012

Anuraag R. Kansal, Sonja V. Sorensen, Ray Gani, Paul Robinson, Feng Pan, Jonathan M. Plumb, and Martin R. Cowie. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. Heart 98 (7):573-578, 2012.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Decision Analytic Model **Approach to analysis:** Markov model **Perspective:**. UK NHS **Time horizon:** lifetime **Treatment effect duration:** Follow up of RE-LY trial was 2 years,	**Population:** People with non valvular AF with a high to moderate risk of stroke (mean $CHADS_2$ score of 2.1), with subgrouping of patients under and over 80 years old **Cohort settings (mean):** Start age = 71.5 M =63.6% **Intervention 1:** No antithrombotic therapy	**Total costs (mean per patient):** Intvn 1: 20475 Intvn 2: 19645 (drug costs 35%; stroke follow up costs 47%; 18% acute event management) Intvn 4: 18561 Intvn 3: 18474 (drug and INR costs 17%; stroke follow up costs 61%; 22% acute event management) **Total costs (mean per patient over**	**QALYs (mean per patient):** Intvn 1: 7.12 Intvn 2: 8.06 Intvn 4: 7.59 Intvn 3: 7.82 (p = NR) **Total QALYs (mean per patient over 80/under 80):** Intvn 1: nr / nr	No treatment was dominated by high dose dabigatran, being more expensive and less effective. Aspirin monotherapy was dominated by warfarin, being more costly and less effective. Dominated options were excluded from incremental analysis. **ICER (Intvn 2 vs. Intvn 3):** £4879 per QALY gained CI:NR Probability Intvn 2 cost-effective (£20K/30K threshold): NR (graph does not show this comparator or dabigatran compared to dominated

with clinical effect applied throughout life time in the model. **Discounting:** Costs = 3.5%; Outcomes = 3.5%	**Intervention 2:** High dose dabigatran 150 mg twice daily (which switched to a dose of 110mg after 80 years of age in age adjusted dosing) **Intervention 3:** Dose adjusted 5mg warfarin ((64% time in therapeutic range) **Intervention 4:** Aspirin monotherapy (162.5mg)	**80/under 80):** Intvn 1: nr / nr Intvn 2: 10424 / nr Intvn 3: 9919 / nr Intvn 4: nr / nr **Currency & cost year:** 2010 UK pounds **Cost components incorporated (UK£):** Stroke or ICH (fatal/independent/moderate disability/totally dependent): 3059/3401/17743/24234; systemic embolism (fatal/non-fatal): 400/2373; TIA: 1064; Extracranial haemorrhage (fatal/non-fatal gastrointestinal/non-fatal gastrointestinal): 1852/2109/1594; minor bleed 84; MI: 2956; **Follow up** stroke costs per quarter (with a stroke history of independence/moderate disability/dependent disability): 331/2868/6089 Annual INR: 415 Per day Dabigatran: 252; Warfarin: 0.04; aspirin: 0.09; Stroke (year 1 /after year 1): 10543/2781; Myocardial infarction(year 1 /after year 1): 2357/829; Pulmonary embolism:1543; Transient ischemic attack: 840; Major/minor bleed: 1685/93; Proton pump inhibitors:185; warfarin (year	Intvn 2: 4.11/ nr Intvn 3: 4.04/ nr Intvn 4: nr / nr	options) **ICER (Intvn 2 vs. Intvn 3):** For population over 80 £7090 per QALY gained For population under 80 (63% probability of being cost effective at 20K) £4831 per QALY gained (98% probability of being cost effective at 20K) **Analysis of uncertainty:** One way deterministic analysis with a tornado diagram showing impact on the ICER for dabigatran versus warfarin showed plausible changes in the RR of stroke, ICH, % of pts. in INR, time horizon, follow up costs and discount rate would have no impact on the conclusions of the analysis. However, authors report that the ICER would increase above 20k if time in INR reached approximately 91% and 80% in patients under and over 80 years of age respectively.

		1/post year 1): 185/41; Dabigatran (both doses): 920; Aspirin: 7		
Data sources				
Health outcomes: Effectiveness estimates derived from the findings of the RE-LY trial (Connollay 2009) and an adaptation of a network meta-analysis (Roskell 2010). **Quality-of-life weights:** Published literature (Sullivan 2006) and a study of 83 patients (Gage 1996). **Cost sources:** MIMS Online (drug costs), NHS reference costs, NICE costing report for AF guideline 2006, estimates derived from a UK stroke registry as reported by Luengo-Fernandiz (2009) for costs associated with stroke				
Comments				
Source of funding: Boehringer-Ingelheim (manufacturer of dabigatran). **Limitations:** Treatment effect for dabigatran came from one source, with results assumed to be extrapolated after a 2 year follow up; however, this was a multinational study (n=18,113). The efficacy of all comparators used in the model (or probability of adverse event) was not specified explicitly and therefore difficult to assess the quality of the results achieved. This alongside a conflict of interest in the study's funding could limit the validity of the conclusions. **Other:** This study superseded three selectively excluded studies (Freeman 2011, Sorenson 2011, Kamel 2012) that also used the RE-LY trial as the principle source, on the account of being more applicable to the UK context. In general, the conclusions from Kansal et al. were comparable to the excluded studies. Please see excluded studies table for more information.				
Overall applicability*: Directly applicable Overall quality: Potentially serious limitations**				

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 137: Jowett 2011

S. Jowett, S. Bryan, L. Poller, A. M. van den Besselaar, F. J. van der Meer, G. Palareti, C. Shiach, A. Tripodi, M. Keown, S. Ibrahim, G. Lowe, M. Moia, A. G. Turpie, and J. Jespersen. The cost-effectiveness of computer-assisted anticoagulant dosage: results from the European Action on Anticoagulation (EAA) multicentre study. J.Thromb.Haemost. 7 (9):1482-1490, 2009.				
Study details	**Population & interventions**	**Costs(£UK)**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Within RCT	**Population:** People with AF (n=973) who were ≥75 years of age **Cohort settings (mean):**	**Total costs (mean per patient):** Intvn 1: 1382 (SD 2004) Intvn 2: 1548 (SD 2468) (Intvn 1-2): - 166 (95% Bootstrapped CI:-452 to 89)	**QALYs (mean per patient):** Intvn 1: 1.685 Intvn 2: 1.665 (Intvn 1-2):0.020 (95%	**ICER (Intvn 1 vs Intvn 2):** Warfarin dominates aspirin being less costly and more effective CI: Potentially aspirin could be the dominant strategy. From inspection of bootstrapped results on the cost

Approach to analysis: Economic evaluation within BAFTA trial based on an intention to treat analysis and bootstrapping to explore uncertainty **Perspective:**. UK NHS **Time horizon:** 4 years **Treatment effect duration:** mean follow up of BAFTA trial was 2.7 years. **Discounting:** Costs = 3.5%*; Outcomes = 3.5%* From year 2 onwards	Start age = 81.5 M =55% **Intervention 1 (n=488):** Dose adjusted 5mg warfarin (INR range 2-3) **Intervention 2 (n=485):** Aspirin monotherapy (75mg daily)	(p = NR) **Currency & cost year:** 2007 UK pounds **Cost components incorporated (mean per patient in warfarin/aspirin over 4 year horizon):** Primary vascular event: 173/318 Secondary vascular events: 317/318 Haemorrhagic events: 52/78 Primary care visits: 507/483 INR visits: 191/38 Long term costs: 143/304	Bootstrapped CI:-0.070 to 0.111) (p = NR)	effectiveness plane the majority of points appear to be in the South East quadrant, however many appear in the South West quadrant, and some appearing in both the North West and North East Quadrants. The percentages are not reported, however this suggests there is a high degree of uncertainty in the results, with Warfarin most likely to be the most cost effective option. **Analysis of uncertainty:** In addition to the probabilistic analysis, the authors stratify the results by age of the cohort. For age groups 75-79 years old, warfarin is the dominant strategy. In age groups 80-84 years old warfarin is less costly (-131) and less effective (-0.009) than aspirin, and aspirin has a cost per QALY of 14556 when compared to Warfarin. In age groups of 85 years plus warfarin is more costly (83) and more effective (0.012) with a cost per QALY of 6917 when compared to aspirin.
Data sources				
Health outcomes: From BAFTA trial (Mant 2007). **Quality-of-life weights:** EQ5D questionnaire administered to the BAFTA study participants, with utility values derived from a UK population. **Cost sources:** resource use was estimated from primary care records, hospital records and death certificates and an anticoagulation clinic. Unit costs for anticoagulation from a published study (Jowett 2006), drug costs were not included, and all other costs from NHS reference costs and the Personal Social Services Research Unit.				
Comments				
Source of funding: Medical Research Council, Midlands Research Practices Consortium and the Primary Care Research Trust. Authors declare various declarations of interest. **Limitations:** Treatment effect and resource use came from one source, time horizon of 4 years (with extrapolated treatment effect using published sources). Unclear which stroke follow up costs were included. Patients were not sub grouped according to risk of stroke. **Other:**				
Overall applicability*: Directly applicable Overall quality: Potentially serious limitations**				

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years

‡ Converted using
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 138: Coleman 2012

Coleman CI, Straznitskas AD, Sobieraj DM, Kluger J, Anglade MW. Cost-effectiveness of clopidogrel plus aspirin for stroke prevention in patients with atrial fibrillation in whom warfarin is unsuitable. American Journal of Cardiology. United States 2012; 109(7):1020-1025. (Guideline Ref ID COLEMAN2012)				
Study details	**Population & interventions**	**Costs (£UK)**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA. **Study design:** Decision analytic Markov model **Approach to analysis:** **Perspective:** Medicare **Time horizon/Follow-up:** 35 years (from age 65) **Treatment effect duration:** Lifetime unless treatment discontinued **Discounting:** Costs: 3% ; Outcomes: 3%	**Population:** Patients with uncomplicated AF, $CHADS_2$ score of 2, low risk of bleeding. **Cohort settings:** Start age: 65 Male: N/A **Intervention 1:** Aspirin 75-100mg, On-going treatment. **Intervention 2:** Clopidogrel plus aspirin, Clop. 75mg, Aspirin 75-100mg, On-going treatment. Discontinued if major haemorrhage occurs.	**Total costs (mean per patient)[(e)] :** Intervention 1: 53,688 Intervention 2: 60,276 Incremental (2−1): 6588 (CI NR; p = NR) **Currency & cost year:** 2011 US dollars (presented here as 2011 UK pounds) **Cost components incorporated:** (*Individual costs not given)* Inpatient Outpatient Drugs Complication Adverse events	**QALYs (mean per patient):** Intervention 1: 9.01 Intervention 2: 9.37 Incremental (2−1): 0.36 (CI NR; p = NR)	**ICER (Intervention 2 versus Intervention 1):** £18,299 per QALY gained (da) CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): 38%/50% (threshold probabilities were estimated visually from the graph) **Analysis of uncertainty:** **PSA:** 10,000 iterations performed but no mean ICER reported. **1-way sensitivity:** The base-case ICER was particularly sensitive to the variables listed below. Initial values are given in brackets. $CHADS_2$ (2) For $CHADS_2$ =4: £3146 per QALY For $CHADS_2$ =0: Dominated by intervention 2 Major bleeding risk (1.3%) At 1.02%: £15,526 per QALY Over 7.5%: Intervention 2 dominated At £33,940($50,000) per QALY threshold the risk was 2.5% RR decrease for ischaemic stroke (0.68)

				At 0.57: £6776 per QALY At 0.80: £54,904 per QALY Utility of clopidogrel plus aspirin (0.987) At 0.95: £87,774 per QALY At 1.0: £15,460 per QALY
Data sources				
Health outcomes: Utilities were sourced from medical literature but no information was given on the measures used. Risks of major haemorrhage, stroke, intracranial bleed, gastrointestinal bleed, myocardial infarction and non-event death came from the ACTIVE-A trial. **Quality-of-life weights:** Unclear **Cost sources:** Drug costs from average wholesale price. Cost of complications from Agency of Healthcare Research, Quality's Healthcare Cost and Utilization Project and previously published estimates.				
Comments				
Source of funding: NR. **Limitations:** US study. Slightly lower discount rate of 3%. Medicare costs different to NHS costs. HRQoL not reported from patients in trial and a value for the disutility of combination therapy was assumed. No description of literature search. PSA results only presented as CEAC. **Other:**				
Overall applicability: Partially applicable **Overall quality: Minor limitations**				

Abbreviations: CCA: cost–consequence analysis; CEA: cost-effectiveness analysis; CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 means worse than death); HRQoL: Health-related quality of life; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years.
(d) Converted using 2011 purchasing power parities[719]

H.6 Bleeding risk

There were no included studies for this review

H.7 Monitoring

There were no included studies for this review

H.8 Left Atrial Appendage Occlusion

Table 139: Singh (2013)[820]

S. M. Singh, A. Micieli, and H. C. Wijeysundera. Economic evaluation of percutaneous left atrial appendage occlusion, dabigatran, and warfarin for stroke prevention in patients with non-valvular atrial fibrillation. Circulation 127 (24):2414-2423, 2013.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: cost per QALY) **Study design:** Decision analytic model **Approach to analysis:** Patient level micro simulation (10,000 patients) **Perspective:** Canadian third party payer. **Time horizon:** lifetime **Treatment effect duration:** NR, assumed lifetime **Discounting:** Costs: 5%; Outcomes: 5%	**Population:** Patients with non valvular AF presenting to an outpatient oral anticoagulant clinic. Baseline proportions of patients with CHA_2DS_2-VASc score of 2 was 8.8%, of 3 was 25.7% and 64.4% had a score greater than 4 **Cohort settings:** Start age: 76 Male:0.5 **Intervention 1:** Dose adjusted warfarin **Intervention 2:** LAA occlusion **Intervention 3:** Dabigatran (150mg, except where lower dose of 110mg was indicted)	**Total undiscounted costs (mean per patient):** Intervention 1: £13,936 Intervention 2: £16,661 Intervention 3: £17,311 Incremental (2−1): £2725 (CI NR; p = NR) **Total discounted costs (mean per patient):** Intervention 1: £11,541 Intervention 3: £13,873 Intervention 2: £14,543 Incremental (2−1): £3002 (CI NR; p = NR) **Currency & cost year:** 2012 Canadian dollars (presented here as 2012 UK pounds[(e)]) **Cost components incorporated:**	**Total undiscounted QALYs (mean per patient):** Not discounted Intervention 1: 6.06 Intervention 2: 6.23 Intervention 3: 6.17 Incremental (2−1): 0.16 (CI NR; p = NR) **Total discounted QALYs (mean per patient):** Intervention 1: 4.55 Intervention 3: 4.64 Intervention 2: 4.68 Incremental (2−1):0.13 (CI NR; p = NR)	**ICER (Intervention 2 versus Intervention 1):** **Not discounted:** Dabigatran dominated by LAAO LAAO vs Warfarin £16,595 per QALY gained **Discounted:** Dabigatran extendedly dominated by LAAO and warfarin. LAAO vs Warfarin: £22,385 per QALY gained Probability Intervention 2 cost-effective (Canadian $50,000/$100,000 threshold): 43%/47% **Analysis of uncertainty:** Deterministic Analysis on the majority of variables (results not reported). Authors report LAAO not being cost effective in comparison to dabigatran when OR for bleeding with aspirin versus warfarin was >0.75. or if the OR for stroke with LAAO versus warfarin was>1.56. Inspection of the scatter plot of the cost

		Medication costs (including monitoring for warfarin at 36$ per month), stroke, TIA, ICH, Major and minor bleeds, MI, LAAO (deice, anaesthetics, nursing fee, physician fee, overnight hospital stay, TEE at procedure and follow up), LAAO complications (pericardial effusion, device embolization, procedure related stroke)		effectiveness plane comparing LAAO with warfarin shows great uncertainty, with many points along the line of no differential cost and points for incremental QALYS in all four quadrants.
Data sources				
Health outcomes: RE-LY and PROJECT AF trails informed concomitant warfarin and dual antiplatelets, and dabigatran, with LAAO respectively. Clinical events were modelled using the RELY trial, stroke determined by the CHA_2DS_2-VASc risk score, and bleeding by the HAS-BLED score. (list key sources of baseline event and effectiveness data and study type; include references for effectiveness sources). OR of stroke with LAA was 1.34* OR of warfarin (0.31). **Quality-of-life weights:** derived from Canadian general population using time trade off method, utility decrement of LAAO assumed the same as percutaneous coronary revisualisation . **Cost sources:** Ontario Drug Benefits Formulary. LAAO was the cost of device, overnight stay, staff fees and lab costs. Staff costs from Ontario Schedule of Benefits. Overall costing based on a similar procedure of percutaneous transluminal catheter assisted closure of secundum atrial septal defect. Clinical events from the Ontario Case costing Initiative.				
Comments				
Source of funding: (Canadian Institutes of Health Research). **Limitations:** Limited applicability as costing from the Canadian health care system, and discount rate of 5% applied and one comparator was outside the scope of the guideline (Dabigatran). Although PSA performed, due to the reporting of the threshold in Canadian dollars, it is unclear what the results would have been using a £20,000 threshold. Results of deterministic analysis not reported in full. **Other:**				
Overall applicability[(f)]: partially applicable Overall quality[(g)]: minor limitations				

Abbreviations: CI: 95% confidence interval; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; ICH = Intracranial Haemorrhage; LAAO = Left atrial appendage occlusion; MI: Myocardial Infarction; NR: not reported; OR = Odds Ratio, pa: probabilistic analysis; QALYs: quality-adjusted life years; TIA = Transient Ischemic Attack,

(e) Converted using 2012 purchasing power parities[719]

(f) Directly applicable / Partially applicable / Not applicable

(g) Minor limitations / Potentially serious limitations / Very serious limitations

H.9 Rate versus Rhythm

Table 140: Hagens 2004

Hagens VE, Vermeulen KM, TenVergert EM, et al. Rate control is more cost-effective than rhythm control for patients with persistent atrial fibrillation – results from the Rate Control versus Electrical cardioversion (RACE) study. European Heart Journal 25: 1542-1549, 2004.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (Health outcome = primary endpoint avoided = composite of morbidity/mortality) (a) **Study design:** Within-trial analysis (RCT) (RACE). **Approach to analysis:** Costs applied to resource use data collected in the RCT and compared to end points from this prospective study. **Perspective:** Societal, however breakdown of costs allows a provider perspective, **Mean Follow up:** 2.3 years (±0.6 years) **Treatment effect duration:** Assumed for duration of follow up **Discounting:** 4% for both.	**Population:** Persistent AF. M=63%. Mean age = 69. **Interventions:** (b) 1. Rate control=digitalis, CCC, BB or a combination of all three. 2. Rhythm control=serial electrical CV + AAD	**Currency & cost year:** Euros 2000 **Total costs (mean per patient): £(€)** Between randomisation and study end at 3 years. (c) **Societal perspective:** Rate control = £5343 (€7386) Rhythm control =£5992 (€8284) Incremental (2-1) = £640 (€898) **Provider perspective** Rate control = £3422 (€4731) Rhythm control = £4116 (€5690) Incremental (2-1) = £694 (€959) **Cost components incorporated (€/yr.):** Only costs associated with a primary endpoint (d) were included in the analysis. (e) CV at uni hosp (258), CV at gen hosp (153), medication (varied), OP visit uni hosp (74.50), OP visit gen hosp (42), uni hosp admission (340), gen hosp admission (242), GP visit,	**Primary endpoint.** (d) Rate control = 17.5% of patients reached primary endpoint Rhythm control = 21.2% of patients reached primary endpoint Incremental = 3.7% less patients reached primary endpoint using rate control than rhythm control.	Rate control dominated rhythm (more effective and less costly) Probability Intvn cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Deterministic Sensitivity Analysis performed to explore to what extent the total costs were influenced by varying costs on the different cost categories by -20% and +20%. These variations did not affect the cost effectiveness conclusions.

		thrombosis lab, district nurse, (family help and informal care included in societal perspective).		
Data sources:				
Health outcomes: RACE study RCT[879] **Quality-of-life weights:** Not applicable. **Cost sources:** Resource use data from patient questionnaires.				
Comments:				
a) *Results from RACE study did not show any statistically significant differences between rate control and rhythm control treatment groups with regard to primary endpoint or secondary endpoints (Quality of life or event burden), hence a rationale for performing a cost minimisation study was given by the authors. The authors then went on to perform a cost-effectiveness analysis using the reported (non-statistically significant) difference in primary endpoint from the RACE trial.* ***b)*** *Anti-arrhythmic drug therapy first choice was sotalol, thereafter class 1c AADs and at last amiodarone.* ***c)*** *Mean costs include direct non-medical costs such as informal care and travel costs. These made up 36% and 31% of costs in the rate control and rhythm control groups, respectively. Productivity costs were excluded because only 4 patients were working.* ***d)*** *Primary endpoint was the composite of cardiovascular mortality, heart failure, thrombo-embolic complications, bleeding, pacemaker implantation, or severe adverse effects of antiarrhythmic drugs.* ***e)*** *Treatment cost data collected at scheduled visits during RCT were not included. Information on costs made outside the treatment centres were collected from self-administered patient questionnaires. Costs of a pacemaker or stent were not recorded, but costs of a hospital admission and/or post intervention outpatient visits and other related costs were included.* ***Source of funding****: The RACE study was supported by grants from the Center for Health Care Insurance, the Interuniversity Cardiology Institute, the Netherlands, and by 3M Pharma, the Netherlands.* ***Limitations****: Netherlands setting. Results from RACE study did not show any statistically significant differences between treatment groups with regard to primary endpoint or secondary endpoints (Quality of life or event burden), hence the authors of the study performed a cost minimisation study. The authors then went on to perform a cost-effectiveness analysis using the reported (non-statistically significant) difference in primary endpoint from the RACE trial. There was no justification given for doing this, and the reported treatment differences were not subject to sensitivity analysis. Societal perspective and 4% discount rate used.*				
Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations.				

Abbreviations: AAD= antiarrhythmic, AF = Atrial fibrillation; Ami = Amiodarone, ASA = aspirin; BB=beta-blocker; CCC=calcium channel blocker; CV=cardioversion; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs = quality-adjusted life years; W = Warfarin; Quin = Quinidine:
‡ Converted using 2000 purchasing power parities[719]
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 141: Marshall 2002

Marshall DA, Levy AR, Vidaillet H et al. Cost-effectiveness of rhythm versus rate control in atrial fibrillation. Annals of Internal Medicine141: 653-661, 2002.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (Health outcome = survival; i.e. cost per	**Population:** AF and likely to be recurrent, and to cause morbidity and	**Currency & cost year: US $ 2002** **Total costs (mean per patient): £($)** (c)	**Primary endpoint.** Mean survival time (years) from	Rate control dominated rhythm (more effective and less costly)

life year gained) (a) **Study design:** Retrospective economic evaluation using data from AFFIRM trial. **Approach to analysis:** **Perspective:** Third party payer USA **Time horizon:** 3.5 years = mean follow up **Treatment effect duration:** **Discounting:** 3% for both costs and effects.	long-term treatment warranted. M=61%. Mean age = 69.7 yrs. **Interventions:** (b) 1. Rate control= BBs or CCBs or digoxin or a combination of all three. 2. Rhythm control= AAD + CV if required.	Rate control = £12,895 ($20,546) Rhythm control = £16,082 ($25,623) **Incremental (2-1):** £3187 ($5167) **Cost components incorporated $US :** The analysis considered costs of all hospitalizations (1535-1,627 per day), cardiac procedures (pacemaker=9,788, dual chamber=11,995, implanted defib=34,311, angioplasty=848, CABG=2958, valve surgery=3110, ablation=555), cardioversion (ECV=150-633, PCV=106, combined=256-739), short-stay or emergency department visits (569), and medications used to treat AF.	randomisation to end of study follow-up.(d) Rate control = 4.67 Rhythm control = 4.60 **Incremental (2-1):** -0.07	Probability Intvn cost-effective (£20K/30K threshold): Ninety-five of the bootstrap samples were observed in the northwest quadrant of the scatter plot. That is, rhythm control was associated with lower survival at an additional cost relative to rate control. **Analysis of uncertainty:** For each measure of resource use, 3 different unit costs were derived and considered in separate analyses: a base case for most likely scenario, a low estimate and a high estimate. Rhythm control strategy was dominated for all three cost scenarios (base case, low and high).
Data sources:				
Health outcomes: Survival from the AFFIRM trial[915] **Quality-of-life weights:** Not applicable. **Cost sources:** Resource use data collected from each patient at each follow-up visit. Cost data from hospitals in Wisconsin and from national sources such as Healthcare Cost and Utilization project.				
Comments:				
a) *Results from Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) RCT, n=4060.* ***b)*** *In the **rhythm-control group**, the AAD was chosen by the treating physician. Attempts to maintain sinus rhythm could include cardioversion as necessary. The following drugs were acceptable for use: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, and combinations of these drugs. When dofetilide became available, it also could be used. In the **rate-control group**, drugs that were acceptable were beta-blockers, calcium-channel blockers (verapamil and diltiazem), digoxin,* and combinations of these drugs. ***c)*** *Data on use of specific health care resources for all 4060 AFFIRM patients was obtained from randomization to end of study follow-up.*				

d) *To obtain an unbiased estimate of mean survival, exposure was truncated at 5.65 years, which was the longest follow-up observed in AFFIRM.*
Source of funding*: The National Heart, Lung and Blood Institute.* ***Limitations****: 3% discount rate used. Not a CUA*

Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations.

Abbreviations: AAD= antiarrhythmic, AF = Atrial fibrillation; AFFIRM= Atrial Fibrillation Follow-up Investigation of Rhythm Management; BB=beta-blocker; CABG=coronary artery bypass graft; CCC=calcium channel blocker; CEA=cost effectiveness analysis; CV=cardioversion; ECV=electrical CV; ICER = incremental cost-effectiveness ratio; NR = not reported; PCV= pharmacological CV; QALYs = quality-adjusted life years.
‡ Converted using 2002 purchasing power parities[719]
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 142: Perez 2011

Perez A, Touchette DR, DiDomenico RJ, Stamos TD, Walton SM. Comparison of Rate Control versus Rhythm Control for Management of Atrial Fibrillation in Patients with Coexisting Heart Failure: A Cost Effectiveness Analysis. Pharmacotherapy 31(6): 552-565, 2011.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA (Health outcome = QALY) **Study design:** Markov model. 3 month cycles. **Approach to analysis:** health states = treatment response, hospitalization for AF and/or HF, and severe AEs leading to drug discontinuation. **Perspective:** Third party payer USA **Time horizon:** Lifetime. **Treatment effect duration:** **Discounting:** Rate varied from 0% to 5% in sensitivity analysis.	**Population:** Persistent or paroxysmal AF and heart failure. M=NR. Mean age = ≥65 yrs. **Interventions:** (a) 1. Rate control= BBs or CCBs or digoxin. 2. Rhythm control= ECV +AAD. If successful then AAD continuous. If unsuccessful repeat ECV. Patients who started with rhythm control initially could move to rate control based on transition state history, and vice versa.	**Currency & cost year: US $ 2009** **Total costs (mean per patient): $ (£)** Rate control = £4,644 ($7,231) Rhythm control = £10,463 ($16,291) **Incremental (2-1):** £5819 ($9060) **Cost components incorporated $US:** Hospitalization costs for ECV+amiodarone (4757), ECV (653), telemetry (3630), total ablation (19,965), AF (8272), acute decompensation of heart failure (11,098), pulmonary toxicity (10,406), amiodarone-induced hyperthyroidism	**Primary endpoint.** QALYs. Rate control = 2.395 [95% CI 2.366-2.424] Rhythm control = 2.197 [95%CI 2.155-2.237] **Incremental (2-1):** -0.198 (95% CI -0.129 to -0.369)	Rate control dominated rhythm (more effective and less costly) **Analysis of uncertainty:** One-way sensitivity analyses conducted on all model parameters, discount rate, and starting age showed that rate control as the initial treatment strategy was less costly and more effective than rhythm control as the initial treatment strategy. PSA results support the base case conclusion such that rate control was found to be less costly and more effective than rhythm control as the initial treatment strategy. The acceptability curve showed that the probability that rhythm control is cost-effective was 0% across a range of willingness-to-pay ratios ($0 - $200,000) including the most commonly used reference cases ($50,000/QALY and $100,000/QALY). That is, £32.112 and £64,225)

		(7,046). Drug costs for 3 months = 105 for any of the following: warfarin+monitoring, total b-blocker, total digoxin, total CCB. Total amiodarone maintenance (333).		

Data sources:

Health outcomes: Systematic review done for best data sources for transition probabilities (treatment success or failure, hospitalization for AF or HF or hyperthyroidism or pulmonary fibrosis, or HF leading to drug discontinuation). Sources = trials x 3: 1) (AF-CHF)[788], 2) Canadian Trial of Atrial Fibrillation Investigators studies [788] and 3) AFFIRM trial [915] **Quality-of-life weights:** For HF utility and cardiac dysrrhthymia disutility used Preference-based EQ-5D Index Scores for Chronic Conditions in the United States catalogue. For short-term adjustment for hospitalizations and AEs used published study. **Cost sources:** Inpatient costs for AF and heart failure hospitalisations and short term management of amiodarone-induced hyperthyroidism were obtained from the Healthcare Cost and Utilization Project database. Costs for ECV and ablation procedures and pulmonary fibrosis treatment were extracted from a published CEA. Amiodarone costs were obtained from the 2009 Red Book. Costs of rate-slowing drugs and warfarin were obtained from a pharmacy chain drug discount programme. Warfarin monitoring costs were obtained from a local pharmacist-run anticoagulation clinic.

Comments:

Initial rhythm control was ECV+amiodarone. Treatment failure was defined as converting back to AF. The second state was maintenance amiodarone if treatment successful. If treatment unsuccessful patients underwent repeat ECV.

***Source of funding**: Not reported. **Limitations**: Data derived from published studies, third party payer perspective.*

Overall applicability*: Partially applicable **Overall quality**:** Minor limitations.

Abbreviations: AAD= antiarrhythmic, AF = Atrial fibrillation; AF-CHF = Atrial Fibrillation and Congestive Heart Failure study; AFFIRM= Atrial Fibrillation Follow-up Investigation of Rhythm Management; BB=beta-blocker; CABG=coronary artery bypass graft; CCB=calcium channel blocker; CEA=cost effectiveness analysis; CUA=cost utility analysis; CV=cardioversion; ECV=electrical CV; HF=heart failure; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs = quality-adjusted life years.

‡ Converted using 2009 purchasing power parities[719]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.10 Rate

There were no included studies for this review

H.11 Restoration of sinus rhythm

There were no included studies for this review

H.12 Maintenance of sinus rhythm

There were no included studies for this review

H.13 Catheter ablation

H.13.1 First line catheter ablation

Table 143: Chan 2006

P. S. Chan, S. Vijan, F. Morady, and H. Oral. Cost-effectiveness of radiofrequency catheter ablation for atrial fibrillation. J.Am.Coll.Cardiol. 47 (12):2513-2520, 2006.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Decision analytic model **Approach to analysis:** Markov, 3 month cycle **Perspective:** The study reports a societal perspective, although the exclusion of productivity costs means that the analysis is closer to a US payer perspective. **Time horizon:** lifetime **Treatment effect duration:** lifetime. **Discounting:** Costs =	**Population:** 55-65 year old patients with AF at moderate to low risk stroke **Cohort settings:** Start age = 65 (low-moderate risk of stroke) and 55 (moderate risk of stroke) M = NR **Intervention 1:** Left Atrial Catheter Ablation (LACA) (Assumed efficacy of 80% with 30% redo rate in first year, AF relapse rate of 2%) **Intervention 2:** Amiodarone (Assumed to have an overall success rate	**Total costs - mean per patient $ (UK pounds‡):** **Moderate stroke risk 65 years | 55 years** RC+W =$39391|$50509 (£24915|£31947) Ami + W =$43358 |$55795 (£27424|£36291) LACA + W = $52369 |$59380 (£33124|£37558) **Low stroke risk 65 years** RC+ASA = $24540 (£15522) Ami+ASA = $38425 (£24304) LACA+ASA= $43036 (£27221) **Currency & cost year:** 2004 USA Dollars **Cost components incorporated ($):** Ablation: 16,500 (13,500–19,500); Complications from ablation:	**QALYs (mean per patient):** **Moderate stroke risk 65 years | 55 years** RC+W = 10.81|13.95 Ami + W = 10.75|13.81 LACA + W = 11.06|14.26 **Low stroke risk 65 years** RC+ASA = 11.21 Ami+ASA = 11.02 LACA+ASA = 11.40	**ICER (Intvn 2 vs Intvn 1):** $ (£) per QALY gained (deterministic) **Moderate stroke risk 65 years | 55 years** RC+W = Reference Ami + W = Dominated |Dominated LACA + W =$40226| $22288 (£32764|£18153) **Low stroke risk 65 years** RC+ASA = Reference Ami+ASA = Dominated LACA+ASA = $76803 (£62555) **Analysis of uncertainty:** Probabilistic Sensitivity Analysis indicated that LACA compared to RC would be cost effective in 25% and 72% of simulations using a threshold of $40K (£25300) for a cohort aged 65 and 55 respectively, and would be cost effective in 1% and 38% of

3.5% ; Outcomes = 3.5%	of 85%, and a reversion rate of 30% in the first 6 months and 5% thereafter) **Intervention 3:** Rate control therapy: a combination of digoxin and atenolol (Assumed to have initial conversion rate to NSR of 38%, and a relapse rate of 5% thereafter) **Stroke prevention in all three strategies:** Warfarin was given concurrently for moderate risk patients, and either warfarin or aspirin was given concurrently to low risk patients.	11,000 (5000–20,000); Atrioesophageal fistula: 50,000 (20,000–100,000); Cardioversion: 540 (300–1200); Telemetry unit admission: 3000 (1800–4800); Amiodarone pulmonary toxicity: 8600 (6900–10,400); Intracranial bleed or stroke - No residual defects: 6,400 (3,000–12,000); Mild residual defects: 7,830 (3,500–15,000); Moderate to severe residual defects:12,490 (6,000–25,000); Extracranial haemorrhage: 3,730 (1,500–6,000); Death: 9,000 (0–17,900); Aspirin: 13 (10–20); Warfarin, including every 4-week monitoring: 600 (200–600); Amiodarone: 1200 (1000–1500); Digitalis, including every 6-month monitoring: 140 (100–200); Atenolol: 260 (200–300); Intracranial bleed or stroke - Mild disability: 2,600 (1300–5,100); Moderate to severe disability: 23,000 (10,000–40,000); Pulmonary toxicity caused by amiodarone: 3,500 (1,400–9,000)		simulations using a $20K threshold for a cohort aged 65 and 55 respectively. Authors report that sensitive parameters in the 65 year old moderate risk group analyses is the relative risk of stroke for those on warfarin and LACA efficacy (i.e. annual risk of stroke in NSR would need to decrease by 42% to yield an ICER below $50,000). LACA efficacy rates of less than 75% would require a >50% risk reduction in stroke with NSR. Lower LACA efficacy rates are required for younger patients which are exposed to risks of anticoagulation for longer. Results for other parameter variation were not tabulated.
Data sources				
Health outcomes: An efficacy rate for LACA of 80%, including a 30% redo ablation rate; an assumed 2% annual rate of relapse; an annual restoration rate to NSR of 5% (AFFIRM trial with 5 year follow up); rates for amiodarone efficacy, adverse events and relapse to AF were derived published sources. Complication rates due to LACA for tamponade, stroke, atrioesophageal fistula, death and other events were included. Baseline stroke risks were estimated from decision analytic models and meta-analysis, with annual risk reduction with aspirin of 22% (for both risk groups), and a further 45% and 35% risk reduction with warfarin (compared to aspirin). The low risk cohort assumed a 0.5% risk of stroke, representing a 19% relative risk reduction compared to low risk AF patients on warfarin. A similar risk reduction was assumed for the moderate risk cohorts. Differential mortality and disability rates associated with stroke severity for patients on antithrombotic therapy was derived from published literature. The risk of further stroke doubled on its first occurrence. Baseline risks of haemorrhage were derived from a meta-analysis. **Quality-of-life**				

weights:. For clinical events (stroke, haemorrhage, drug toxicity and LACA complications) a disutility of 0.5 was applied for the duration of the event, utility for health states were derived from published literature. **Cost sources:** Cost estimates were based on hospital accounting information, inflation adjusted values from published literature and the Red Book for whole sale drug costs.
Comments
Source of funding: Authors report consulting relationship with Biosense Webstar. **Limitations:** No consideration of quality of life improvements with symptoms **Other:**
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

Abbreviations: AF = Atrial fibrillation; Ami = Amiodarone, ASA = aspirin; ADD = Anti arrhythmic drug; $CHADS_2$ = Congestive heart failure, hypertension, age 75, diabetes mellitus and prior stroke; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; INR = International Normalized Ratio; LACA = Left atrial catheter ablation; NR = not reported; NSR=normal sinus rhythm; pa = probabilistic analysis; PVI = Pulmonary Vein Isolation ; QALYs = quality-adjusted life years; RC = Rate control; RFCA = radiofrequency catheter ablation; W = Warfarin;
‡ Converted using 2004 purchasing power parities
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 144: Khaykin 2009

Y. Khaykin, X. Wang, A. Natale, O. M. Wazni, A. C. Skanes, K. H. Humphries, C. R. Kerr, A. Verma, and C. A. Morillo. Cost comparison of ablation versus antiarrhythmic drugs as first-line therapy for atrial fibrillation: An economic evaluation of the RAAFT pilot study. J.Cardiovasc.Electrophysiol. 20:7-12:7-12, 2009.				
Study details	**Population & interventions**	**Costs** (UK pounds‡):	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost comparison study **Study design:** Decision analytic model **Approach to analysis:** Decision tree **Perspective:** Canadian payer perspective **Time horizon:** 2 years **Treatment effect duration:** 2 years **Discounting:** Costs =	**Population:** Patients who experienced monthly symptomatic AF episodes for at least 3 months **Cohort settings:** Start age = NR M = NR **Intervention 1:** RFCA therapy consisted of PVI with 3 months of	**Initial treatment cost:** RFA = $10, 465 (£1586) AAD = $2, 556 (£1830) **1 year follow up** RFA = $12,823 (£6722) AAD = $6,053 (£3173) **2 year follow up** RFA = $15, 303 (£8022) AAD = $14,392 (£7544) **Currency & cost year:** 2005 Canadian Dollars **Cost components incorporated (CAD$):**	**QALYs (mean per patient):** **Not applicable**	**Incremental cost:** **Between year 1 and 2 of** the study: RFCA: $2358 (£1236) AAD: $3492 (£1830) **Between year 1 and 2 of the study:** RFA: $2480 (£1300) AAD: $8339 (£4371) Authors suggest therefore that between years 2 and 3 cost neutrality will occur **Analysis of uncertainty:** Costs of anticoagulation therapy, ablation, telemetry admission, days spent in hospital, timing of recurrence,

3% ; Outcomes = NA	warfarin anticoagulation for at least 3 months post ablation. **Intervention 2:** AAD therapy consisted of flecainide titrated to 100-150mg twice per day, propafenone 225-300mg three times per day and Sotalol 120-160mg twice daily. Amiodarone used in drug refractory patients. Patients were anticoagulated within INR range of 2-3. Patients on AAD cross overed to ablation if drug refractory.	Ablation: $8607; Cardioversion: $1674; Overnight stay on telemetry unit $ 596; Baseline annual follow up $500 Monthly costs of Anticoagulation therapy: $132; Flecainide: $90; Propafenone: $93; Amiodarone: $39.48; Sotalol: $39; B blocker:$10.16; Calcium channel blocker: $27.96		cross over rate to ablation, and bridging therapy were varied in a deterministic sensitivity analysis with 2 year follow up costs for AAD ranging from $13643 to $15066, and for RFCA ranging from $13796 to $16810. However within each analysis cost difference did not equate more than $1500. It remains uncertain when cost neutrality would occur.

Data sources

Health outcomes: Based on the Randomised Trial of Radio Frequency Ablation versus Anti-arrhythmic Drugs as First Line Treatment of Symptomatic Atrial Fibrillation (RAAFT) (Wazni et al. 2005). **Quality-of-life weights:**. NA. **Cost sources:** Canadian reference lists and published literature.

Comments

Source of funding: None reported. Authors report affiliation with Biosense Webster, St Jude Medical, Medtronic, and Boston Scientific **Limitations:** Probabilistic sensitivity analysis was not considered. A potentially serious limitation is the assumption that quality of life was not considered and cost minimisation would only infer cost effectiveness if RFA is assumed to be more clinically effective (in terms of symptom control and reduction in adverse events including stroke) than AAD. The cost of stroke was not considered in this costing; this and the short time horizon of 2 years make it unclear whether the conclusions of the analysis are reasonable. **Other:**

Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

Abbreviations: Abbreviations: Abbreviations: AF = Atrial fibrillation; Ami = Amiodarone, ASA = aspirin; ADD = Anti arrhythmic drug; $CHADS_2$ = Congestive heart failure, hypertension, age 75, diabetes mellitus and prior stroke; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; INR = International Normalized Ratio; LACA = Left atrial catheter ablation; NR = not reported; NSR=normal sinus rhythm; pa = probabilistic analysis; PVI = Pulmonary Vein Isolation ; QALYs = quality-adjusted life years; RC = Rate control; RFCA = radiofrequency catheter ablation; W = Warfarin;
‡ Converted using 2005 purchasing power parities
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.13.2 Second line catheter ablation

Table 145: McKenna (2009); Rogers (2008)

C. McKenna, S. Palmer, M. Rodgers, D. Chambers, N. Hawkins, S. Golder, Hout S. Van, C. Pepper, D. Todd, and N. Woolacott. Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom. Heart 95 (7):542-549, 2009. **M. Rodgers, C. McKenna, S. Palmer, D. Chambers, Hout S. Van, S. Golder, C. Pepper, D. Todd, and N. Woolacott. Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation. Health Technol.Assess.Rep. 12 (34), 2008.**				
Study details	**Population & interventions**	**Costs:**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Systematic review and meta-analysis **Approach to analysis:** Probabilistic decision analytic model (Decision tree feeding into Markov model) **Perspective:** UK NHS perspective **Time horizon:** lifetime and 5 year **Treatment effect duration:** 5 years extrapolated to lifetime **Discounting:** Costs =	**Population:** Adults with AF refractory to at least one ADD (majority had paroxysmal **Cohort settings:** Start age = 52 years M = 80% **Intervention 1:** Radiofrequency catheter ablation (RFCA) **Intervention 2:** Long term antiarrhythmic drug (AAD) therapy: Amiodarone (200mg daily, pa)	**Total costs (mean per patient):** **Lifetime horizon** Intvn 1: $CHADS_2$ 0 = £25240 $CHADS_2$ 1 = £26027 $CHADS_2$ 2 = £26987 $CHADS_2$ 3 = £28343 **Lifetime horizon** Intvn 2: $CHADS_2$ 0 = £14417 $CHADS_2$ 1 = £15367 $CHADS_2$ 2 = £16157 $CHADS_2$ 3 = £18107 **5 year horizon** Intvn 1: $CHADS_2$ 0 = 11.53 $CHADS_2$ 1 = 11.18 $CHADS_2$ 2 = 10.97 $CHADS_2$ 3 = 10.67 **5 year horizon** Intvn 2: $CHADS_2$ 0 = 10.96 $CHADS_2$ 1 = 10.76 $CHADS_2$ 2 = 10.52	**QALYs (mean per patient):** **Lifetime horizon** Intvn 1: $CHADS_2$ 0 = 12.37 $CHADS_2$ 1 = 12.14 $CHADS_2$ 2 = 11.87 $CHADS_2$ 3 = 11.49 Intvn 2: $CHADS_2$ 0 = 10.98 $CHADS_2$ 1 = 10.77 $CHADS_2$ 2 = 10.52 $CHADS_2$ 3 = 10.19 **5 year horizon** Intvn 1: $CHADS_2$ 0 = 11.53 $CHADS_2$ 1 = 11.18	**ICER (Intvn 2 versus Intvn 1):** £ per QALY gained (pa) and probability Intvn 2 cost-effective (£20K/30K threshold): **Lifetime horizon** $CHADS_2$ 0 = 7763 (98.3%/99.6%) $CHADS_2$ 1 = 7780 (98.1%/99.6%) $CHADS_2$ 2 = 7765 (98.6%/99.9%) $CHADS_2$ 3 = 7910 (99.2%/100%) **5 year horizon** $CHADS_2$ 0 = 27745 (9.1%/57.7%) $CHADS_2$ 1 = 25510 (16.5%/68.8%) $CHADS_2$ 2 = 23202 (26.5%/78.6%) $CHADS_2$ 3 = 20831 (41.8%/88.1%) **Analysis of uncertainty:** **Scenario Analyses:** Use of different effectiveness evidence,

3.5% ; Outcomes = 3.5%		$CHADS_2$ 3 = 10.18 (CI NR; p = NR) **Currency & cost year:** 2006 UK pounds **Cost components incorporated:** RFCA accumulated cost: £9810 (total consumables, £5687, 2 day ward stay, £182, 200 minutes lab time, £1979, plus VAT and administration); Complications from: cardiac tamponade: £815; PV stenosis: £3217; Outpatient initiation of amiodarone: £154; Amiodarone pa: £32; AF and NSR health states pa: £646; Stroke (year 1): £9431 Stroke (year 2+): £2488; Warfarin (5mg daily pa): £19; Aspirin (75mg daily, pa): £20; Toxic event: £1497; Reversible toxicity (per day): £0.43; Irreversible toxicity (50mg daily): £158; Major bleeding event: £1573; Minor bleeding event: £87	$CHADS_2$ 2 = 10.97 $CHADS_2$ 3 = 10.67 Intvn 2: $CHADS_2$ 0 = 10.96 $CHADS_2$ 1 = 10.76 $CHADS_2$ 2 = 10.52 $CHADS_2$ 3 = 10.18	equality in prognosis for NSR and AF states, no differential impact of treatment and change in annual probability of reversion back to AF did not change the conclusion of the analysis using the 20K threshold for either the lifetime or 5 year time horizons. However, the ICER increased above the 30K threshold in some scenarios with a 5 year horizon e.g. a change in the prognosis of the NSR state; increasing the probability of recurrent AF to above 15% and no differential utility between the states increased the ICER above £30k in the 5 year horizon analysis. Duration of benefits is likely to be a key determinant of cost effectiveness.

Data sources

Health outcomes: Three USA RCTS: Kittayaphong 2006; Pappone (2006); Wazni (2005). A range of case series and survey data was considered to estimate RFCA UK baseline event rate. **Quality-of-life weights:** EQ5D UK tariff used for baseline utility and NSR states; Other AAD and RFCA states used utilities derived from Sf36 scores mapped to the EQ5D. Utility decrements estimated from baseline of 1 day were applied to clinical adverse events. Utility associated with stroke from published source applied. **Cost sources:** Procedural costs from NHS reference costs, otherwise estimates derived from expert opinion and 2 costing studies were used.

Comments

Source of funding: National Institute of Health Research, UK. **Limitations:** QoL estimates mapped from SF36 to EQ5D, however detail of estimation not specified; extrapolation of clinical effect of RFCA post 5 years; stroke risk estimated from population which did not have RFCA; population predominantly paroxysmal AF . **Other:** Limitations seem reasonable given available data to populate model.

Overall applicability*: Directly applicable Overall quality: Minor Limitations**

Abbreviations: AF = Atrial fibrillation; Ami = Amiodarone, ASA = aspirin; ADD = Anti arrhythmic drug; $CHADS_2$ = Congestive heart failure, hypertension, age 75, diabetes mellitus and prior stroke; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death);

ICER = incremental cost-effectiveness ratio; INR = International Normalized Ratio; LACA = Left atrial catheter ablation; NR = not reported; NSR=normal sinus rhythm; pa = probabilistic analysis; PVI = Pulmonary Vein Isolation ; QALYs = quality-adjusted life years; RC = Rate control; RFCA = radiofrequency catheter ablation; W = Warfarin;
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 146: ECKARD 2009

N. Eckard, T. Davidson, H. Walfridsson, and L. A. Levin. Cost-effectiveness of catheter ablation treatment for patients with symptomatic atrial fibrillation. Journal of Atrial Fibrillation 1 (8):461-470, 2009.				
Study details	**Population & interventions**	**Costs USA$** (UK pounds‡):	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Decision analytic model **Approach to analysis:** Decision tree feeding into a Markov model with health states of controlled AF, uncontrolled AF, stroke and death. **Perspective:** Swedish societal perspective quoted in the paper, however from the inputs listed this model takes a payer perspective **Time horizon:** Lifetime **Treatment effect duration:** Lifetime	**Population:** Patients with paroxysmal or persistent drug refractory AF **Cohort settings:** Start age = NR M = NR **Intervention 1:** RFA (0.780 probability of being AF free at 12 months) **Intervention 2:** ADD (0.090 probability of being AF free at 12 months)	**Total costs (mean per patient):** **Intervention 1:$ 25460 (£15953)** **Intervention 2: $ 30440 (£19073)** **Incremental (Invn 2-1): Dominated** **Currency & cost year:** 2006 USA Dollars **Cost components incorporated ($):** Single RFA procedure = 9860 (inc. 3-4 hospital days, diagnostic examinations and disposables such as catheters) Complications inc. tamponade, bleeding, pulmonary vein stenosis, stroke, oesophageal fistula = 2190 Annual ADD treatment = 7000 Annual anticoagulation (inc. monitoring and loss of production) = 770	**QALYs (mean per patient):** **Intervention 1: 9.46** **Intervention 2: 8.68** **Incremental (Invn 2-1): Dominated**	**ICER (Intvn 2 versus Intvn 1):** **£ per QALY gained (deterministic):** In the base case where benefits are sustained over a life time (assuming no rate of reversion post year 1), RFA was less costly and more beneficial than antiarrhythmic therapy, and therefore was the dominant option. **Analysis of uncertainty:** Probabilistic sensitivity analysis was performed and inspection of cost effectiveness plane suggests the majority of simulations showed RFA to be a dominant strategy (no probability reported) **One way deterministic analyses:** Annual reversion post 12 months at 5%, 10% and 15% gave cost per QALY estimates of $8280 (£5888), $26,460 (£16580) and $48310 (£30271) respectively. An elevated stroke risk in the AF state disfavoured the ADD strategy as a greater proportion of these patients remained in that state for longer than in the RFA strategy (this was not quantified in the study).

Discounting: Costs = 3% ; Outcomes = 3%		Annual cost of stroke (year 1) = 19180 Annual cost of stroke (post year 1) = 4380		
Data sources				
Health outcomes: Studies (including RCTs) of drug refractory AF patients were used to inform treatment effect [Krittayaphong (2007); Stabile (2006), Pappone (2006) and Cauchmez (2008)]. **Quality-of-life weights**. Age adjusted QALY weights based on a Swedish population were applied as a reference and a decrement of 0.1 for uncontrolled AF and 0.25 for stroke was applied. **Cost sources:** Unclear – sources quoted in Swedish.				
Comments				
Source of funding: None reported **Limitations:** Quality of life was reviewed; however it is unclear how the literature informed quality of life decrements or how the treatment effect and resource use estimates were derived. It is unclear whether the best source of unit cost was used. Although the model was constructed probabilistically, the results were only reported graphically. Results were only reported for only one deterministic sensitivity analysis in an incremental manner. It is unclear how a different stroke risk in the AF state would have impacted results in this analysis. **Other:** All effectiveness data used in the model used RFA as a second line treatment to ADD. Other included evidence could have greater applicability and fewer limitations.				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: AF = Atrial fibrillation; Ami = Amiodarone, ASA = aspirin; ADD = Anti arrhythmic drug; $CHADS_2$ = Congestive heart failure, hypertension, age 75, diabetes mellitus and prior stroke; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; INR = International Normalized Ratio; LACA = Left atrial catheter ablation; NR = not reported; NSR=normal sinus rhythm; pa = probabilistic analysis; PVI = Pulmonary Vein Isolation ; QALYs = quality-adjusted life years; RC = Rate control; RFCA = radiofrequency catheter ablation; W = Warfarin;
‡ Converted using 2006 purchasing power parities
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 147: Reynolds 2009

M. R. Reynolds, P. Zimetbaum, M. E. Josephson, E. Ellis, T. Danilov, and D. J. Cohen. Cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation. Circulation, Arrhythmia and Electrophysiology 2 (4):362-369, 2009.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Decision	**Population:** Drug refractory paroxysmal AF without severe structural heart disease	**Total costs (direct healthcare costs only):** **Intervention 1:** $26 584 (£16792) **Intervention 2:** $19 898 (£12586)	**QALYs (mean per patient):** Intervention 1: 3.51 Intervention 2: 3.38 **Incremental (Invn 1-2):**	**ICER (Intvn 2 versus Intvn 1) :** **$51, 431 (£32531)** **Analysis of uncertainty:** Probabilistic analysis not undertaken

analytic model **Approach to analysis:** Markov model **Perspective:** The study reports a societal perspective, although the exclusion of productivity costs means that the analysis is closer to a US payer perspective. **Time horizon:** 5 year **Treatment effect duration:** Assumed to be 5 years **Discounting:** NR	**Cohort settings:** Mean age = 60 M = 100% **Intervention 1:** RFA ± AAD (RFA assumed to have a 60% efficacy rate, with 25% rate of repeat procedures and a 10% overall failure rate) **Intervention 2:** AAD (AAD assumed to have a 25% AF recurrence rate as first line treatment and 35% as second line treatment)	**Incremental (Invn 1-2):** $6650 (£4206) (CI =NR ; p = NR) **Currency & cost year:** USA $, Date NR (various sources reported whose costs are dated from 2004 onwards) **Cost components incorporated:** Procedures and complications: Ablation procedure: $15000; Vascular access: $8000; Perforation or tamponade: $7500; Stroke:$8200; TIA: $7800; PV stenosis: $7800; Pnuemothorax/hemothorax:$13 000; Telemetry admission: $5000 Drug toxicity fatal/non-fatal with: 1st line drug: $10000/$5100 Amiodarone: $10000/$5000 Costs associated with the following health states: Rate control and anticoagulation: $2800/yr. Well post ablation: $1300 yr1;then $200/yr. Well on first line drug:$4000 Well on amiodarone $3500	**0.13** (CI = NR; p = NR)	A scenario whereby age and sex related background mortality was removed from the analysis reduced the cost per QALY to $47,333 (£29939) One way sensitivity analysis for all inputs was plotted on a tornado diagram which showed the results were most sensitive to change in the following (in order of most sensitive to least sensitive) utility associated with ablation success, the time horizon, the cost of ablation, the utility associated with rate control, and cost of rate control. From inspection of the diagram, it seems that a longer time horizon, reduced ablation cost (i.e. to $10,000), increased rate control cost (i.e. to $5000) and increased single procedure success rate (i.e. to 70%) were the factors which were most likely to result in RFA being cost effective using the £20,000 threshold. Two way sensitivity analysis on utility of NSR post ablation and of the rate control health state. Suggests that only when the utility of the rhythm control and anticoagulation therapy states is lower than the base case (i.e. above 0.75)and the utility of the well post ablation states is higher than the base case (i.e. above 0.79) is the cost per QALY associated with RFA+ADD likely to decrease sufficiently to be cost effective using a £20,000 threshold (from inspection of graph)
Data sources				
Health outcomes: A series of published sources were used, with three RCTs informing efficacy and recurrence of AF rates for the interventions (Jais 2008, Pappone 2006 and Stabile 2006) **Quality-of-life weights:** For ADD health states, the SF12 data from the FRACTAL registry were mapped using Brazier algorithm. For other utilities, data collated from the SF36 questionnaire in prospective cohorts and trials were used. **Cost sources:** Costs of drug therapy derived from FRACTAL registry and AFFRIM trial, procedural				

costs were derived from hospital accounting systems and national reference lists from the USA and Canada.
Comments
Source of funding: National Institutes of Health, authors received consulting fees from Biosense Webster and Sanofi-Aventis. **Limitations:** No probabilistic sensitivity analysis performed. Results from the deterministic sensitivity analysis reported only in graphical format and using threshold of $50,000 making interpretation difficult when applying £20,000 threshold. 5 year horizon applied **Other:** Assumes that ablation does not decrease risk of stroke.
Overall applicability*: Partially applicable Overall quality: Potentially Serious Limitations**

Abbreviations: Abbreviations: AF = Atrial fibrillation; Ami = Amiodarone, ASA = aspirin; ADD = Anti arrhythmic drug; $CHADS_2$ = Congestive heart failure, hypertension, age 75, diabetes mellitus and prior stroke; CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; INR = International Normalized Ratio; LACA = Left atrial catheter ablation; NR = not reported; NSR=normal sinus rhythm; pa = probabilistic analysis; PVI = Pulmonary Vein Isolation ; QALYs = quality-adjusted life years; RC = Rate control; RFCA = radiofrequency catheter ablation; W = Warfarin;

‡ Converted using 2004 purchasing power parities
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.14 Ablation which is concurrent with cardiac surgery.

Table 148: Lamotte 2007

M. Lamotte, L. Annemans, B. Bridgewater, S. Kendall, and M. Siebert. A health economic evaluation of concomitant surgical ablation for atrial fibrillation. Eur.J.Cardiothorac.Surg. 32:702-710:702-710, 2007.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Decision analysis **Approach to analysis:** Markov model **Perspective:** UK NHS perspective	**Population:** Patients with coronary or valvular disease undergoing CABG or valve replacement/repair with concomitant AF **Cohort settings:** Start age = NR	**Total costs (mean per patient):** **Permanent AF** No ablation: 2513 Classic maze: 3233 Surgical ablation: 4567 Percutaneous ablation: 5538 **Persistent AF** No ablation: 2318 Classic maze: 3203	**QALYs (mean per patient):** **Permanent AF** No ablation: 2.5297 Classic maze: 3.0658 Surgical ablation: 3.0425 Percutaneous ablation: 2.9593	**Incremental cost-effectiveness ratio compared with previous (non-dominated) strategy):** £ per QALY gained (deterministic) **Permanent AF** Classic maze versus no ablation: £1343 Surgical ablation: dominated by Classic Maze Percutaneous ablation: dominated by surgical ablation **Persistent AF** Classic maze versus no ablation: £3471 Surgical ablation versus classic maze: £40251

Time horizon:5 years **Treatment effect duration:** 5 years **Discounting:** Costs = 3.5% ; Outcomes =3.5%	M = NR **Intervention 1:** No ablation **Intervention 2:** Classical Maze Procedure **Intervention 3:** Surgical Ablation **Intervention 4:** Percutaneous ablation	Surgical ablation: 4487 Percutaneous ablation: 5497 **Paroxysmal AF** No ablation: 2317 Classic maze: 3173 Surgical ablation: 4457 Percutaneous ablation: 5438 (CI NR; p = NR) **Currency & cost year:** 2005 UK pounds **Cost components incorporated:** Maze procedure: £1025 Percutaneous ablation £3468 Cardiac death: £1227 Acute stroke: £3978 Stroke follow up per 3 months : £455 Pacemaker: £3445 Surgical ablation: £2500 Pacemaker follow up per 3 months: £78 Drug cost for AF per 3 months: £28	**Persistent AF** No ablation: 2.8835 Classic maze: 3.1385 Surgical ablation: 3.1747 Percutaneous ablation: 3.0665 **Paroxysmal AF** No ablation: 2.8843 Classic maze: 3.1704 Surgical ablation: 3.2056 Percutaneous ablation: 3.1285	Percutaneous ablation: dominated by surgical ablation **Paroxysmal AF** Classic maze versus no ablation: £2992 Surgical ablation versus classic maze: £36477 Percutaneous ablation: dominated by surgical ablation **Analysis of uncertainty:** No probabilistic sensitivity analysis performed **One way deterministic analyses:** Increased risk of early mortality and stroke in the MAZE and surgical ablation group reduced cost effectiveness, however the ICER remained below £20,000 when compared to no ablation. Note this analysis used a 5 year horizon. Increasing the cost of complications, changing the discount rate to 6% and changing the utility of post stroke states were reported to have minimal impact on cost effectiveness. If surgical ablation compared to no ablation is to remain cost effective using the £20K threshold, utility in the AF health states needs to be below 0.97, 0.98 and 0.98 in the permanent, persistent and paroxysmal subgroups respectively. Change in utility values for AF and post stroke states did not change the conclusion that the MAZE procedure was optimal. If percutaneous ablation compared to no ablation is to remain cost effective using the £20K threshold, utility in the AF health states needs to be below 0.92, 0.89 and 0.84 in the permanent, persistent and paroxysmal subgroups respectively (read from graph) Use of a 10 year horizon did not change the conclusions of the analysis, with a reduction of the ICER by 50% for all treatment options compared with no ablation. Percutaneous ablation remained a dominated strategy. Cost of the initial procedure by ±50% led to a 50% change in the ICER. Percutaneous ablation was most sensitive strategy to a change in cost of the procedure (inspection of graph).
Data sources				
Health outcomes: A retrospective single centre study informed clinical effectiveness for the MAZE procedure (Raanani et al. 2001), a multicentre trial informed effectiveness of surgical ablation (Ninet et al. 2005); Two single centre observational trials informed clinical effectiveness of no ablation (Eguchi et al. 2005 and				

Raanani et al. 2001, and a sing observational case finding study informed effectiveness of percutaneous ablation (Pappone et al. 2001). Two RCTs were identified but not used to inform effectiveness of surgical ablation due HIFU assistance being reported. Catheter ablation included the additional cost of the device. The respective 3 month recurrence free rate for conventional therapy was 23%, 57% and 57% for permanent , persistent and paroxysmal AF .The respective 3 month recurrence free rate for MAZE was 85%, 90% and 95% for permanent , persistent and paroxysmal AF. The respective 3 month recurrence free rate for surgical ablation was 81%, 95% and 100% for permanent, persistent and paroxysmal AF. The respective 3 month recurrence free rate for catheter ablation was 72%, 79% and 89% for permanent, persistent and paroxysmal AF.

Quality-of-life weights: The Euro Heart Survey EQ5D values were provided by investigators (not published). **Cost sources:** NHS reference costs, British National Formulary, and expert opinion, Clarke (2003) and Kavanagh (1999). Utility applied in an AF state varied from 00.69-1. Utility applied to major, moderate and minor stroke states were 0.52, 0.68 and 0.87 respectively. Bleeding and complications assumed only to affect utility in acute phase and a penalty of 0 utility is applied for 1 week.

Comments

Source of funding: Unrestricted grant from St Jude Medical. **Limitations:** Uncertain whether comparators appropriate given MAZE procedure is not common practice. It is uncertain whether the definitions used for type of AF (permanent, persistent and paroxysmal AF) in the study applicable to current understanding. Incremental analysis was performed by NCGC using total costs and QALYs presented (the study reported results using no ablation as reference), no probabilistic analysis performed, lifetime horizon was not adopted and rate of stroke was equal for all options. If higher rates of early stroke and mortality were used for surgical options and a lifetime perspective was used, it is uncertain whether these options would remain optimal. However, it is likely all options would be cost effective in comparison to no ablation. It is unclear whether the model oversimplified the need for anticoagulation and stroke risk for all strategies. **Other:** Health states consisted of complication free procedure, procedure with complications, mortality, stroke, cardiac tamponade or bleeding leading to intervention and pacemaker. Ablation could lead to NSR or continued AF requiring ablation or pharmaceutical treatment.

Overall applicability*: Directly applicable Overall quality: Potentially Limitations**

Abbreviations: CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 149: van Breugel 2011

N. H. van Breugel, E. Bidar, B. A. Essers, F. H. Nieman, R. E. Accord, J. L. Severens, R. Vrakking, and J. G. Maessen. Cost-effectiveness of ablation surgery in patients with atrial fibrillation undergoing cardiac surgery. Interact Cardiovasc Thorac Surg 12 (3):394-398, 2011.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome =	**Population:** Patients with AF undergoing	**Total costs (direct healthcare costs only):** **Intervention 1:**	**QALYs (mean per patient):** Intervention	**ICER (Intvn 2 versus Intvn 1) [Applying lower and upper confidence interval of direct costs]:** **€** 71650 per QALY gained (via bootstrap) [**€** 46350 - **€** 98800]

QALY) **Study design:** Prospective multicentre RCT (n=150) **Approach to analysis:** Within trial analysis with bootstrapping to assess uncertainty **Perspective:** Dutch societal, however payer perspective possible due to disaggregation of costs. **Time horizon:**1 year follow up **Treatment effect duration:** 1 year **Discounting:** Not applicable	usual cardiac surgery (n=132) **Cohort settings:** Mean age = NR M = NR **Intervention 1:** Concomitant surgical microwave ablation with usual cardiac surgery **Intervention 2:** Usual cardiac surgery	**€18390 (SD €5189)** £13 365 (SD £3771) Intervention 2: **€14091 (SD €4389)** £**10241** (SD £3190) Mean difference =**€**4299 (CI **€**2781 to **€**5928; p = NR) **Currency & cost year:** 2004 Euros **Cost components incorporated:** Direct healthcare costs included general practice costs including home visits, consultant consultation, emergency hospital visits, blood tests and diagnostic examinations, physiotherapist, domestic care. Direct non healthcare costs included informal care. Indirect healthcare costs included opportunity cost of paid and voluntary work.	1: 0.75 Intervention 2: 0.69 Mean difference =**0.06** (CI **= NR**; p = NR)	£53,167 per QALY gained (via bootstrap) [£33683 - £71800] **Analysis of uncertainty:** 92% of bootstrap replications showed concurrent ablation to be more costly and more effective than normal surgery. 8% of bootstrap replications showed concurrent ablation to be more costly and less effective than usual cardiac surgery. The ICER was below £20,000 (€27519) in approximately 8% of bootstrap replications (inspection of graph).
Data sources				
Health outcomes: Treatment effect estimated using results from the same RCT in which costing was conducted. **Quality-of-life weights:** EuroQol questionnaire transformed to utility using Dolan algorithm. **Cost sources:** Hospital information systems, empirical time registrations and hospital finance department. Standardised cost prices from the Dutch manual in healthcare research and the Dutch Pharmacotherapeutic Compass was used for drug costing				

Comments
Source of funding: University Hospital Maastricht **Limitations:** Health effects and resource use estimated from only one source. Short time horizon of one year will not take into account downstream effects and costs. The impact of adverse events was not detailed specifically. **Other:** Patients were reported to have similar characteristics, however no detail was provided on this or the actual intervention itself within the published paper. The EuroQoL health questionnaire was given at baseline, 3,6, and 12 months to calculate the QALY.
Overall applicability*: Partially applicable Overall quality: Potentially Serious Limitations**

Abbreviations: CI = 95% confidence interval; CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.15 Catheter versus surgical ablation

There were no included studies for this review.

H.16 Pace and ablate

There were no included studies for this review.

H.17 Acute

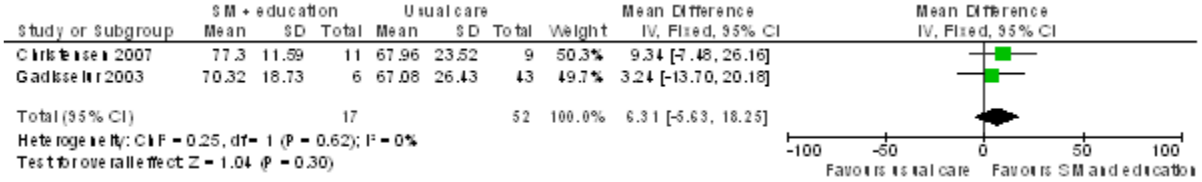
There were no included studies for this review.

Appendix I: Forest plots

I.1 Education

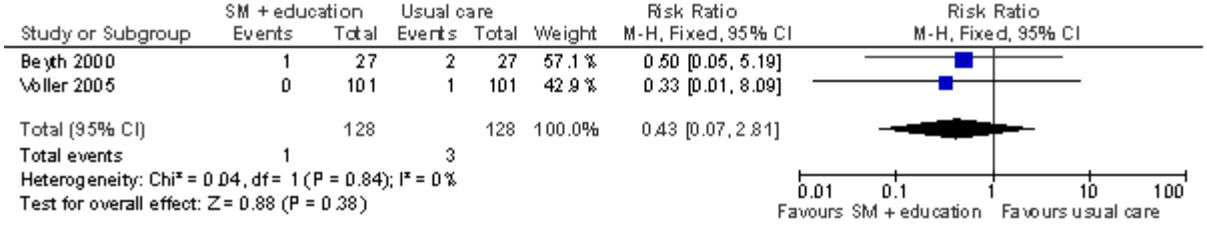
I.1.1 Self-monitoring and education versus usual care

Figure 1: Time in therapeutic range (TTR)



Clarkesmith DE, Pattison HM, Lane DA. Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation (Review).Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD008600. DOI: 10.1002/14651858.CD008600.pub2 Copyright Cochrane Collaboration, reproduced with permission.

Figure 2: Stroke or thromboembolic events



I.1.2 Education versus usual care

Figure 3: TTR

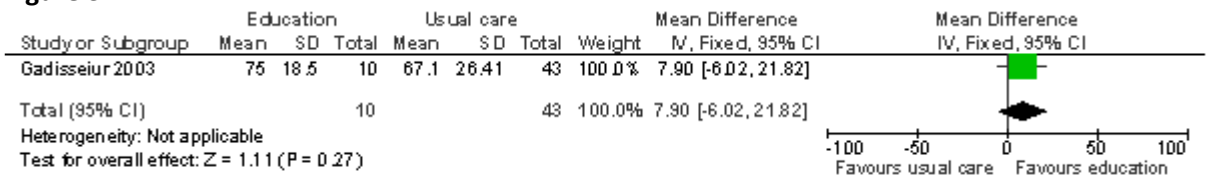
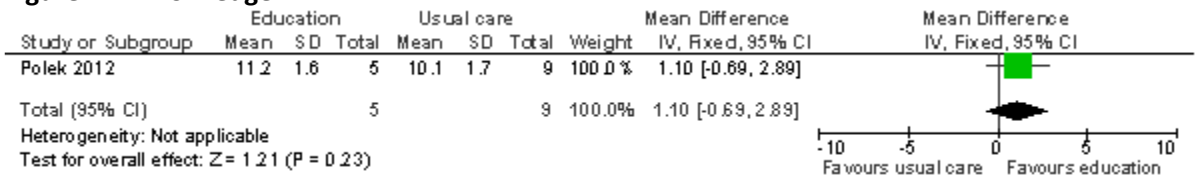


Figure 4: Knowledge



I.1.3 Decision aids versus usual care

Figure 5: Hospitalisation

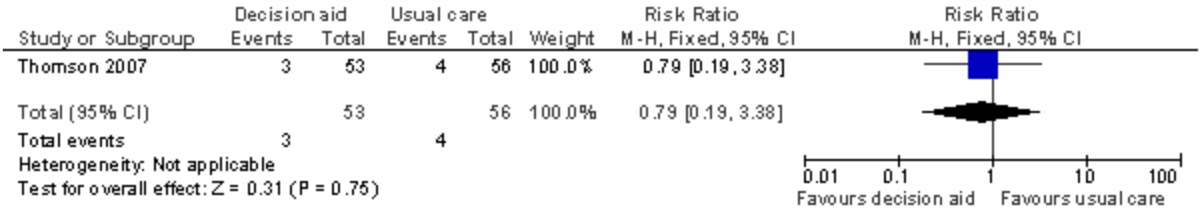
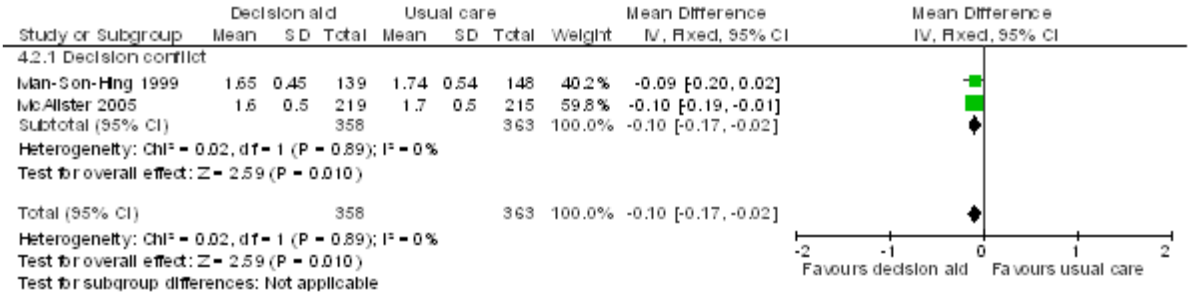
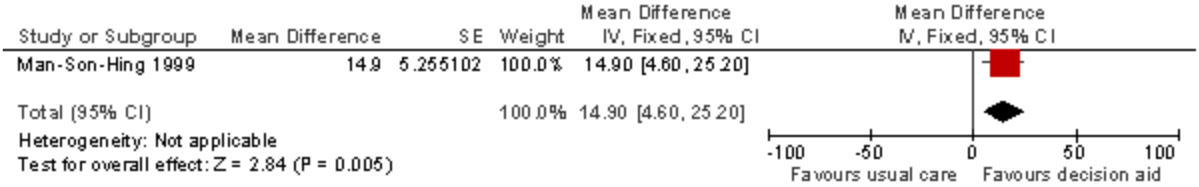


Figure 6: Decision conflict



Clarkesmith DE, Pattison HM, Lane DA. Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation (Review).Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD008600. DOI: 10.1002/14651858.CD008600.pub2 Copyright Cochrane Collaboration, reproduced with permission.

Figure 7: Knowledge – warfarin related



I.2 Referral to specialist AF services compared to usual care

Figure 8: Cardiovascular mortality

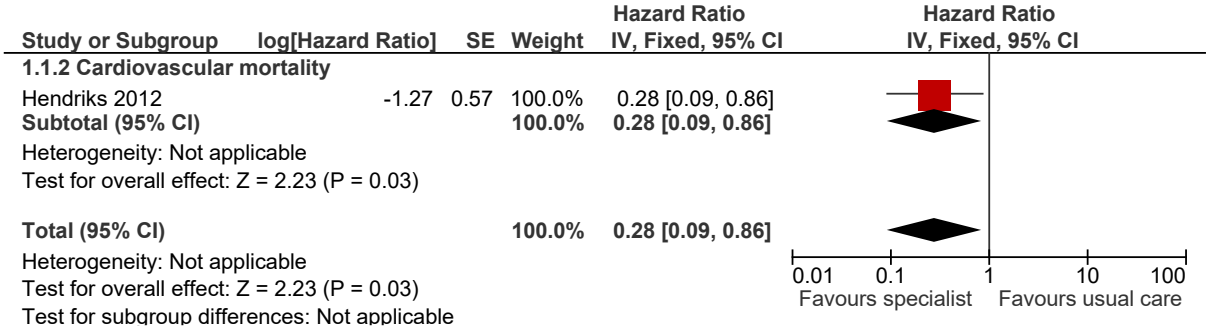


Figure 9: Stroke or thromboembolic event

Study or Subgroup	Specialist Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hendriks 2012	4	356	11	356	100.0%	0.36 [0.12, 1.13]
Total (95% CI)		**356**		**356**	**100.0%**	**0.36 [0.12, 1.13]**
Total events	4		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)

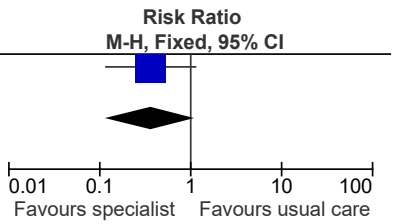


Figure 10: Cardiovascular hospitalisation

Study or Subgroup	Specialist Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hendriks 2012	48	356	68	356	100.0%	0.71 [0.50, 0.99]
Total (95% CI)		**356**		**356**	**100.0%**	**0.71 [0.50, 0.99]**
Total events	48		68			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.01 (P = 0.04)

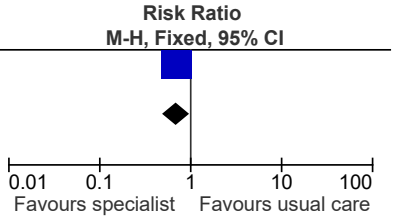


Figure 11: Guideline adherence

Study or Subgroup	Specialist Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hendriks 2012	292	356	135	356	100.0%	2.16 [1.88, 2.49]
Total (95% CI)		**356**		**356**	**100.0%**	**2.16 [1.88, 2.49]**
Total events	292		135			

Heterogeneity: Not applicable
Test for overall effect: Z = 10.68 (P < 0.00001)

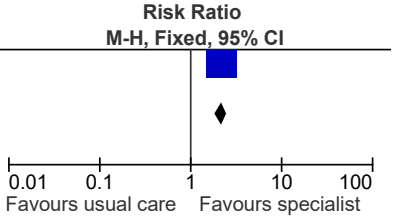
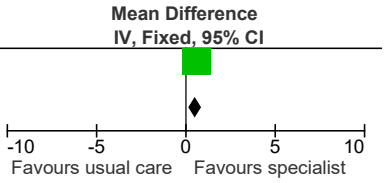


Figure 12: Disease awareness

Study or Subgroup	Specialist Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hendriks 2012	8.23	2.16	286	7.66	2.09	248	100.0%	0.57 [0.21, 0.93]
Total (95% CI)			**286**			**248**	**100.0%**	**0.57 [0.21, 0.93]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.09 (P = 0.002)



I.3 Stroke risk tools

Figure 13: Stroke

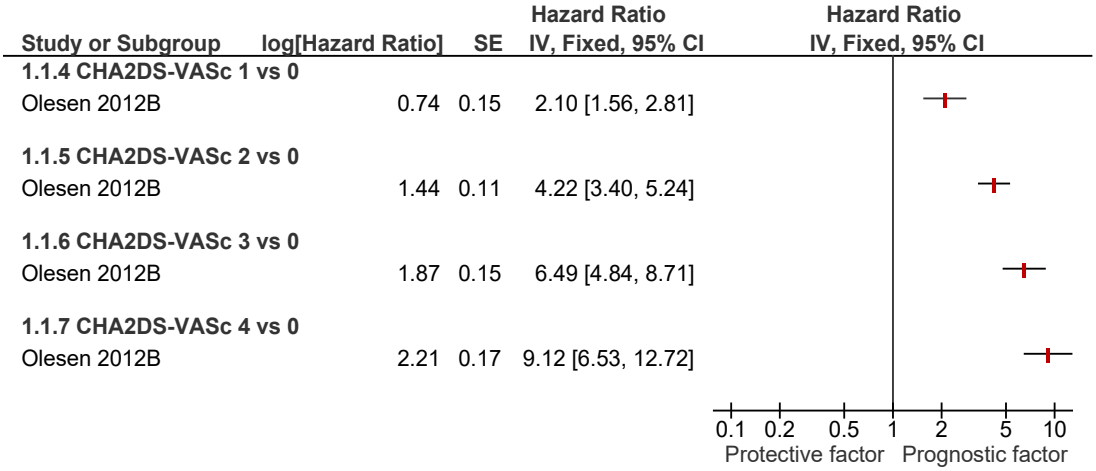


Figure 14: Stroke (continuous)

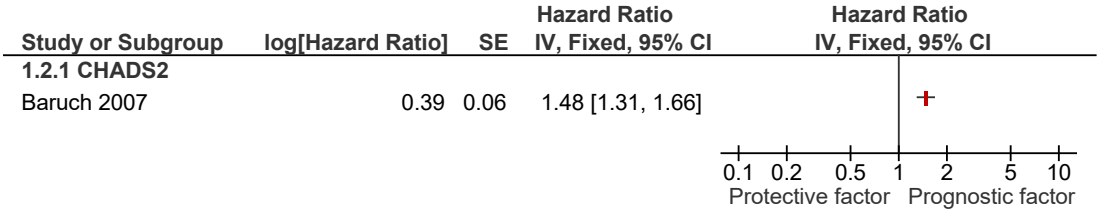


Figure 15: Stroke – 3 strata continuous

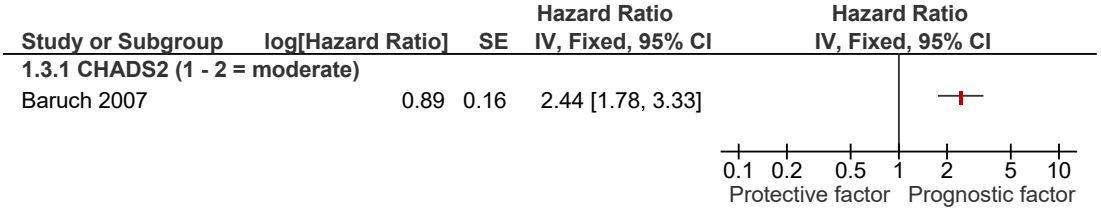


Figure 16: Thromboembolism

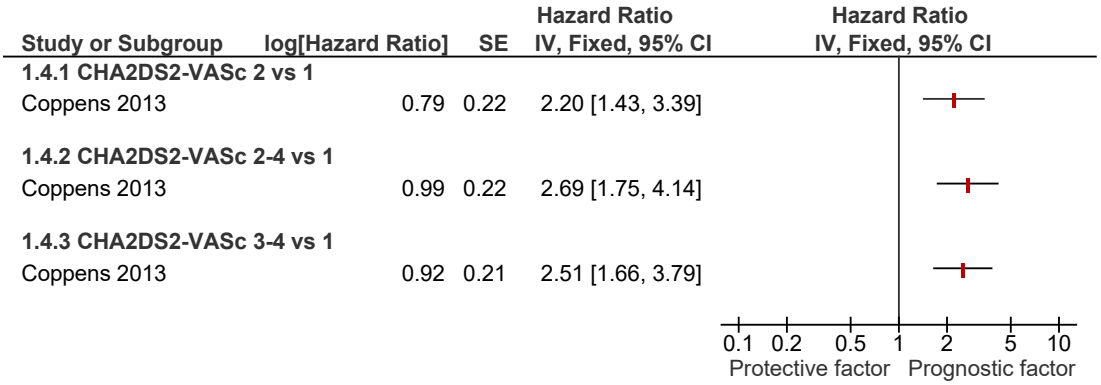


Figure 17: Thromboembolism – 3 strata continuous

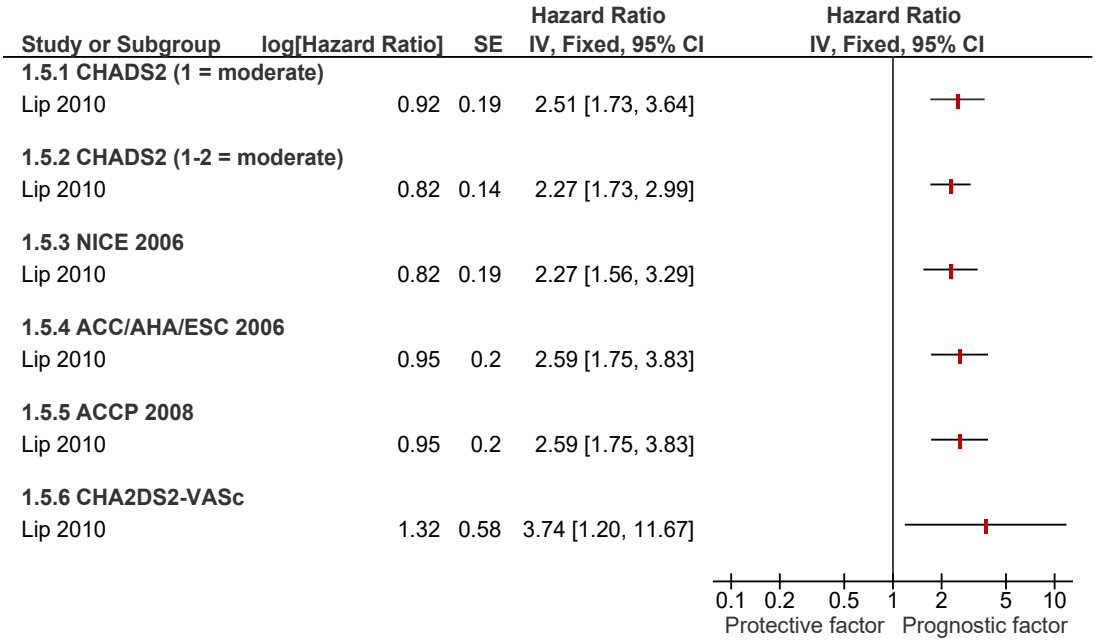
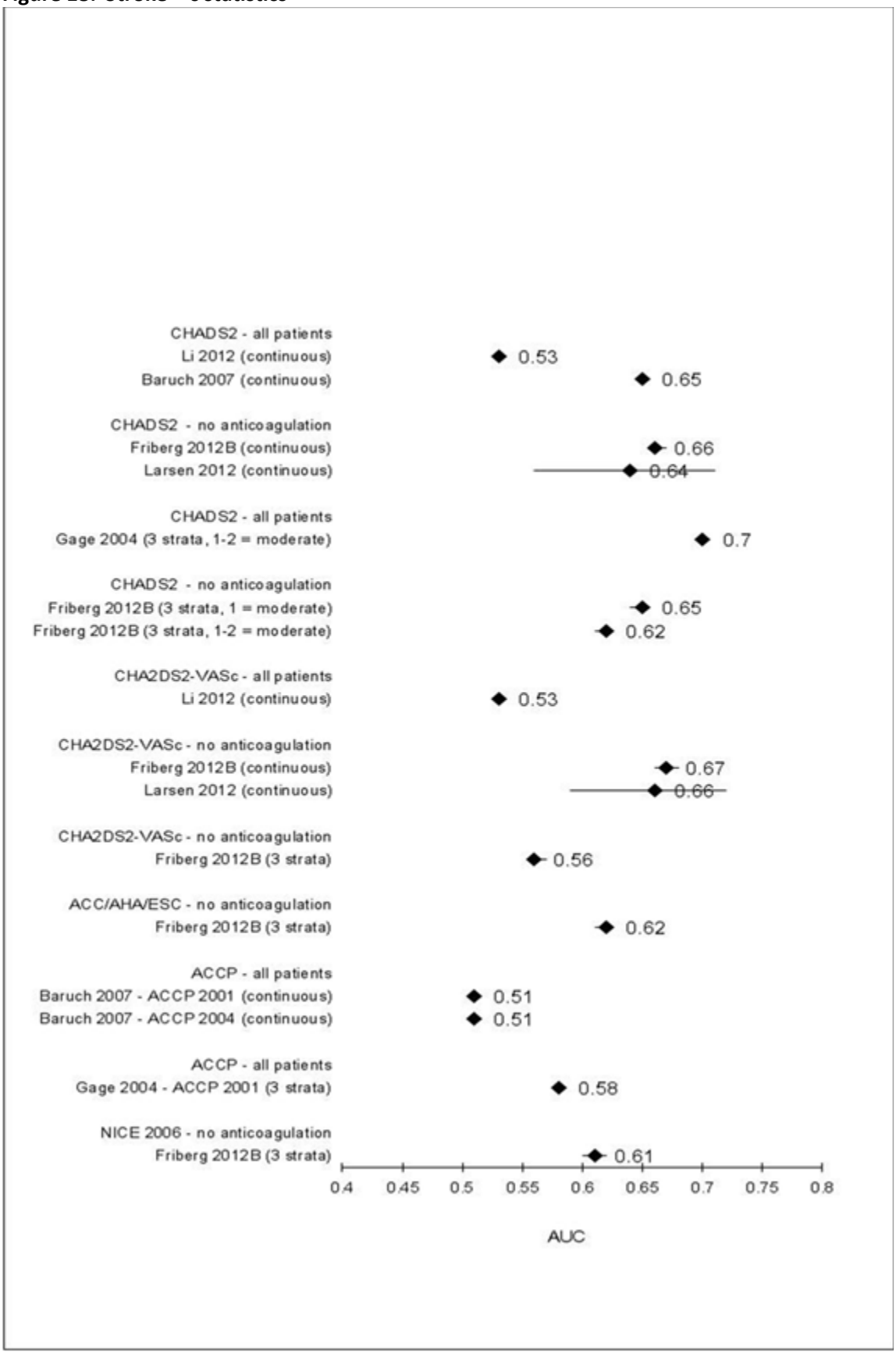
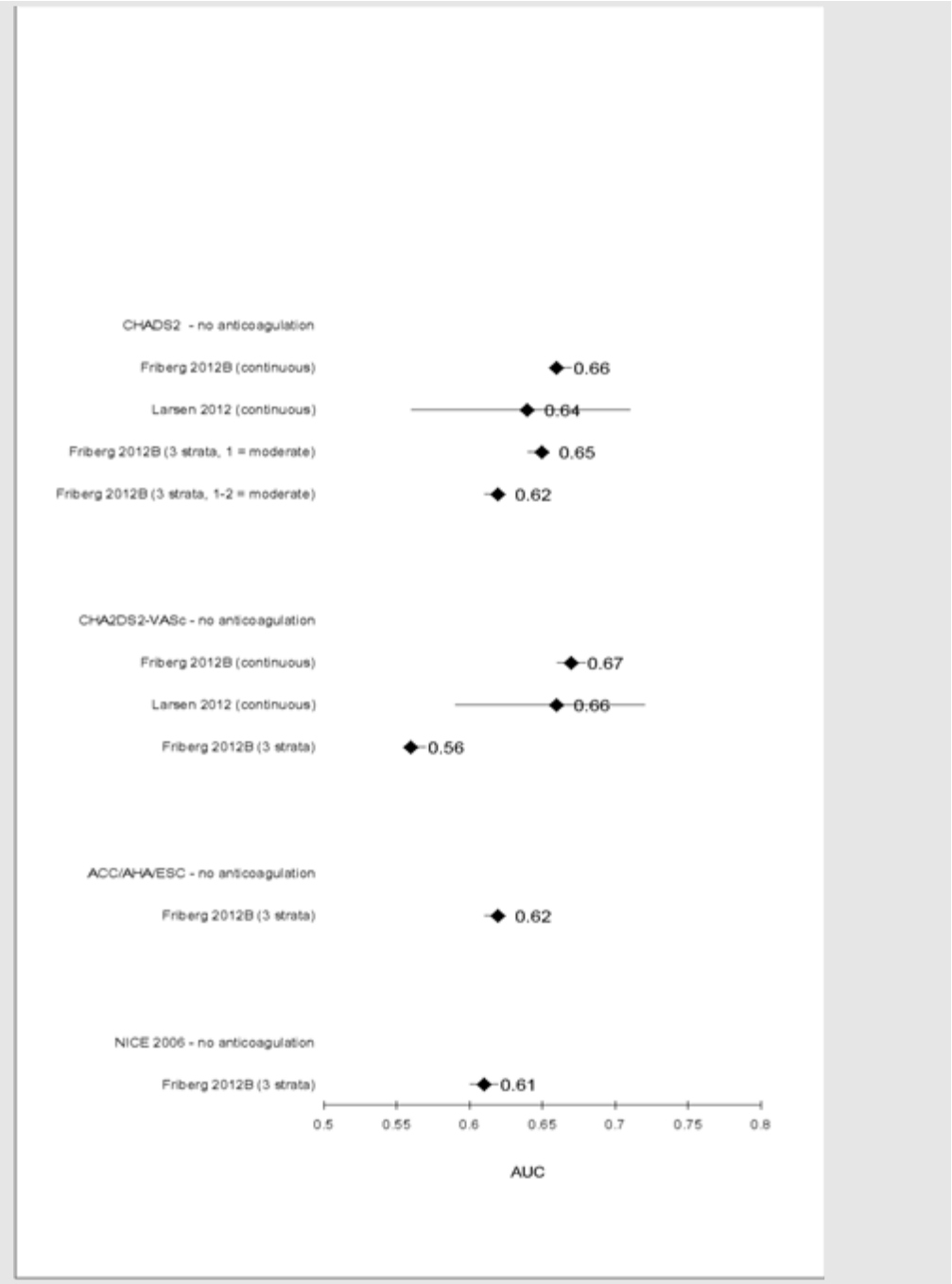


Figure 18: Stroke – c statistics



Stroke – c statistics			
Study	**Lower CI**	**Point estimate**	**Upper CI**
CHADS2 - all patients			
Li 2012 (continuous)	-	0.53	-
Baruch 2007 (continuous)	-	0.65	-
CHADS2 - no anticoagulation			
Friberg 2012B (continuous)	0.66	0.66	0.67
Larsen 2012 (continuous)	0.56	0.64	0.71
CHADS2 - all patients			
Gage 2004 (3 strata, 1-2 = moderate)	-	0.7	-
CHADS2 - no anticoagulation			
Friberg 2012B (3 strata, 1 = moderate)	0.64	0.65	0.65
Friberg 2012B (3 strata, 1-2 = moderate)	0.61	0.62	0.62
CHA2DS2-VASc - all patients			
Li 2012 (continuous)	-	0.53	-
CHA2DS2-VASc - no anticoagulation			
Friberg 2012B (continuous)	0.66	0.67	0.68
Larsen 2012 (continuous)	0.59	0.66	0.72
CHA2DS2-VASc - no anticoagulation			
Friberg 2012B (3 strata)	0.56	0.56	0.57
ACC/AHA/ESC - no anticoagulation			
Friberg 2012B (3 strata)	0.61	0.62	0.62
ACCP - all patients			
Baruch 2007 - ACCP 2001 (continuous)	-	0.51	-
Baruch 2007 - ACCP 2004 (continuous)	-	0.51	-
ACCP - all patients			
Gage 2004 - ACCP 2001 (3 strata)	-	0.58	-
NICE 2006 - no anticoagulation			
Friberg 2012B (3 strata)	0.6	0.61	0.62

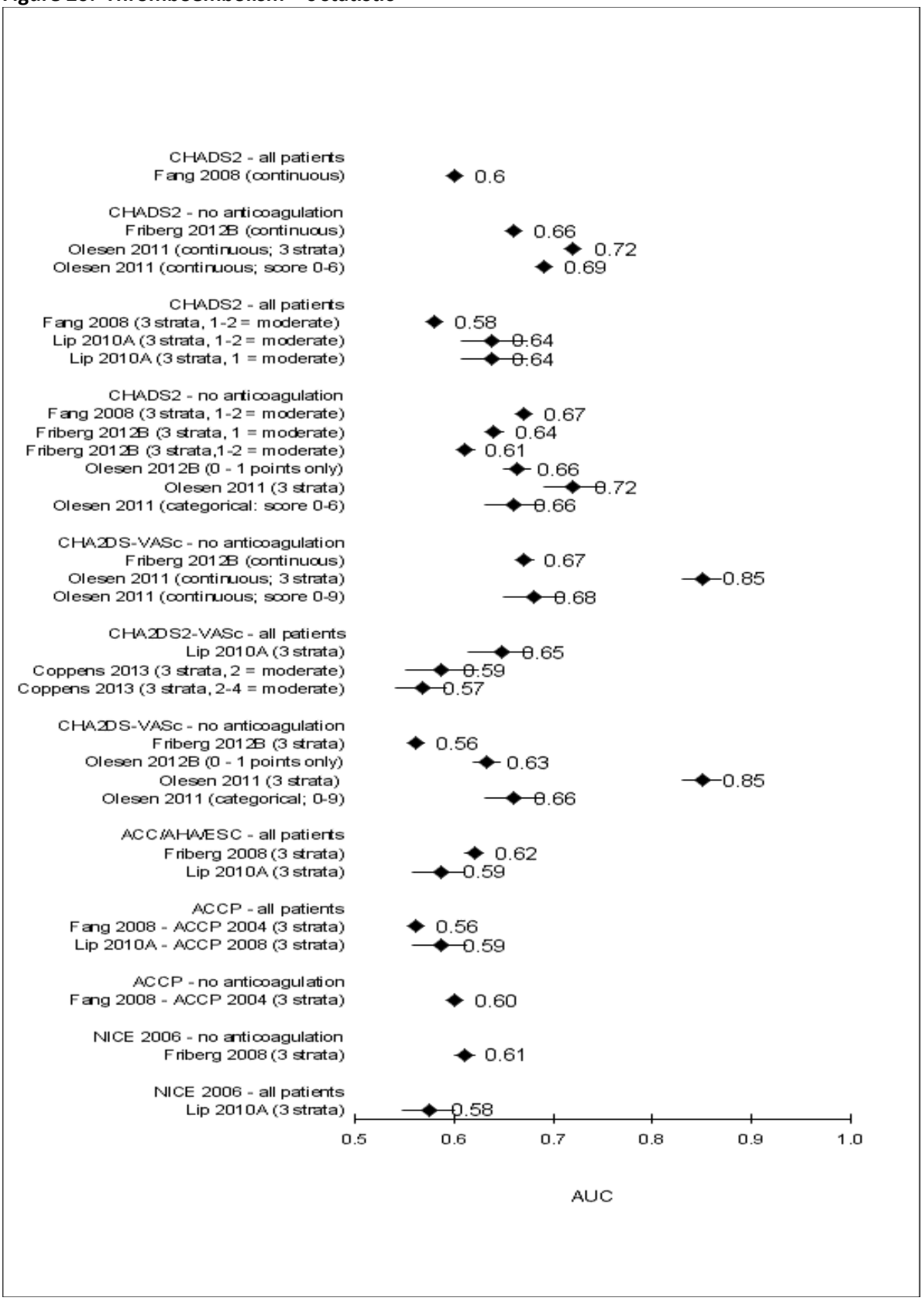
Figure 19: Stroke – no anticoagulation (c statistics)



Stroke – no anticoagulation - c statistics			

CHADS2 - no anticoagulation			
CHA2DS2-VASc - no anticoagulation			
ACC/AHA/ESC - no anticoagulation			
NICE 2006 - no anticoagulation			
Stroke – no anticoagulation - c statistics			
Study	**Lower CI**	**Point estimate**	**Upper CI**
Friberg 2012B (continuous)	0.66	0.66	0.67
Larsen 2012 (continuous)	0.56	0.64	0.71
Friberg 2012B (3 strata, 1 = moderate)	0.64	0.65	0.65
Friberg 2012B (3 strata, 1-2 = moderate)	0.61	0.62	0.62
Friberg 2012B (continuous)	0.66	0.67	0.68
Larsen 2012 (continuous)	0.59	0.66	0.72
Friberg 2012B (3 strata)	0.56	0.56	0.57
Friberg 2012B (3 strata)	0.61	0.62	0.62
Friberg 2012B (3 strata)	0.6	0.61	0.62

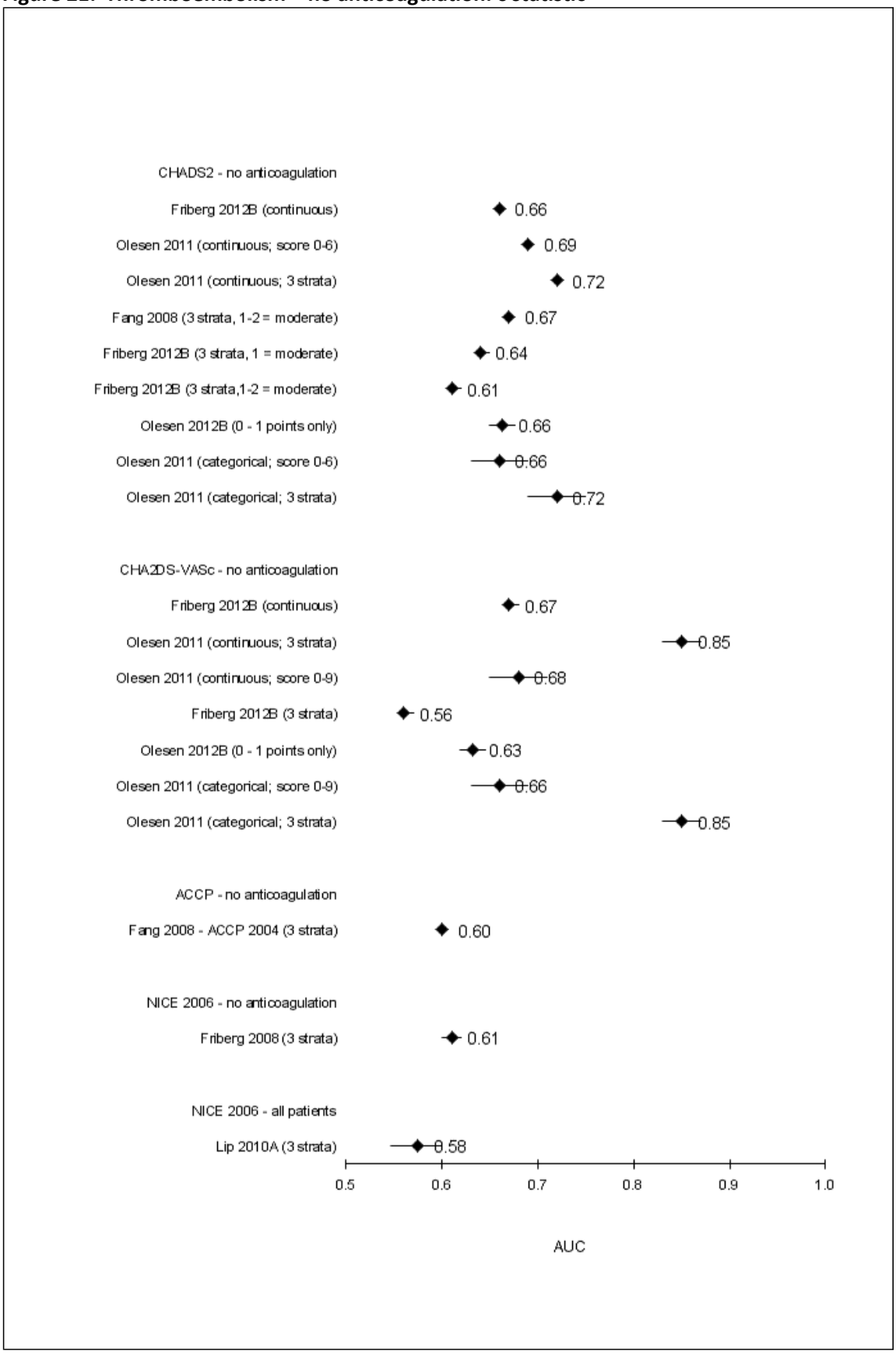
Figure 20: Thromboembolism – c statistic



Thromboembolism – c statistic			
Study	**Lower CI**	**Point estimate**	**Upper CI**
$CHADS_2$ - all patients			
Fang 2008 (continuous)	-	0.6	-
$CHADS_2$ - no anticoagulation			
Friberg 2012B (continuous)	0.65	0.66	0.66
Olesen 2011 (continuous; 3 strata)	0.69	0.72	0.75
Olesen 2011 (continuous; score 0-6)	0.66	0.69	0.72
$CHADS_2$ - all patients			
Fang 2008 (3 strata, 1-2 = moderate)	-	0.58	-
Lip 2010A (3 strata, 1-2 = moderate)	0.61	0.64	0.67
Lip 2010A (3 strata, 1 = moderate)	0.61	0.64	0.67
$CHADS_2$ - no anticoagulation			
Fang 2008 (3 strata, 1-2 = moderate)	-	0.67	-
Friberg 2012B (3 strata, 1 = moderate)	0.64	0.64	0.65
Friberg 2012B (3 strata,1-2 = moderate)	0.61	0.61	0.62
Olesen 2012B (0 - 1 points only)	0.65	0.66	0.68
Olesen 2011 (3 strata)	0.69	0.72	0.75
Olesen 2011 (categorical: score 0-6)	0.63	0.66	0.69
CHA_2DS_2-VASc - no anticoagulation			
Friberg 2012B (continuous)	0.67	0.67	0.68
Olesen 2011 (continuous; 3 strata)	0.83	0.85	0.87
Olesen 2011 (continuous; score 0-9)	0.65	0.68	0.71
CHA_2DS_2-VASc - all patients			
Lip 2010A (3 strata)	0.61	0.65	0.68
Coppens 2013 (3 strata, 2 = moderate)	0.55	0.59	0.62
Coppens 2013 (3 strata, 2-4 = moderate)	0.54	0.57	0.59
CHA_2DS_2-VASc - no anticoagulation			
Friberg 2012B (3 strata)	0.56	0.56	0.57
Olesen 2012B (0 - 1 points only)	0.62	0.63	0.65
Olesen 2011 (3 strata)	0.83	0.85	0.87
Olesen 2011 (categorical; 0-9)	0.63	0.66	0.69
ACC/AHA/ESC - all patients			
Friberg 2008 (3 strata)	0.61	0.62	0.62
Lip 2010A (3 strata)	0.56	0.59	0.61

Thromboembolism – c statistic			
ACCP - all patients			
Fang 2008 - ACCP 2004 (3 strata)	-	0.56	-
Lip 2010A - ACCP 2008 (3 strata)	0.56	0.59	0.61
ACCP - no anticoagulation			
Fang 2008 - ACCP 2004 (3 strata)	-	0.60	-
NICE 2006 - no anticoagulation			
Friberg 2008 (3 strata)	0.60	0.61	0.62
NICE 2006 - all patients			
Lip 2010A (3 strata)	0.55	0.58	0.60

Figure 21: Thromboembolism – no anticoagulation: c statistic



Thromboembolism – no anticoagulation, c statistic			
Study	**Lower CI**	**Point estimate**	**Upper CI**
CHADS2 - no anticoagulation			
Friberg 2012B (continuous)	0.65	0.66	0.66
Olesen 2011 (continuous; score 0-6)	0.66	0.69	0.72
Olesen 2011 (continuous; 3 strata)	0.69	0.72	0.75
Fang 2008 (3 strata, 1-2 = moderate)	-	0.67	-
Friberg 2012B (3 strata,1-2 = moderate)	0.61	0.61	0.62
Friberg 2012B (3 strata, 1 = moderate)	0.64	0.64	0.65
Olesen 2012B (0 - 1 points only)	0.65	0.66	0.68
Olesen 2011 (categorical: score 0-6)	0.63	0.66	0.69
Olesen 2011 (3 strata)	0.69	0.72	0.75
CHA2DS-VASc - no anticoagulation			
Friberg 2012B (continuous)	0.67	0.67	0.68
Olesen 2011 (continuous; 3 strata)	0.83	0.85	0.87
Olesen 2011 (continuous; score 0-9)	0.65	0.68	0.71
Friberg 2012B (3 strata)	0.56	0.56	0.57
Olesen 2012B (0 - 1 points only)	0.62	0.63	0.65
Olesen 2011 (categorical; 0-9)	0.63	0.66	0.69
Olesen 2011 (3 strata)	0.83	0.85	0.87
ACCP - no anticoagulation			
Fang 2008 - ACCP 2004 (3 strata)	-	0.60	-
NICE 2006 - no anticoagulation			
Friberg 2008 (3 strata)	0.60	0.61	0.62

I.4 Anticoagulation

I.4.1 Antiplatelet versus control

Figure 22: All-cause mortality

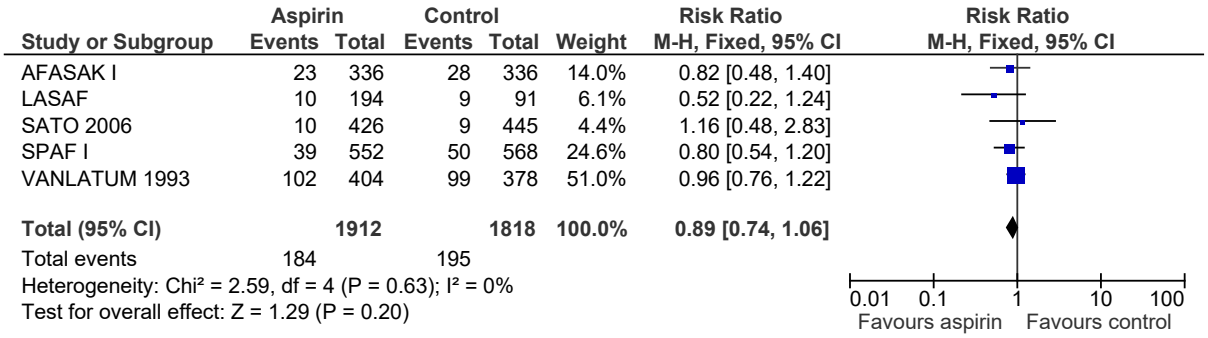


Figure 23: Mortality – hazard ratio

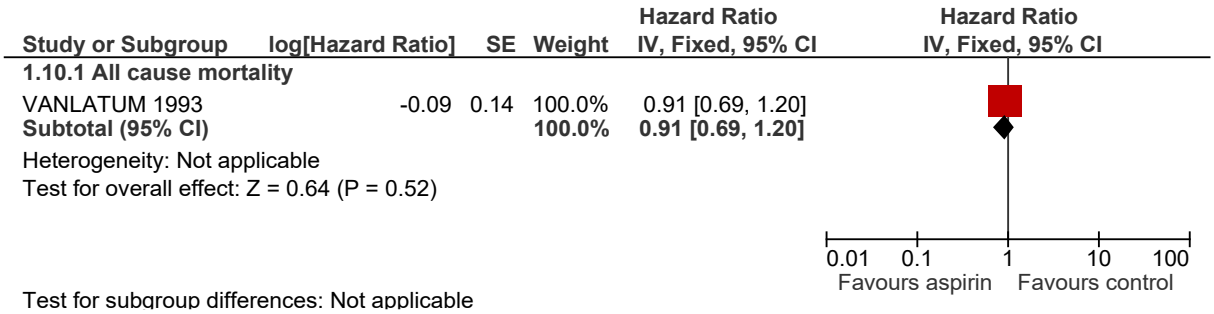


Figure 24: Ischaemic stroke

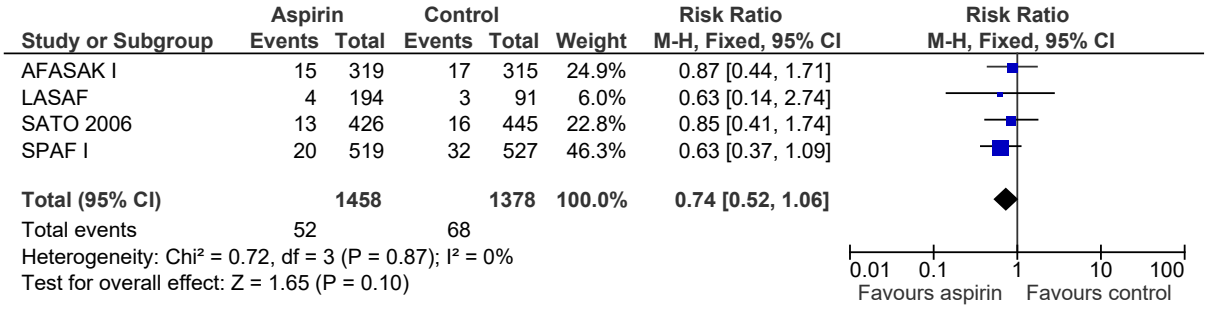


Figure 25: Intracranial haemorrhage

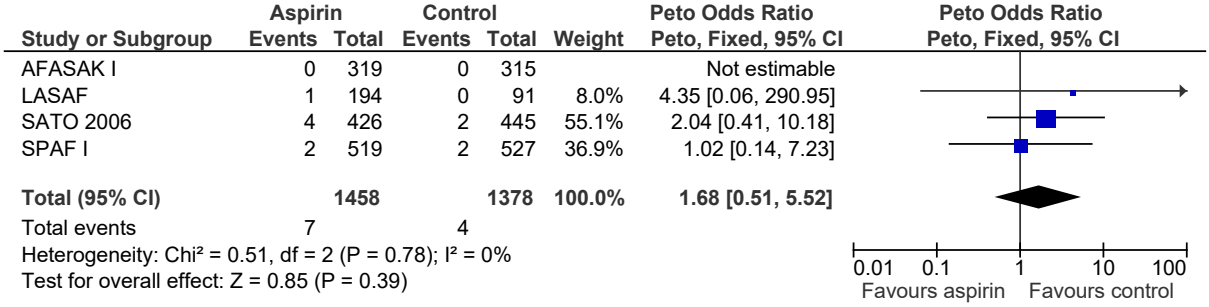


Figure 26: Systemic emboli

Study or Subgroup	Aspirin Events	Aspirin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK I	1	319	2	315	13.2%	0.49 [0.04, 5.42]
LASAF	0	194	0	91		Not estimable
SPAF I	3	519	4	527	26.0%	0.76 [0.17, 3.39]
VANLATUM 1993	6	404	9	378	60.9%	0.62 [0.22, 1.74]
Total (95% CI)		**1436**		**1311**	**100.0%**	**0.64 [0.29, 1.42]**
Total events	10		15			

Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.27)

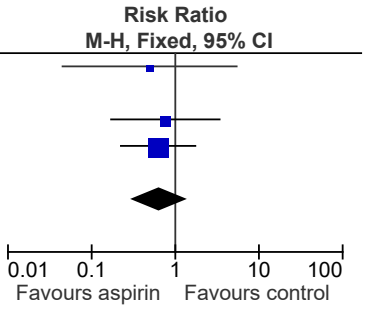
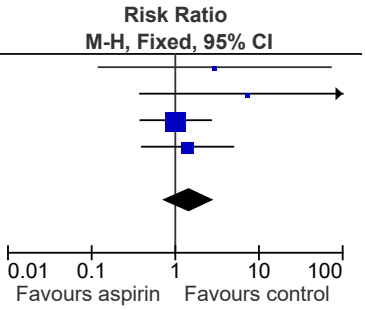


Figure 27: Major bleeding

Study or Subgroup	Aspirin Events	Aspirin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK I	1	319	0	315	3.9%	2.96 [0.12, 72.45]
SATO 2006	3	426	0	445	3.7%	7.31 [0.38, 141.13]
SPAF I	8	519	8	527	60.8%	1.02 [0.38, 2.69]
VANLATUM 1993	6	404	4	378	31.6%	1.40 [0.40, 4.93]
Total (95% CI)		**1668**		**1665**	**100.0%**	**1.45 [0.72, 2.92]**
Total events	18		12			

Heterogeneity: Chi² = 1.86, df = 3 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)



I.4.2 Anticoagulation versus control

Figure 28: All-cause mortality

Study or Subgroup	Anticoagulant Events	Anticoagulant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK I	20	335	28	336	19.0%	0.72 [0.41, 1.25]
BAATAF	11	212	26	208	17.8%	0.42 [0.21, 0.82]
CAFA	10	187	8	191	5.4%	1.28 [0.52, 3.16]
EAFT 1993	41	225	44	214	30.6%	0.89 [0.60, 1.30]
SPAF I	6	210	8	211	5.4%	0.75 [0.27, 2.13]
SPINAF	22	281	29	290	19.4%	0.78 [0.46, 1.33]
SPINAF	5	21	4	25	2.5%	1.49 [0.46, 4.84]
Total (95% CI)		**1471**		**1475**	**100.0%**	**0.78 [0.62, 0.98]**
Total events	115		147			

Heterogeneity: Chi² = 6.13, df = 6 (P = 0.41); I² = 2%
Test for overall effect: Z = 2.14 (P = 0.03)

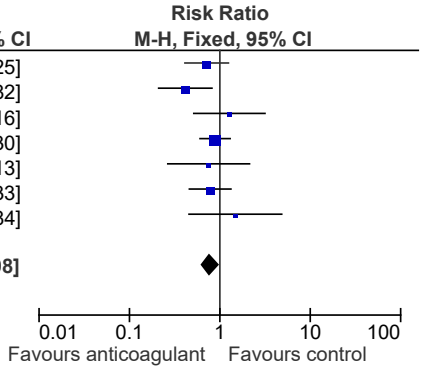


Figure 29: All-cause mortality – hazard ratio

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
4.3.1 Mortality - HR				
EAFT 1993	-0.2	0.22	100.0%	0.82 [0.53, 1.26]
Subtotal (95% CI)			**100.0%**	**0.82 [0.53, 1.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)

Total (95% CI)			**100.0%**	**0.82 [0.53, 1.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable

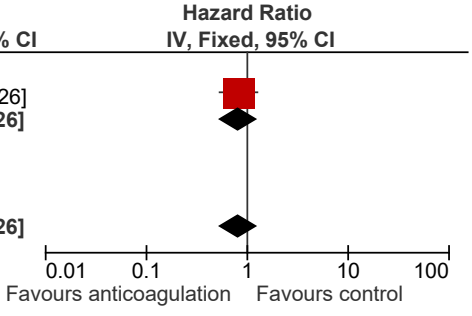


Figure 30: Ischaemic stroke

Study or Subgroup	Anticoagulant Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK I	6	315	17	315	23.5%	0.35 [0.14, 0.88]
BAATAF	2	205	11	201	15.3%	0.18 [0.04, 0.79]
CAFA	5	181	9	184	12.3%	0.56 [0.19, 1.65]
SPAF I	5	193	13	194	17.9%	0.39 [0.14, 1.06]
SPINAF	4	260	19	265	26.0%	0.21 [0.07, 0.62]
SPINAF	2	21	4	25	5.0%	0.60 [0.12, 2.93]
Total (95% CI)		**1175**		**1184**	**100.0%**	**0.33 [0.21, 0.53]**
Total events	24		73			

Heterogeneity: Chi² = 2.86, df = 5 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.74 (P < 0.00001)

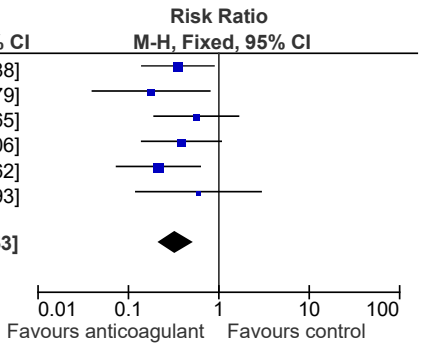


Figure 31: Haemorrhagic stroke

Study or Subgroup	Anticoagulant Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK I	0	315	0	315		Not estimable
BAATAF	1	205	0	201	14.5%	2.94 [0.12, 71.79]
CAFA	1	181	0	184	14.2%	3.05 [0.13, 74.37]
SPAF I	2	193	2	194	57.1%	1.01 [0.14, 7.06]
SPINAF	0	21	0	25		Not estimable
SPINAF	1	260	0	265	14.2%	3.06 [0.13, 74.71]
Total (95% CI)		**1175**		**1184**	**100.0%**	**1.87 [0.51, 6.82]**
Total events	5		2			

Heterogeneity: Chi² = 0.65, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.34)

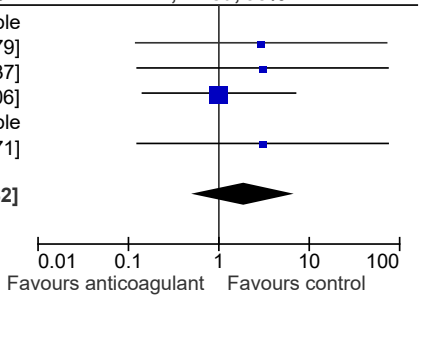


Figure 32: Systemic embolic

Study or Subgroup	Anticoagulant Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
AFASAK I	0	315	2	315	13.4%	0.13 [0.01, 2.16]
BAATAF	0	205	0	201		Not estimable
CAFA	1	181	2	184	20.0%	0.52 [0.05, 5.03]
EAFT 1993	1	225	4	214	33.2%	0.28 [0.05, 1.65]
SPAF I	0	193	2	194	13.4%	0.14 [0.01, 2.17]
SPINAF	2	260	1	265	20.0%	1.99 [0.21, 19.22]
Total (95% CI)		**1379**		**1373**	**100.0%**	**0.39 [0.14, 1.07]**
Total events	4		11			

Heterogeneity: Chi² = 3.30, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.83 (P = 0.07)

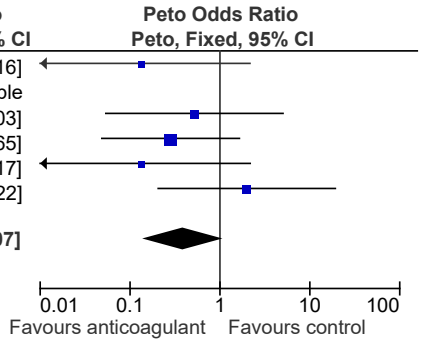
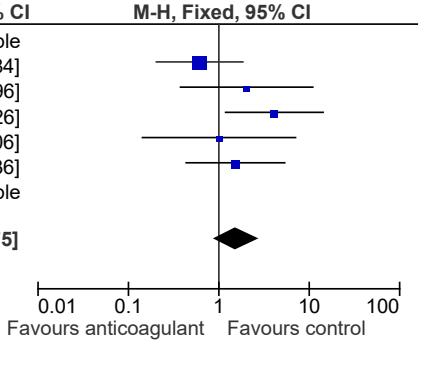


Figure 33: Major bleeding

Study or Subgroup	Anticoagulant Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK I	0	315	0	315		Not estimable
BAATAF	5	205	8	201	42.3%	0.61 [0.20, 1.84]
CAFA	4	181	2	184	10.4%	2.03 [0.38, 10.96]
EAFT 1993	13	225	3	214	16.1%	4.12 [1.19, 14.26]
SPAF I	2	193	2	194	10.4%	1.01 [0.14, 7.06]
SPINAF	6	260	4	265	20.7%	1.53 [0.44, 5.36]
SPINAF	0	21	0	25		Not estimable
Total (95% CI)		**1400**		**1398**	**100.0%**	**1.56 [0.88, 2.75]**
Total events	30		19			

Heterogeneity: Chi² = 5.41, df = 4 (P = 0.25); I² = 26%
Test for overall effect: Z = 1.52 (P = 0.13)



I.4.3 Anticoagulant versus antiplatelet

Figure 34: All-cause mortality – hazard ratio

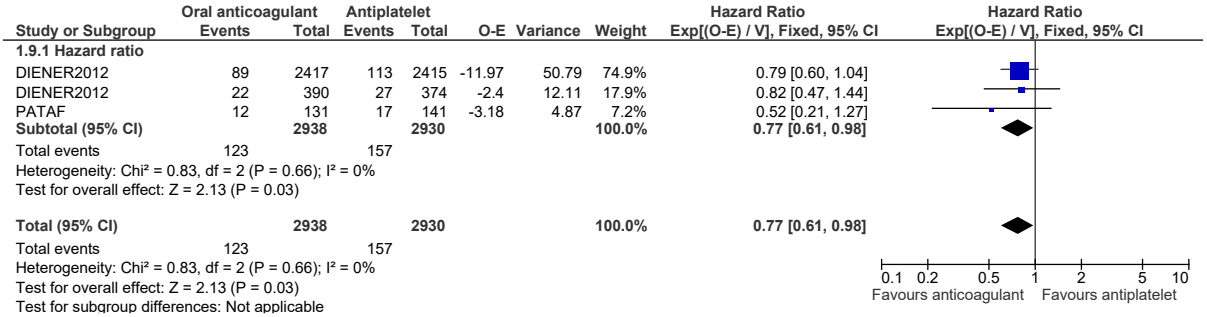


Figure 35: All-cause mortality

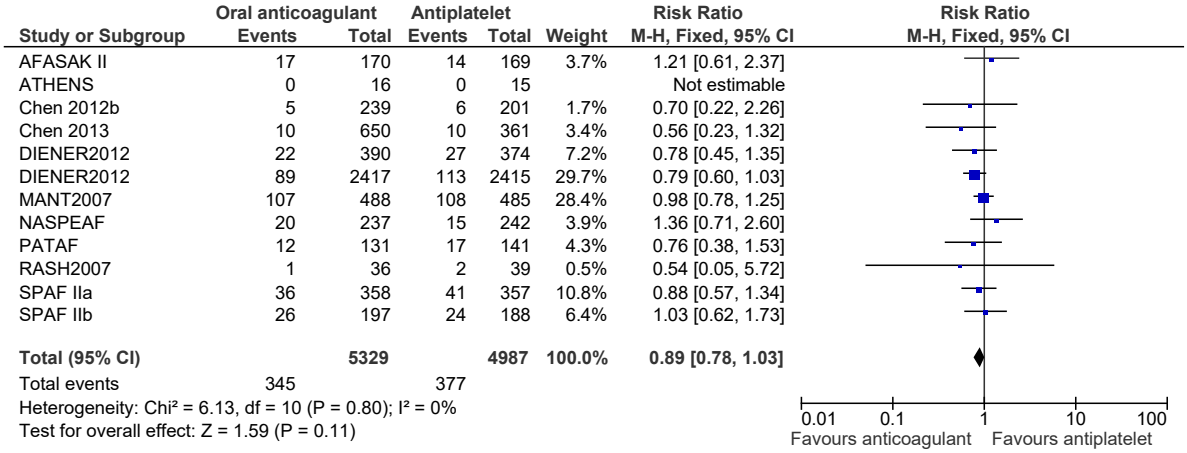


Figure 36: Ischaemic stroke

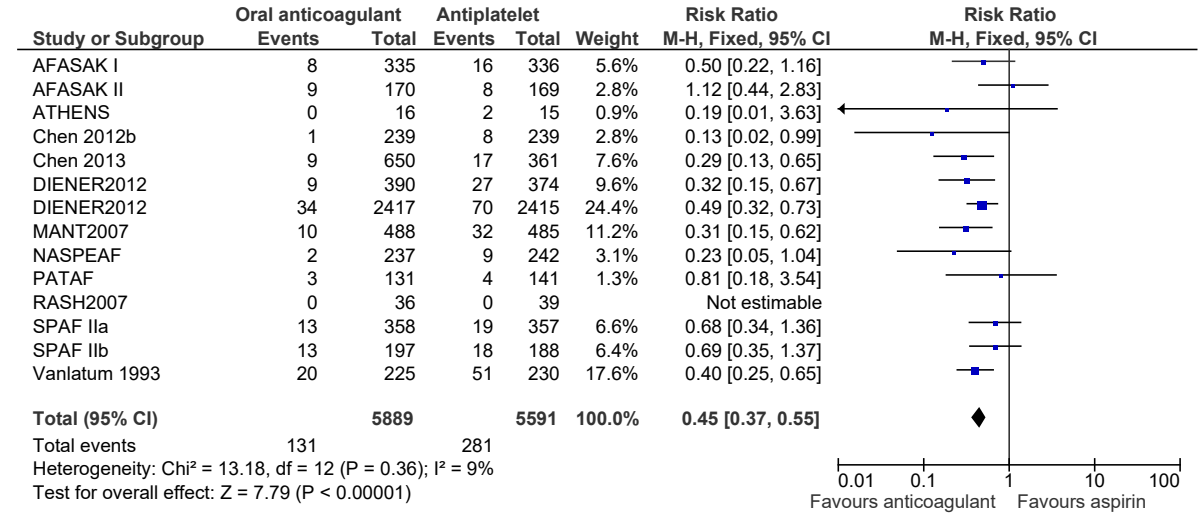


Figure 37: Haemorrhagic stroke

Study or Subgroup	Oral anticoagulant Events	Total	Antiplatelet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK I	1	335	0	336	1.7%	3.01 [0.12, 73.60]
AFASAK II	1	170	1	169	3.5%	0.99 [0.06, 15.76]
ATHENS	1	16	0	15	1.8%	2.82 [0.12, 64.39]
Chen 2012b	1	239	0	201	1.9%	2.52 [0.10, 61.64]
Chen 2013	16	650	3	361	13.5%	2.96 [0.87, 10.10]
DIENER2012	1	390	4	374	14.3%	0.24 [0.03, 2.14]
DIENER2012	5	2417	5	2415	17.5%	1.00 [0.29, 3.45]
MANT2007	6	488	5	585	15.9%	1.44 [0.44, 4.68]
NASPEAF	4	237	2	242	6.9%	2.04 [0.38, 11.04]
PATAF	0	131	0	141		Not estimable
RASH2007	0	36	0	39		Not estimable
SPAF IIa	6	358	2	357	7.0%	2.99 [0.61, 14.72]
SPAF IIb	6	197	3	188	10.7%	1.91 [0.48, 7.52]
Vanlatum 1993	0	225	1	230	5.2%	0.34 [0.01, 8.32]
Total (95% CI)		**5889**		**5653**	**100.0%**	**1.60 [1.00, 2.56]**
Total events	48		26			

Heterogeneity: Chi² = 6.56, df = 11 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)

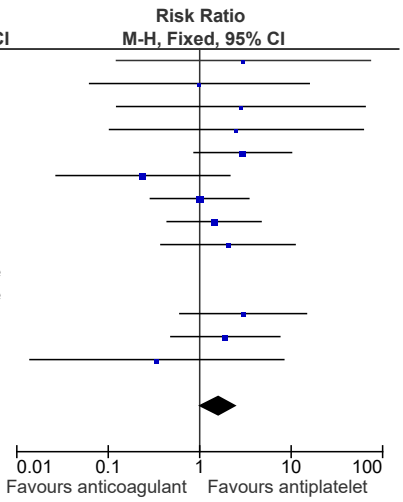


Figure 38: Major bleeding

Study or Subgroup	Oral anticoagulant Events	Total	Antiplatelet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK I	1	335	1	336	1.1%	1.00 [0.06, 15.97]
AFASAK II	2	170	4	169	4.5%	0.50 [0.09, 2.68]
ATHENS	0	16	0	15		Not estimable
Chen 2012b	6	239	1	201	1.2%	5.05 [0.61, 41.57]
Chen 2013	9	650	5	361	7.2%	1.00 [0.34, 2.96]
DIENER2012	14	390	11	374	12.6%	1.22 [0.56, 2.65]
DIENER2012	30	2417	28	2415	31.4%	1.07 [0.64, 1.79]
MANT2007	19	488	20	485	22.5%	0.94 [0.51, 1.75]
NASPEAF	6	232	0	235	0.6%	13.17 [0.75, 232.41]
PATAF	1	131	0	141	0.5%	3.23 [0.13, 78.53]
RASH2007	0	36	3	39	3.8%	0.15 [0.01, 2.89]
SPAF IIa	12	358	8	357	9.0%	1.50 [0.62, 3.62]
SPAF IIb	9	197	3	188	3.4%	2.86 [0.79, 10.41]
Vanlatum 1993	13	225	2	230	2.2%	6.64 [1.52, 29.11]
Total (95% CI)		**5884**		**5546**	**100.0%**	**1.35 [1.03, 1.76]**
Total events	122		86			

Heterogeneity: Chi² = 15.95, df = 12 (P = 0.19); I² = 25%
Test for overall effect: Z = 2.15 (P = 0.03)

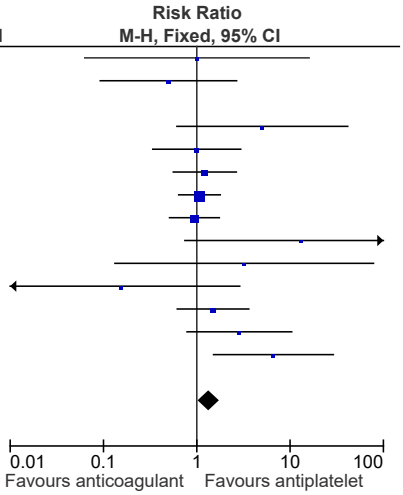
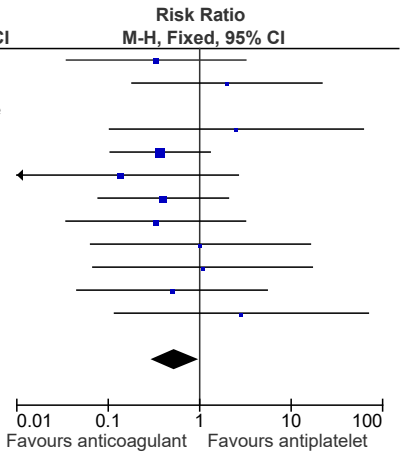


Figure 39: Systemic embolism

Study or Subgroup	Oral anticoagulant Events	Total	Antiplatelet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFASAK I	1	335	3	336	10.6%	0.33 [0.03, 3.20]
AFASAK II	2	170	1	169	3.5%	1.99 [0.18, 21.72]
ATHENS	0	16	0	15		Not estimable
Chen 2012b	1	239	0	201	1.9%	2.52 [0.10, 61.64]
Chen 2013	4	650	6	361	27.3%	0.37 [0.11, 1.30]
Diener 2012	0	390	3	374	12.6%	0.14 [0.01, 2.64]
DIENER2012	2	2417	5	2415	17.7%	0.40 [0.08, 2.06]
MANT2007	1	488	3	485	10.6%	0.33 [0.03, 3.17]
NASPEAF	1	237	1	242	3.5%	1.02 [0.06, 16.23]
PATAF	1	131	1	141	3.4%	1.08 [0.07, 17.03]
SPAF IIa	1	358	2	357	7.1%	0.50 [0.05, 5.47]
SPAF IIb	1	197	0	188	1.8%	2.86 [0.12, 69.86]
Total (95% CI)		**5628**		**5284**	**100.0%**	**0.54 [0.29, 0.99]**
Total events	15		25			

Heterogeneity: Chi² = 5.19, df = 10 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.99 (P = 0.05)



I.4.4 Dual antiplatelet versus antiplatelet

Figure 40: Ischaemic stroke

Study or Subgroup	Dual antiplatelet Events	Total	Antiplatelet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2009	235	3772	343	3782	96.0%	0.69 [0.59, 0.81]
HART2008	14	298	14	285	4.0%	0.96 [0.46, 1.97]
Total (95% CI)		**4070**		**4067**	**100.0%**	**0.70 [0.60, 0.82]**
Total events	249		357			

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 4.53 (P < 0.00001)

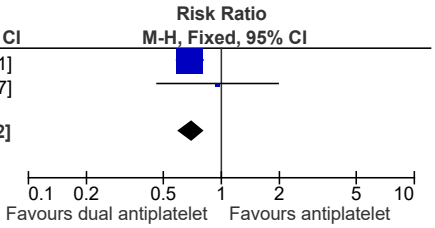


Figure 41: Haemorrhagic stroke

Study or Subgroup	Dual antiplatelet Events	Total	Antiplatelet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2009	30	3772	22	3782	97.7%	1.37 [0.79, 2.37]
HART2008	1	298	0	285	2.3%	2.87 [0.12, 70.15]
Total (95% CI)		**4070**		**4067**	**100.0%**	**1.40 [0.82, 2.40]**
Total events	31		22			

Heterogeneity: Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)

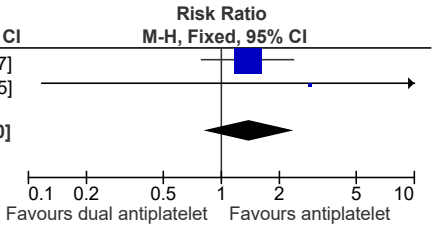


Figure 42: All-cause mortality

Study or Subgroup	Dual antiplatelet Events	Total	Antiplatelet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2009	825	3772	841	3782	97.0%	0.98 [0.90, 1.07]
HART2008	29	298	25	285	3.0%	1.11 [0.67, 1.85]
Total (95% CI)		**4070**		**4067**	**100.0%**	**0.99 [0.91, 1.07]**
Total events	854		866			

Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.76)

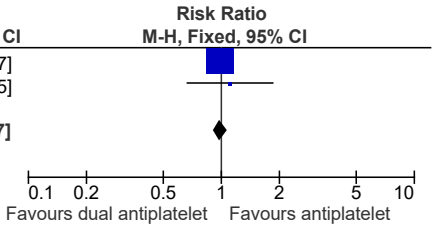


Figure 43: All-cause mortality – hazard ratio

Study or Subgroup	Dual antiplatelet Events	Total	Antiplatelet Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
HART2008	29	298	25	285	1.51	13.36	100.0%	1.12 [0.65, 1.91]
Total (95% CI)		**298**		**285**			**100.0%**	**1.12 [0.65, 1.91]**
Total events	29		25					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

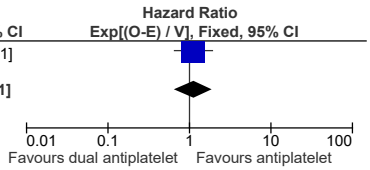


Figure 44: Systemic emboli

Study or Subgroup	Dual antiplatelet Events	Total	Antiplatelet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2009	54	3772	56	3782	100.0%	0.97 [0.67, 1.40]
Total (95% CI)		**3772**		**3782**	**100.0%**	**0.97 [0.67, 1.40]**
Total events	54		56			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

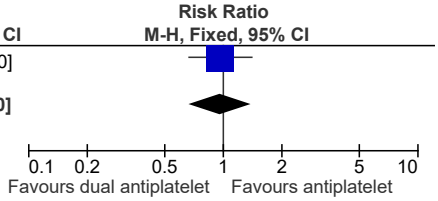


Figure 45: Hospitalisation

Study or Subgroup	Dual antiplatelet Events	Total	Antiplatelet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
HART2008	41	298	43	285	100.0%	0.91 [0.61, 1.35]
Total (95% CI)		**298**		**285**	**100.0%**	**0.91 [0.61, 1.35]**
Total events	41		43			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

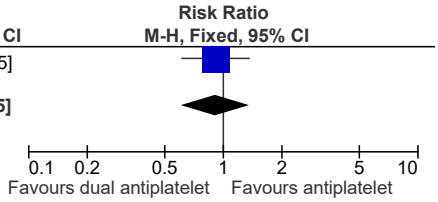
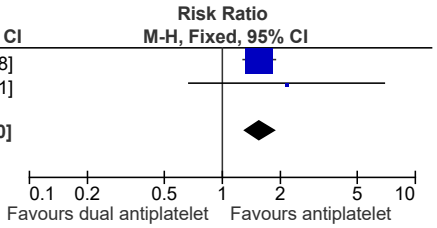


Figure 46: Major bleeding

Study or Subgroup	Dual antiplatelet Events	Total	Antiplatelet Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2009	251	3772	162	3782	97.5%	1.55 [1.28, 1.88]
HART2008	9	298	4	285	2.5%	2.15 [0.67, 6.91]
Total (95% CI)		**4070**		**4067**	**100.0%**	**1.57 [1.30, 1.90]**
Total events	260		166			

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 4.65 (P < 0.00001)



I.4.5 Dual antiplatelet versus anticoagulant

Figure 47: All cause mortality

Study or Subgroup	Dual antiplatelets Events	Total	OAC Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2006	159	3335	158	3371	100.0%	1.02 [0.82, 1.26]
Total (95% CI)		**3335**		**3371**	**100.0%**	**1.02 [0.82, 1.26]**
Total events	159		158			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.88)

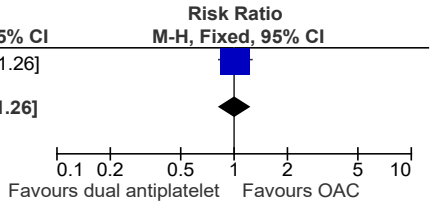


Figure 48: Ischaemic stroke

Study or Subgroup	Dual antiplatelets Events	Total	OAC Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2006	90	3335	42	3371	100.0%	2.17 [1.51, 3.11]
Total (95% CI)		**3335**		**3371**	**100.0%**	**2.17 [1.51, 3.11]**
Total events	90		42			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.17 (P < 0.0001)

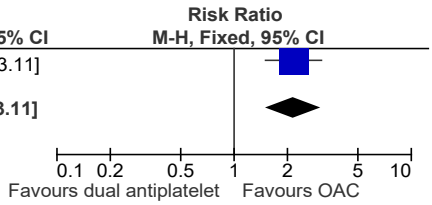


Figure 49: Haemorrhagic stroke

Study or Subgroup	Dual antiplatelets Events	Total	OAC Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2006	5	3335	15	3371	100.0%	0.34 [0.12, 0.93]
Total (95% CI)		**3335**		**3371**	**100.0%**	**0.34 [0.12, 0.93]**
Total events	5		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.11 (P = 0.03)

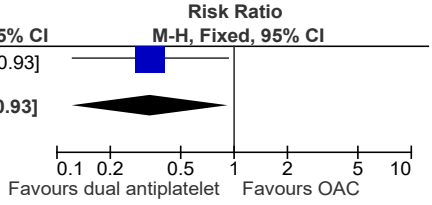


Figure 50: Systemic emboli

Study or Subgroup	Dual antiplatelets Events	Total	OAC Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2006	18	3335	4	3371	100.0%	4.55 [1.54, 13.43]
Total (95% CI)		**3335**		**3371**	**100.0%**	**4.55 [1.54, 13.43]**
Total events	18		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.74 (P = 0.006)

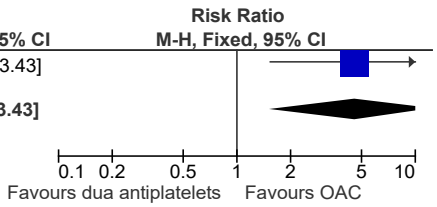
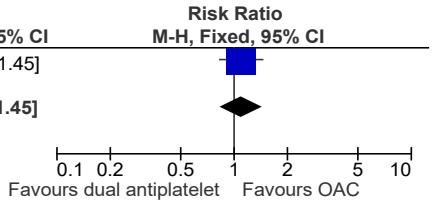


Figure 51: Major bleeding

Study or Subgroup	Dual antiplatelets Events	Total	OAC Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTIVE2006	101	3335	93	3371	100.0%	1.10 [0.83, 1.45]
Total (95% CI)		**3335**		**3371**	**100.0%**	**1.10 [0.83, 1.45]**
Total events	101		93			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



I.4.6 Anticoagulation and dual antiplatelet versus anticoagulation and antiplatelet

Figure 52: All-cause mortality – hazard ratio

Study or Subgroup	OAC+Dual AP Events	Total	OAC+AP Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
DEWILDE2013	18	284	7	297	-4.67	4.96	100.0%	0.39 [0.16, 0.94]
Total (95% CI)		**284**		**297**			**100.0%**	**0.39 [0.16, 0.94]**
Total events	18		7					

Heterogeneity: Not applicable
Test for overall effect: Z = 2.10 (P = 0.04)

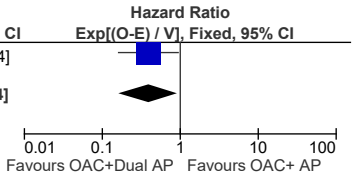


Figure 53: Ischaemic stroke

Study or Subgroup	OAC+Dual AP Events	Total	OAC+AP Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DEWILDE2013	8	284	2	297	100.0%	4.18 [0.90, 19.53]
Total (95% CI)		**284**		**297**	**100.0%**	**4.18 [0.90, 19.53]**
Total events	8		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)

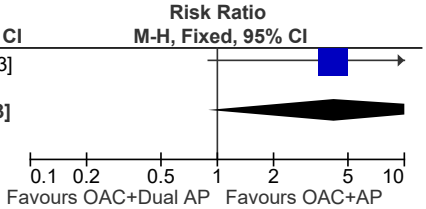


Figure 54: Haemorrhagic stroke

Study or Subgroup	OAC+Dual AP Events	Total	OAC+AP Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DEWILDE2013	0	284	1	297	100.0%	0.35 [0.01, 8.52]
Total (95% CI)		**284**		**297**	**100.0%**	**0.35 [0.01, 8.52]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)

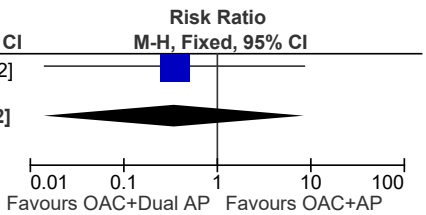
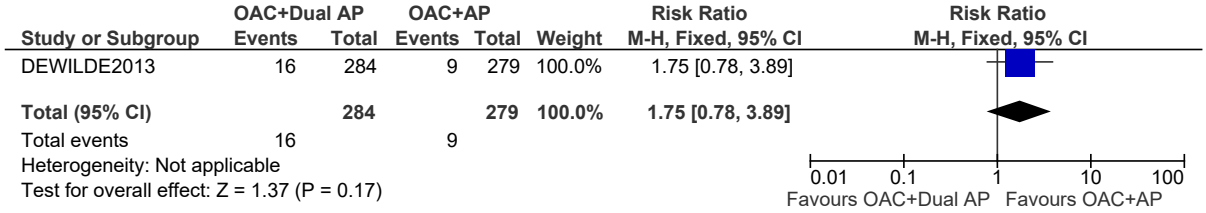


Figure 55: Major bleeding



I.5 Bleeding risk scores

Figure 56: Hazard ratio for bleeding by risk score

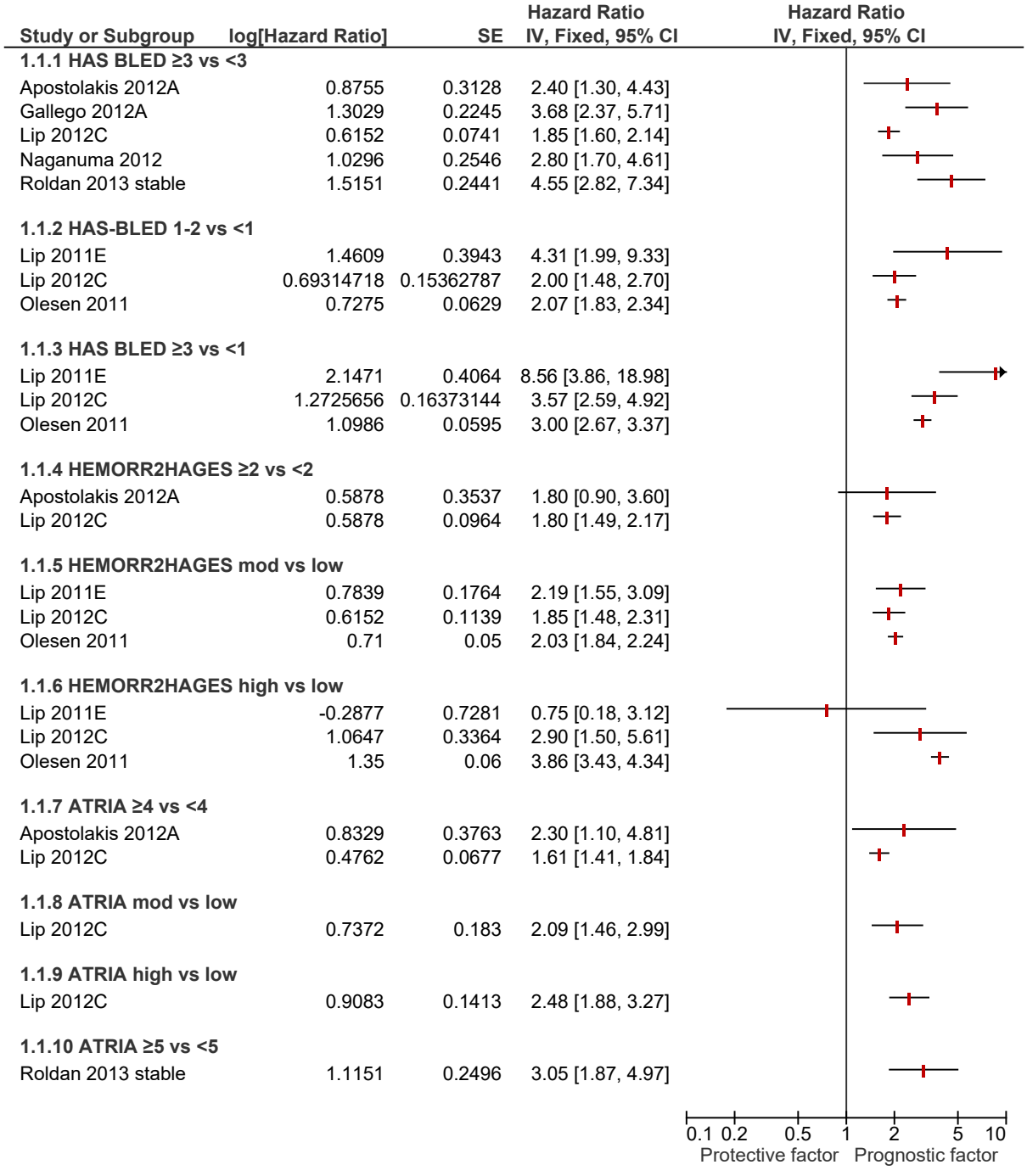
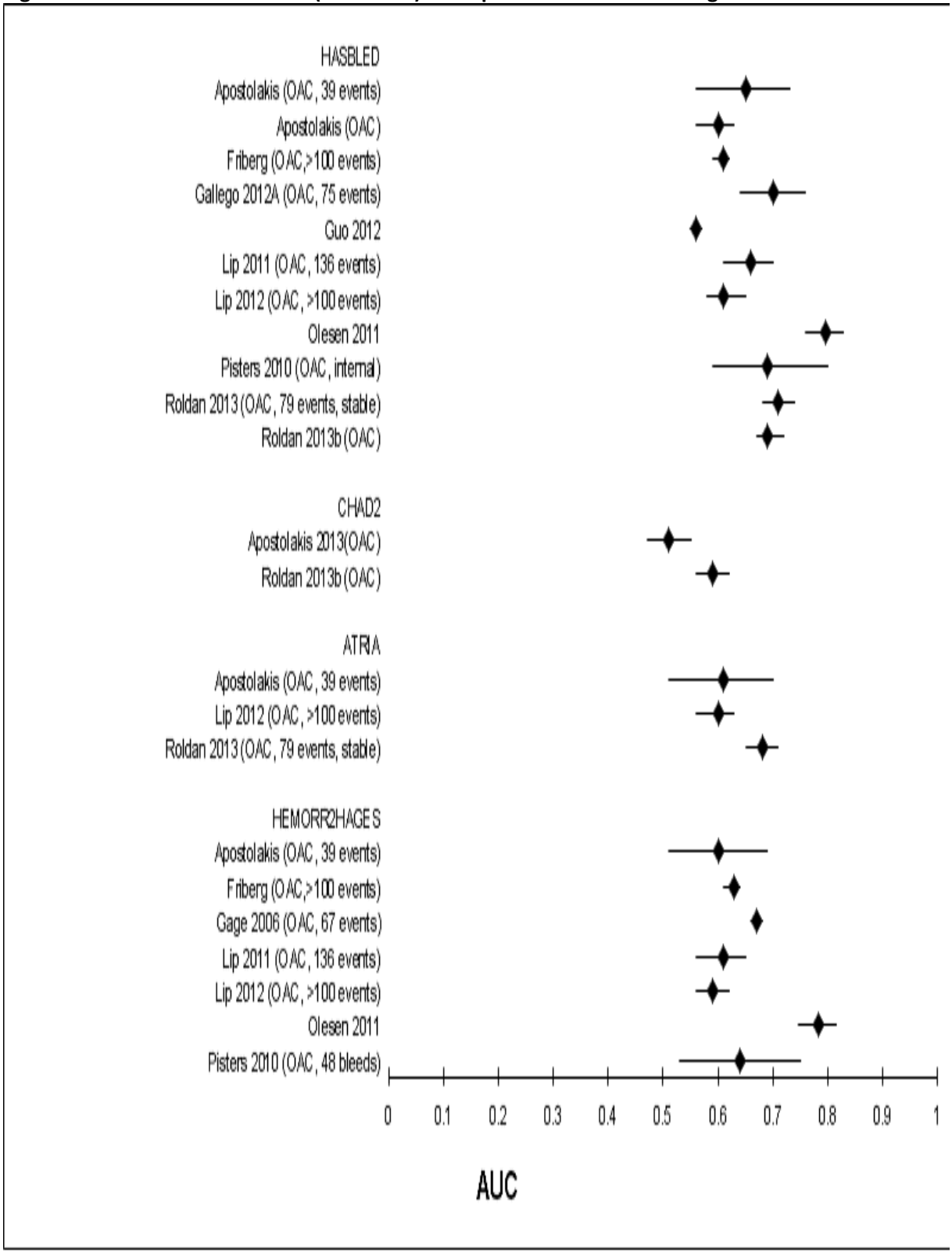


Figure 57: Area under the curve (C-statistic) of AF patients on oral anticoagulants



C-statistics - on oral anticoagulants			
Study	**Lower CI**	**Point estimate**	**Upper CI**
HASBLED			
Apostolakis (OAC, 39 events)	0.56	0.65	0.73
Apostolakis (OAC)	0.56	0.6	0.63
Friberg (OAC,>100 events)	0.59	0.61	0.62
Gallego 2012A (OAC, 75 events)	0.64	0.7	0.76
Guo 2012		0.56	
Lip 2011 (OAC, 136 events)	0.61	0.66	0.7
Lip 2012 (OAC, >100 events)	0.58	0.61	0.65
Olesen 2011	0.759	0.795	0.829
Pisters 2010 (OAC, internal)	0.59	0.69	0.8
Roldan 2013 (OAC, 79 events, stable)	0.68	0.71	0.74
Roldan 2013b (OAC)	0.67	0.69	0.72
CHAD2			
Apostolakis 2013(OAC)	0.47	0.51	0.55
Roldan 2013b (OAC)	0.56	0.59	0.62
ATRIA			
Apostolakis (OAC, 39 events)	0.51	0.61	0.7
Lip 2012 (OAC, >100 events)	0.56	0.6	0.63
Roldan 2013 (OAC, 79 events, stable)	0.65	0.68	0.71
HEMORR2HAGES			
Apostolakis (OAC, 39 events)	0.51	0.6	0.69
Friberg (OAC,>100 events)	0.61	0.63	0.64
Gage 2006 (OAC, 67 events)	0.668042	0.67	0.671958
Lip 2011 (OAC, 136 events)	0.56	0.61	0.65
Lip 2012 (OAC, >100 events)	0.56	0.59	0.62
Olesen 2011	0.745	0.782	0.816
Pisters 2010 (OAC, 48 bleeds)	0.53	0.64	0.75

I.6 Left atrial appendage occlusion

Figure 58: Mortality (2.3 year follow-up)

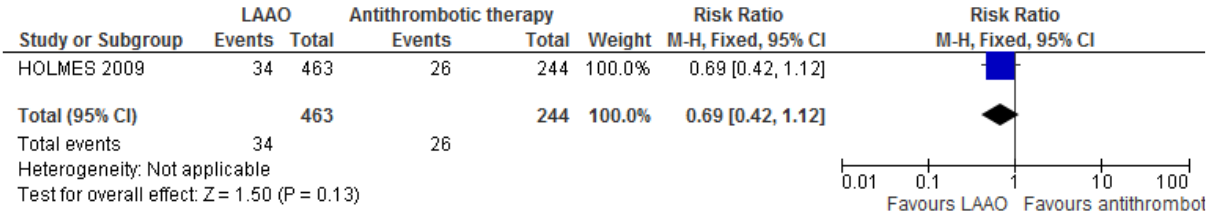


Figure 59: Ischaemic stroke (2.3 year follow-up)

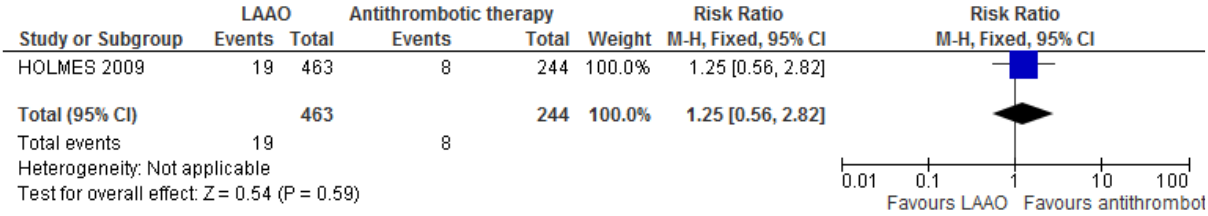


Figure 60: Haemorrhagic stroke (2.3 year follow-up)

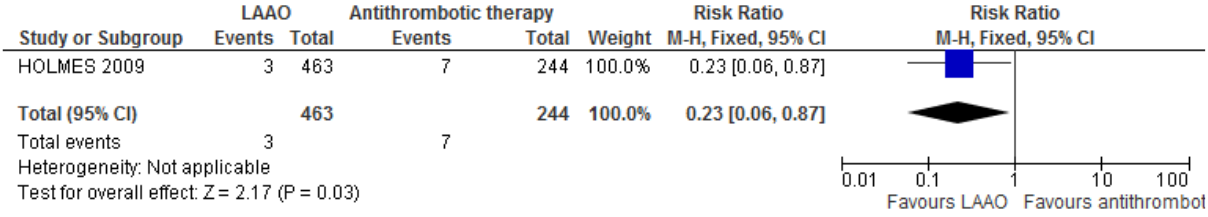


Figure 61: Systemic embolism (2.3 year follow-up)

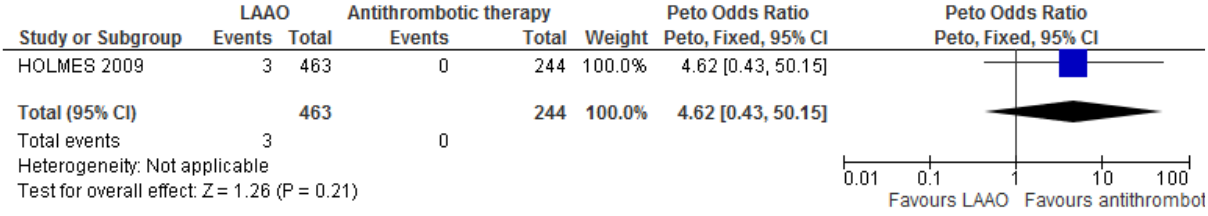
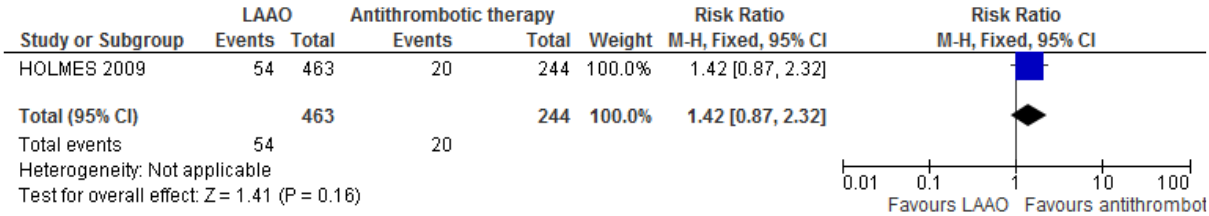


Figure 62: Primary safety (2.3 year follow-up)



I.7 Rate versus rhythm control strategies

Figure 63: All-cause mortality

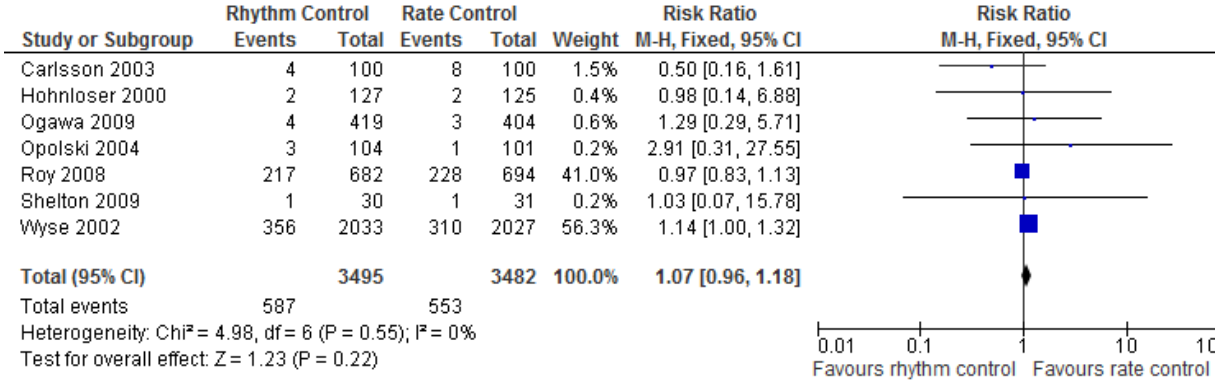


Figure 64: Cardiovascular mortality in heart failure patients

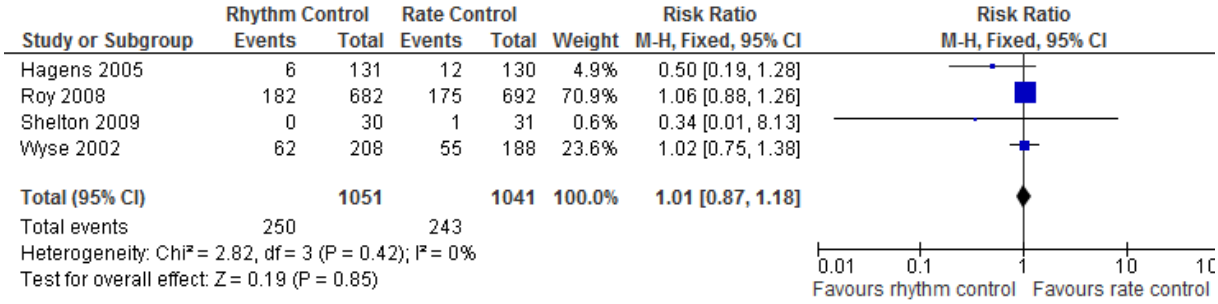


Figure 65: Stroke or thromboembolic complications

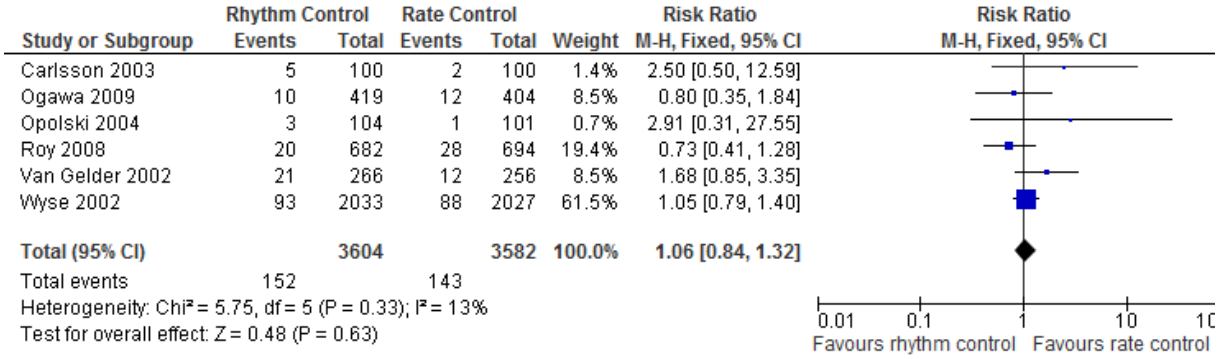


Figure 66: Stroke or thromboembolic complications in patients with heart failure

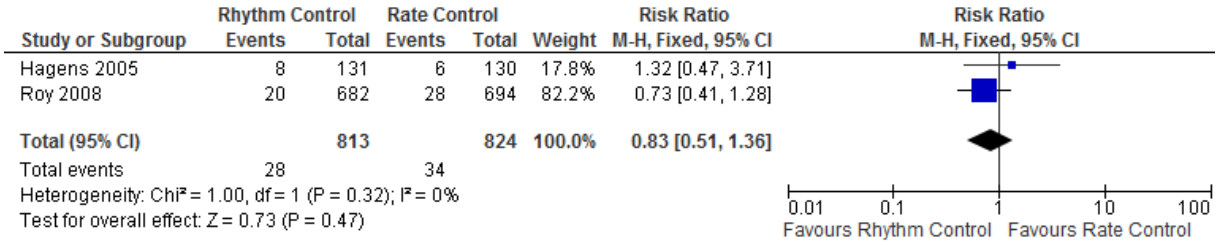


Figure 67: Bleeding

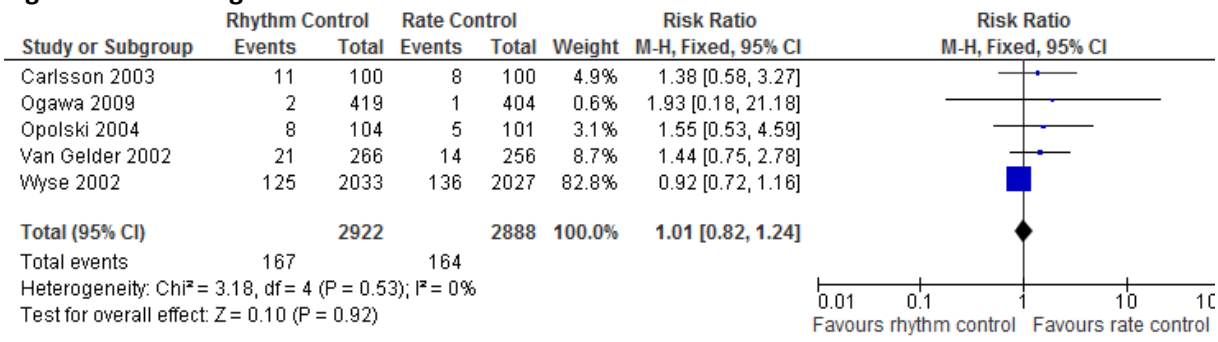


Figure 68: Bleeding in patients with heart failure

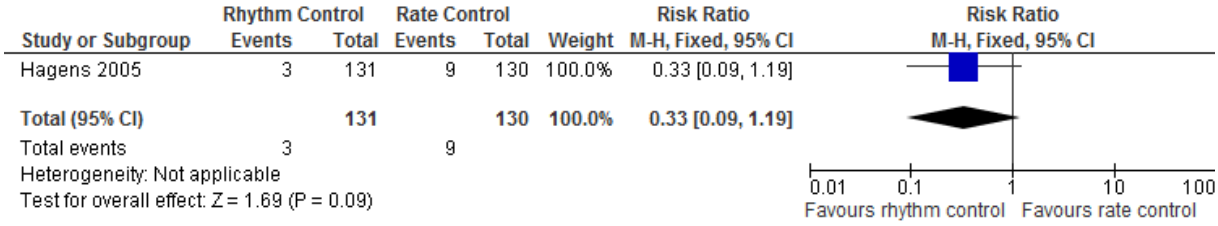


Figure 69: Hospitalisation; random effects

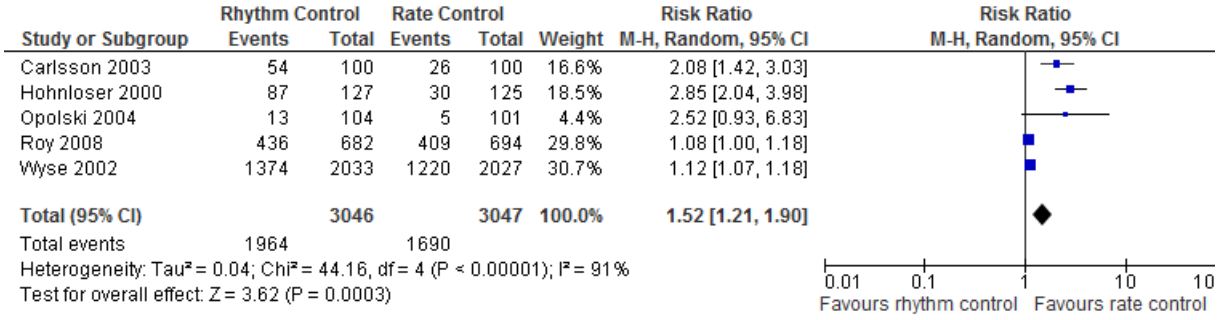


Figure 70: Hospitalisation in patients with heart failure

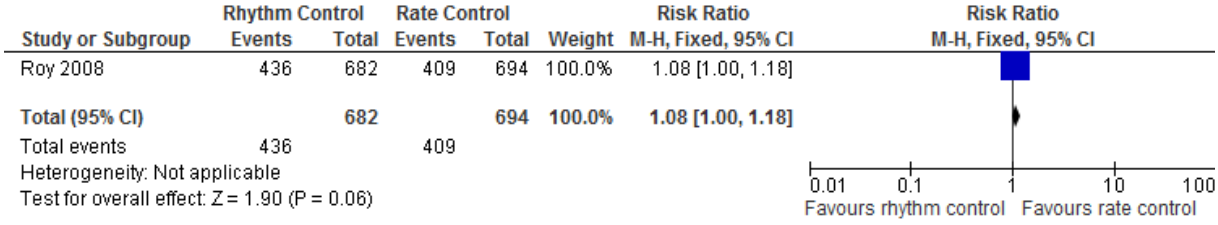


Figure 71: Heart failure – development/worsening of heart failure

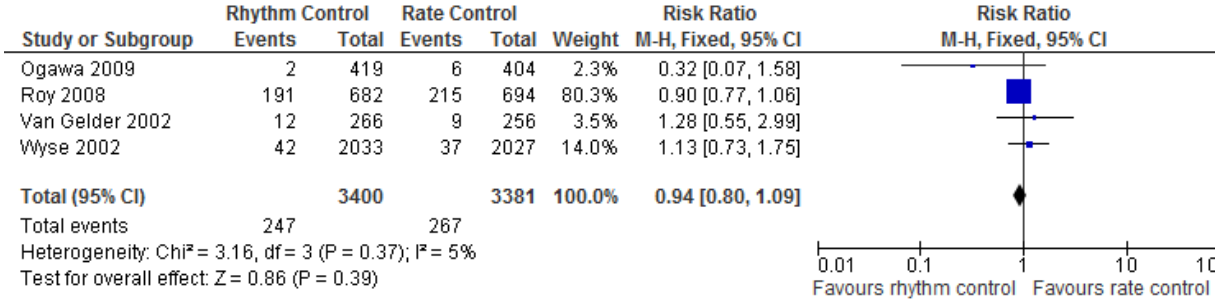


Figure 72: Sinus rhythm at last follow-up; random effects

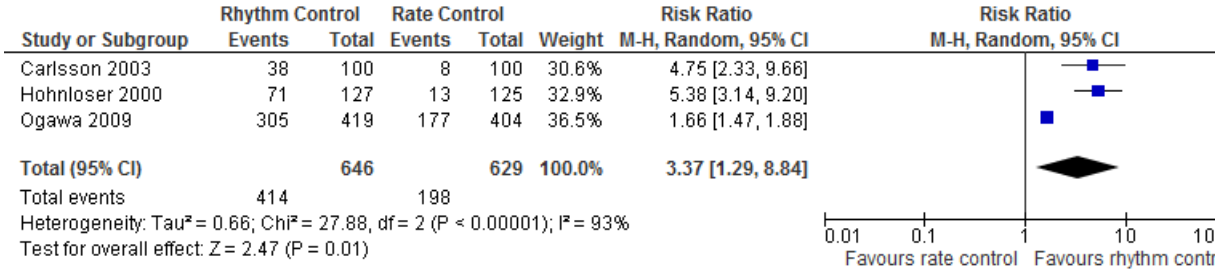


Figure 73: Atrial fibrillation at last follow-up

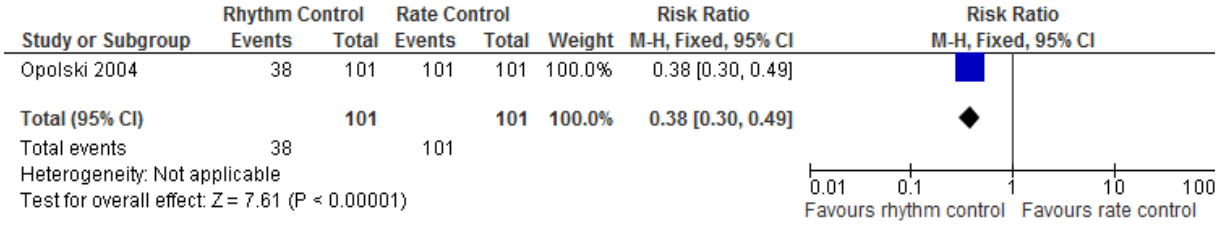


Figure 74: Quality of life SF-36 – general health

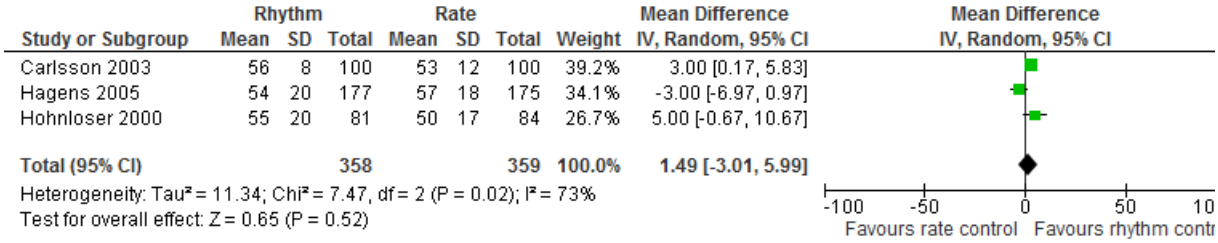


Figure 75: Quality of life SF-36 – physical functioning

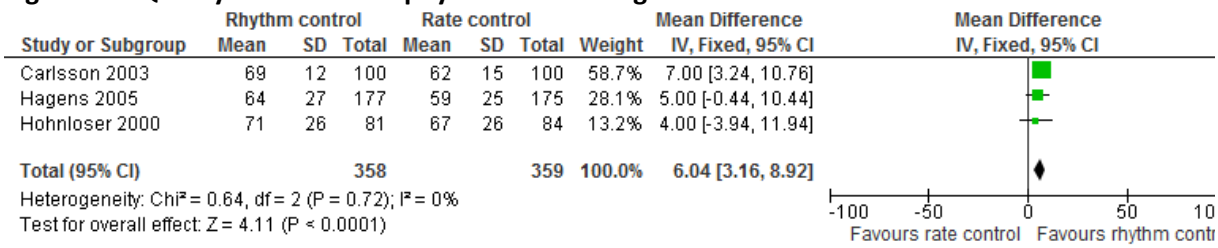


Figure 76: Quality of life SF-36 – physical role function

Study or Subgroup	Rhythm Control Mean	SD	Total	Rate Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Carlsson 2003	62	19	100	55	21	100	68.0%	7.00 [1.45, 12.55]
Hagens 2005	55	45	177	53	44	175	24.2%	2.00 [-7.30, 11.30]
Hohnloser 2000	58	51	81	52	57	84	7.7%	6.00 [-10.49, 22.49]
Total (95% CI)			**358**			**359**	**100.0%**	**5.71 [1.13, 10.29]**

Heterogeneity: Chi² = 0.82, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.44 (P = 0.01)

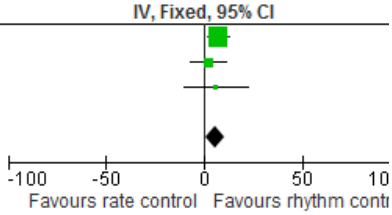


Figure 77: Quality of life SF-36 – bodily pain

Study or Subgroup	Rhythm Control Mean	SD	Total	Rate Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Carlsson 2003	74	15	100	72	17	100	48.1%	2.00 [-2.44, 6.44]
Hagens 2005	80	22	177	79	23	175	42.9%	1.00 [-3.70, 5.70]
Hohnloser 2000	77	36	81	77	31	84	9.0%	0.00 [-10.27, 10.27]
Total (95% CI)			**358**			**359**	**100.0%**	**1.39 [-1.69, 4.47]**

Heterogeneity: Chi² = 0.17, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)

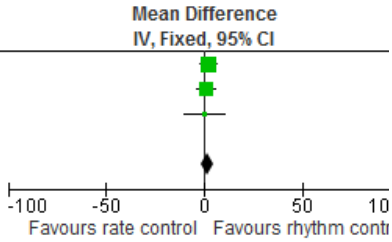


Figure 78: Quality of life SF-36 – mental health

Study or Subgroup	Rhythm Control Mean	SD	Total	Rate Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Carlsson 2003	72	10	100	69	10	100	55.1%	3.00 [0.23, 5.77]
Hagens 2005	76	18	177	76	17	175	31.7%	0.00 [-3.66, 3.66]
Hohnloser 2000	71	17	81	68	20	84	13.2%	3.00 [-2.66, 8.66]
Total (95% CI)			**358**			**359**	**100.0%**	**2.05 [-0.01, 4.11]**

Heterogeneity: Chi² = 1.77, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)

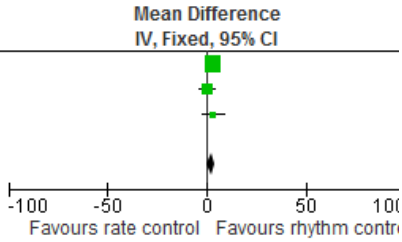


Figure 79: Quality of life SF-36 – social functioning

Study or Subgroup	Rhythm Control Mean	SD	Total	Rate Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Carlsson 2003	83	13	100	79	13	100	56.0%	4.00 [0.40, 7.60]
Hagens 2005	80	23	177	81	21	175	34.4%	-1.00 [-5.60, 3.60]
Hohnloser 2000	84	29	81	80	28	84	9.6%	4.00 [-4.70, 12.70]
Total (95% CI)			**358**			**359**	**100.0%**	**2.28 [-0.42, 4.98]**

Heterogeneity: Chi² = 2.98, df = 2 (P = 0.23); I² = 33%
Test for overall effect: Z = 1.66 (P = 0.10)

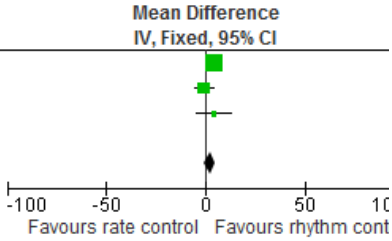


Figure 80: Quality of life SF-36 – role emotional

Study or Subgroup	Rhythm Control Mean	SD	Total	Rate Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Carlsson 2003	71	17	100	75	18	100	67.9%	-4.00 [-8.85, 0.85]
Hagens 2005	74	38	177	73	39	175	24.7%	1.00 [-7.05, 9.05]
Hohnloser 2000	62	45	81	65	51	84	7.4%	-3.00 [-17.66, 11.66]
Total (95% CI)			**358**			**359**	**100.0%**	**-2.69 [-6.69, 1.31]**

Heterogeneity: Chi² = 1.09, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)

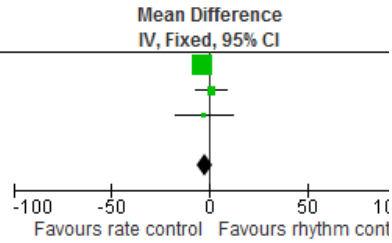
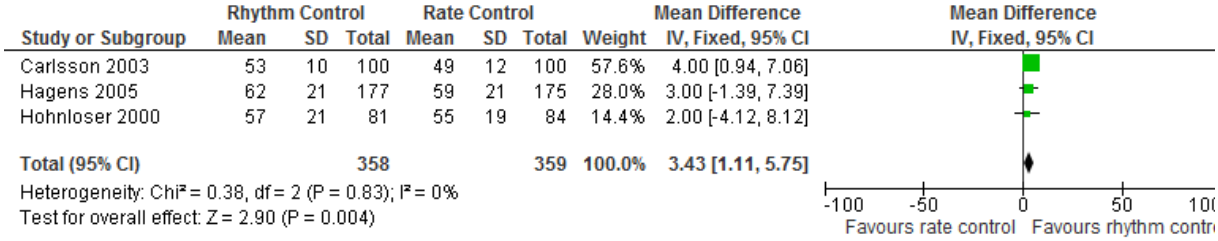


Figure 81: Quality of life SF-36 – vitality



I.8 Rate control strategies

I.8.1 Digoxin versus amiodarone

Figure 82: % reduction in VR during ambulatory exercise

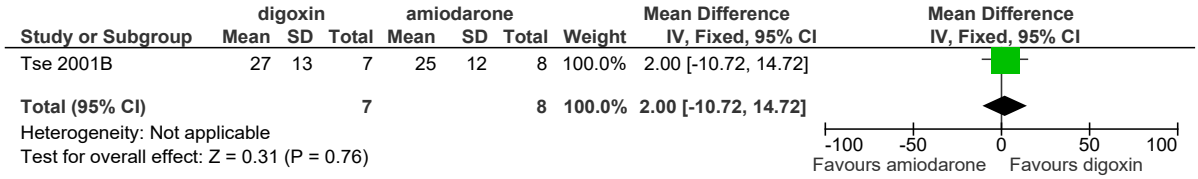
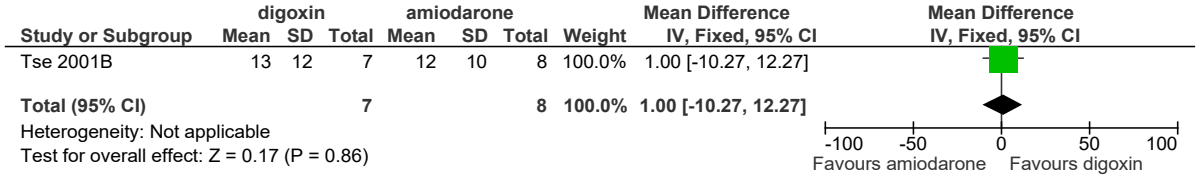


Figure 83: % reduction in VR from baseline during peak exercise



I.8.2 Beta-blocker versus placebo

Figure 84: Mortality

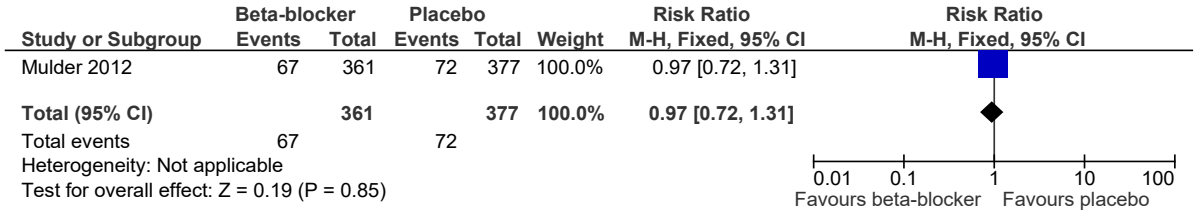
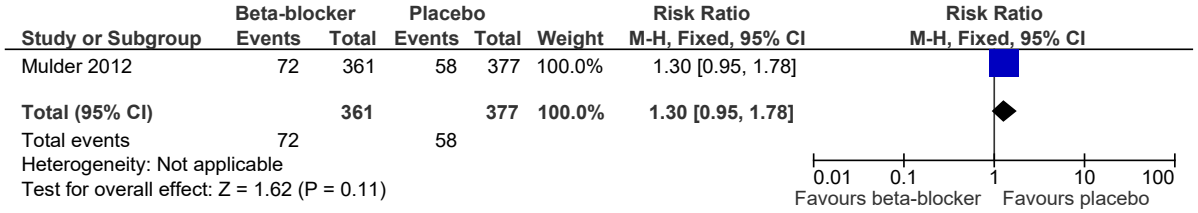


Figure 85: Rehospitalisation's with heart failure



I.8.3 Beta-blocker versus digoxin

Figure 86: 24-h mean HR at 6 months

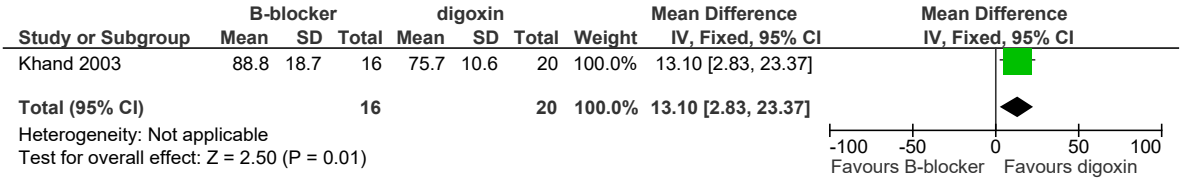
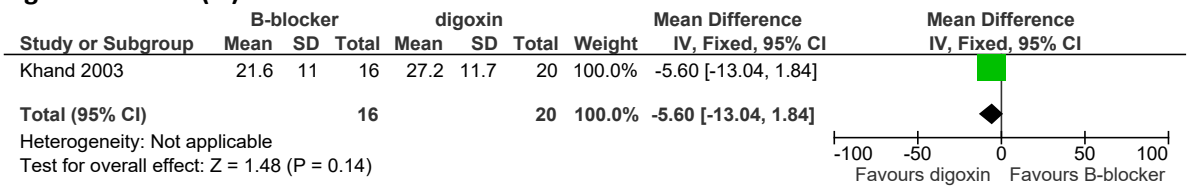


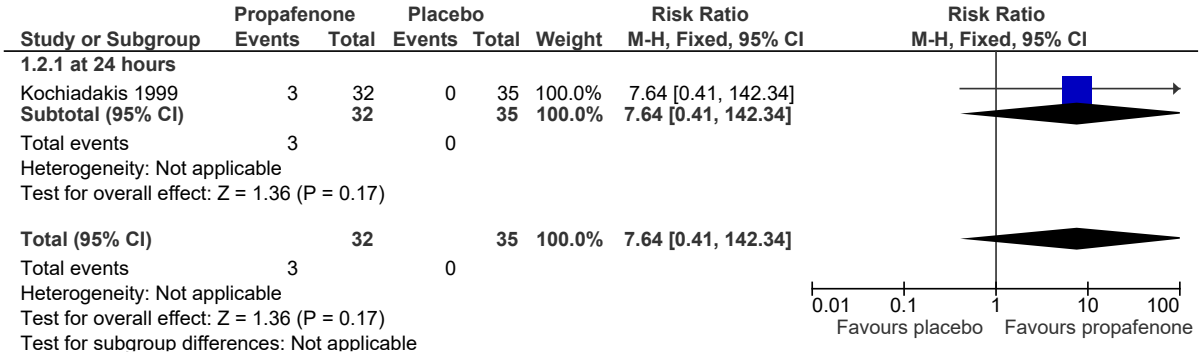
Figure 87: LVEF (%)



I.9 Rhythm control strategies – restoration of sinus rhythm

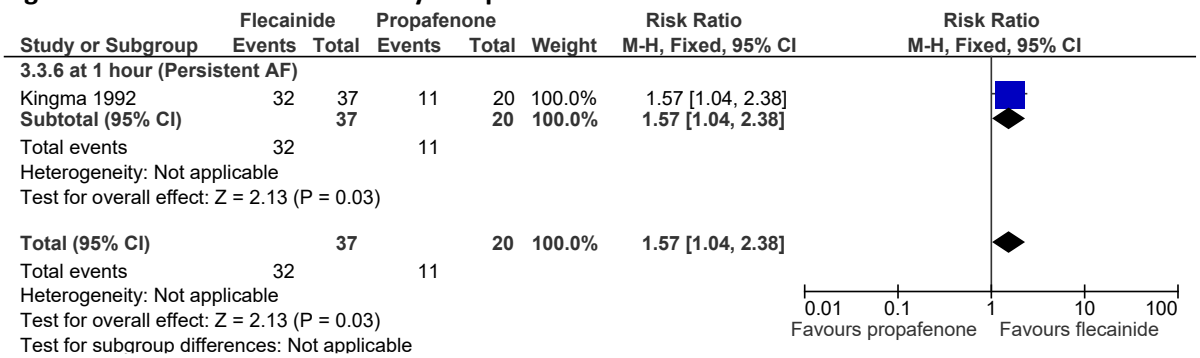
I.9.1 Propafenone versus placebo

Figure 88: Restoration of sinus rhythm- chronic AF



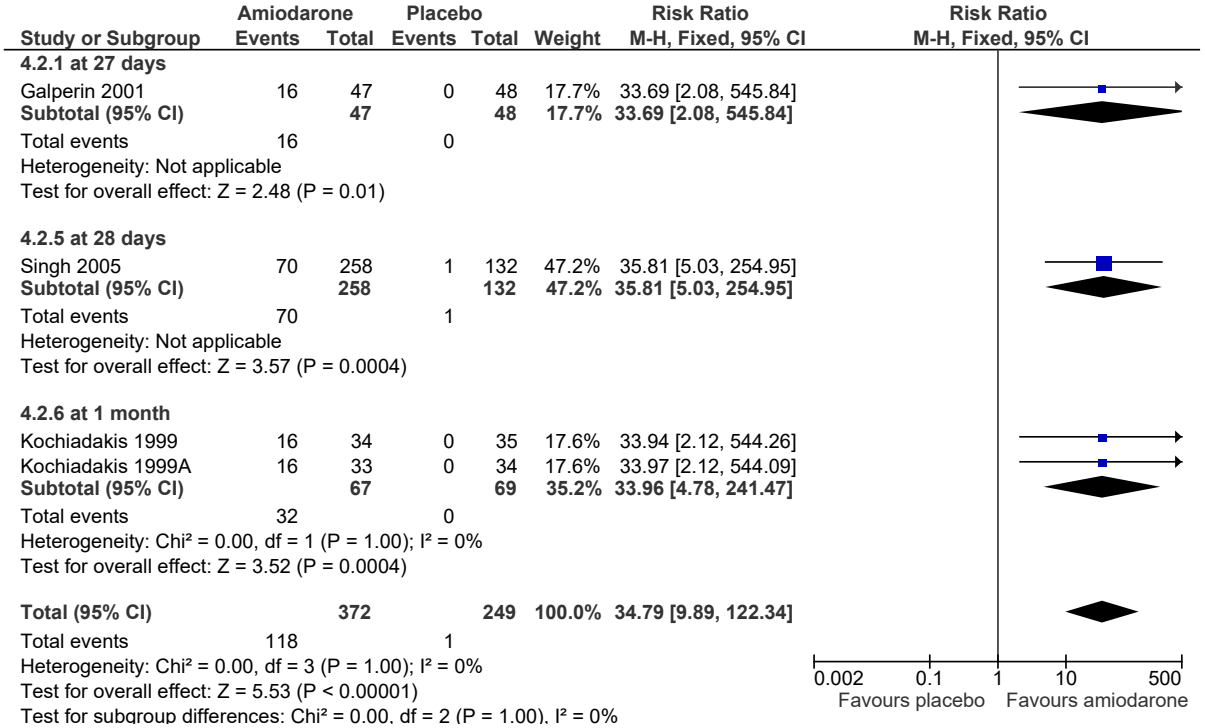
I.9.2 Flecainide versus propafenone

Figure 89: Restoration of sinus rhythm-persistent AF



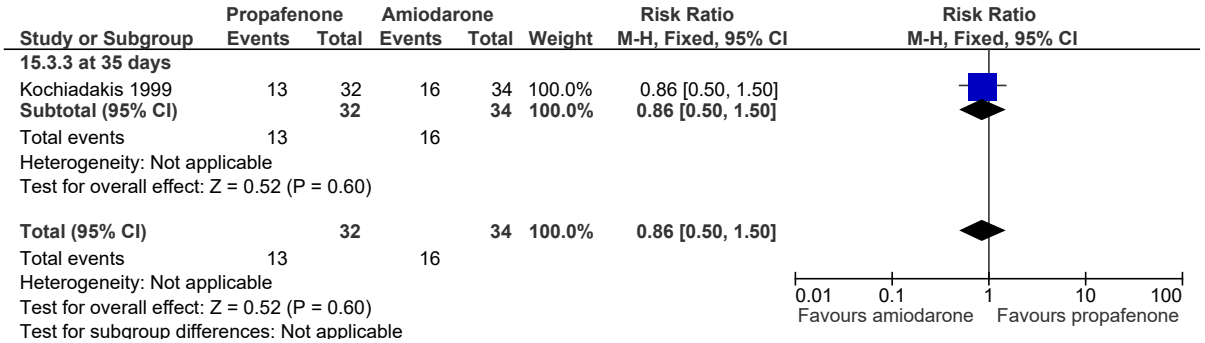
I.9.3 Amiodarone versus placebo

Figure 90: Restoration of sinus rhythm- persistent AF



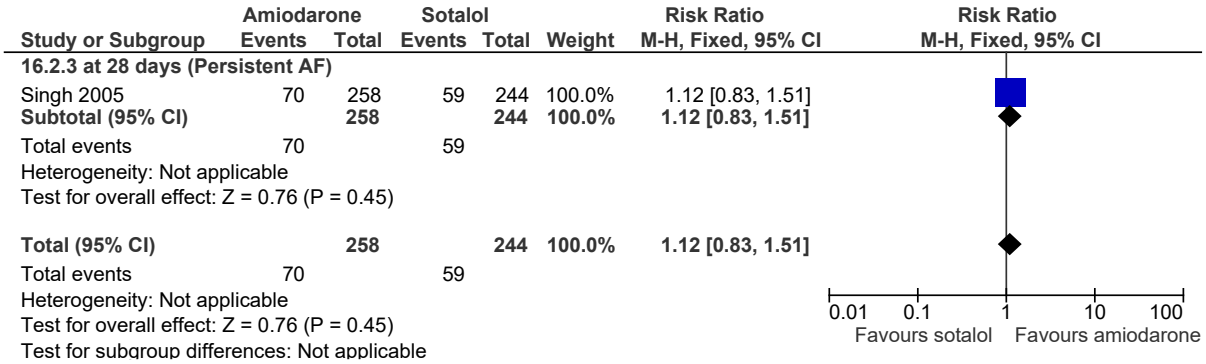
I.9.4 Propafenone versus amiodarone

Figure 91: Restoration of rhythm- chronic AF



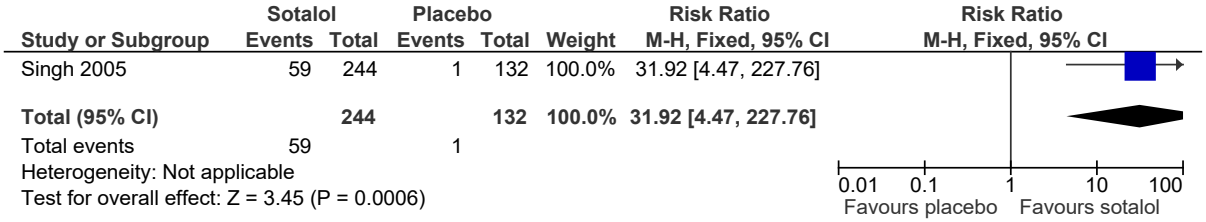
I.9.5 Amiodarone versus sotalol

Figure 92: Restoration of sinus rhythm- persistent AF



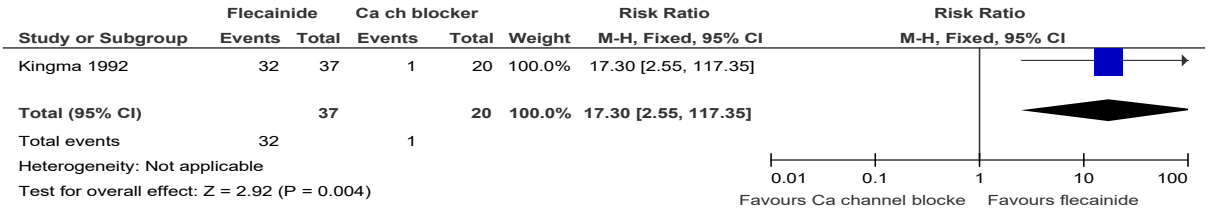
I.9.6 Sotalol versus placebo

Figure 93: Restoration of sinus rhythm- persistent AF



I.9.7 Flecainide versus calcium channel blocker

Figure 94: Restoration of sinus rhythm-persistent AF



I.9.8 ECV plus amiodarone versus ECV alone or ECV plus placebo

Figure 95: Restoration of sinus rhythm

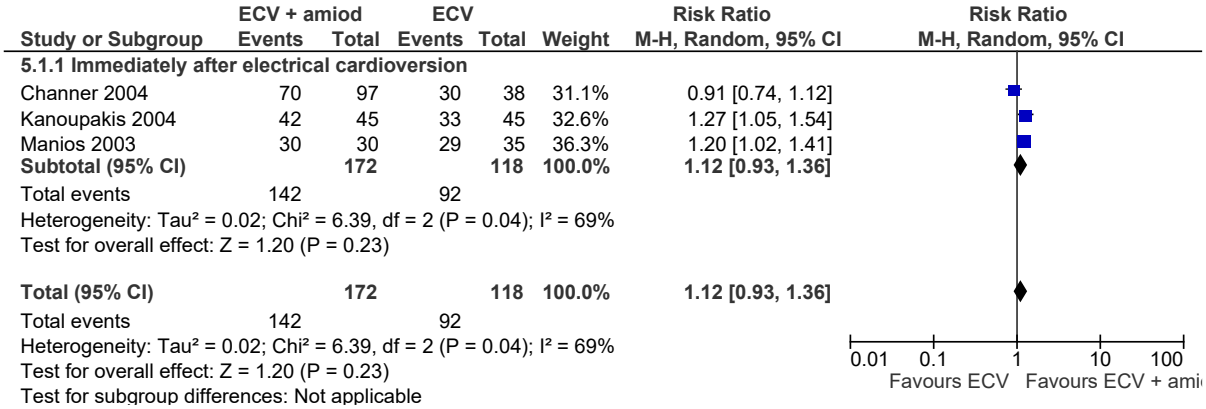


Figure 96: Maintenance of sinus rhythm – 12 months

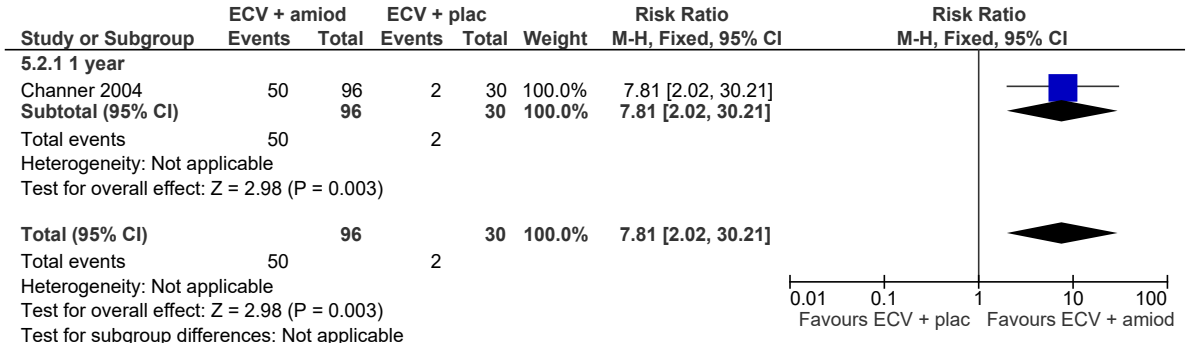
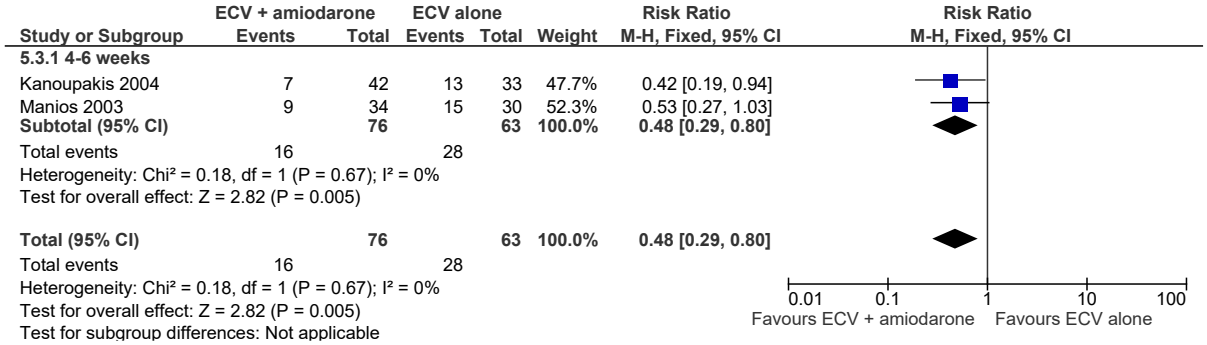


Figure 97: Relapse of AF – 4-6 weeks



I.9.9 ECV plus flecainide versus ECV plus placebo

Figure 98: Restoration of sinus rhythm - immediate

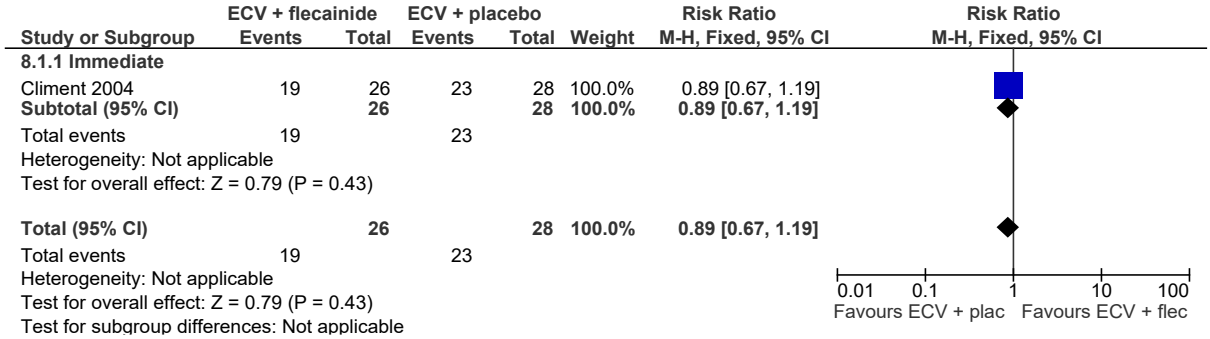
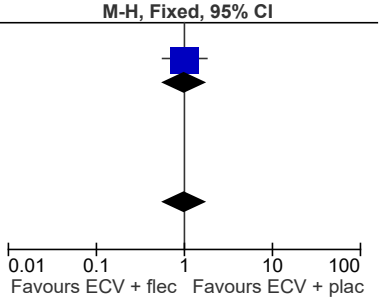


Figure 99: Relapse of AF – 1 month

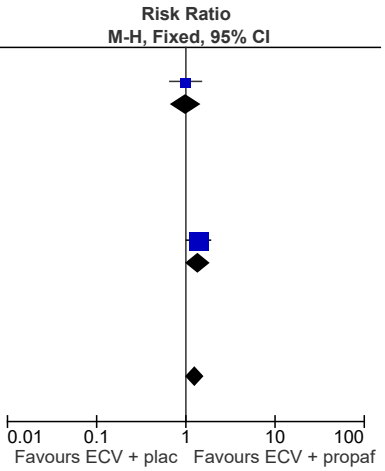
Study or Subgroup	ECV + flecainide Events	Total	ECV + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.2.1 1 month						
Climent 2004	10	19	12	23	100.0%	1.01 [0.57, 1.80]
Subtotal (95% CI)		**19**		**23**	**100.0%**	**1.01 [0.57, 1.80]**
Total events	10		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
Total (95% CI)		**19**		**23**	**100.0%**	**1.01 [0.57, 1.80]**
Total events	10		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Not applicable						



I.9.10 ECV plus propafenone versus ECV plus placebo

Figure 100: Reversion to sinus rhythm

Study or Subgroup	ECV + propafenone Events	Total	ECV + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 Immediate effect						
Bianconi 1993	11	15	14	19	31.8%	1.00 [0.66, 1.49]
Subtotal (95% CI)		**15**		**19**	**31.8%**	**1.00 [0.66, 1.49]**
Total events	11		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
10.1.2 48 hours						
Bianconi 1996	36	49	27	51	68.2%	1.39 [1.02, 1.89]
Subtotal (95% CI)		**49**		**51**	**68.2%**	**1.39 [1.02, 1.89]**
Total events	36		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
Total (95% CI)		**64**		**70**	**100.0%**	**1.26 [0.98, 1.62]**
Total events	47		41			
Heterogeneity: Chi² = 1.68, df = 1 (P = 0.20); I² = 40%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Chi² = 1.63, df = 1 (P = 0.20), I² = 38.6%						



I.9.11 ECV plus beta-blocker versus ECV alone/placebo

Figure 101: Restoration of sinus rhythm - immediate

Study or Subgroup	ECV + beta-blocker Events	Total	ECV + placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.1.1 Immediately after cardioversion						
Kanoupakis 2004	43	47	33	45	41.6%	1.25 [1.02, 1.52]
Nergardh 2007	75	79	75	81	58.4%	1.03 [0.95, 1.11]
Subtotal (95% CI)		**126**		**126**	**100.0%**	**1.11 [0.90, 1.38]**
Total events	118		108			
Heterogeneity: Tau² = 0.02; Chi² = 4.28, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Total (95% CI)		**126**		**126**	**100.0%**	**1.11 [0.90, 1.38]**
Total events	118		108			
Heterogeneity: Tau² = 0.02; Chi² = 4.28, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Not applicable						

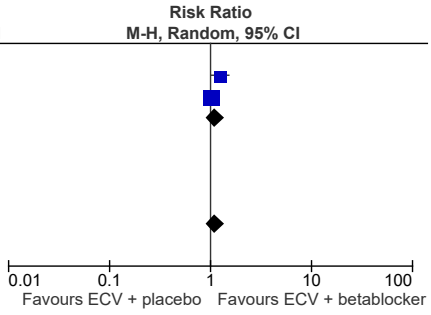


Figure 102: Relapse of AF – 4-6 weeks

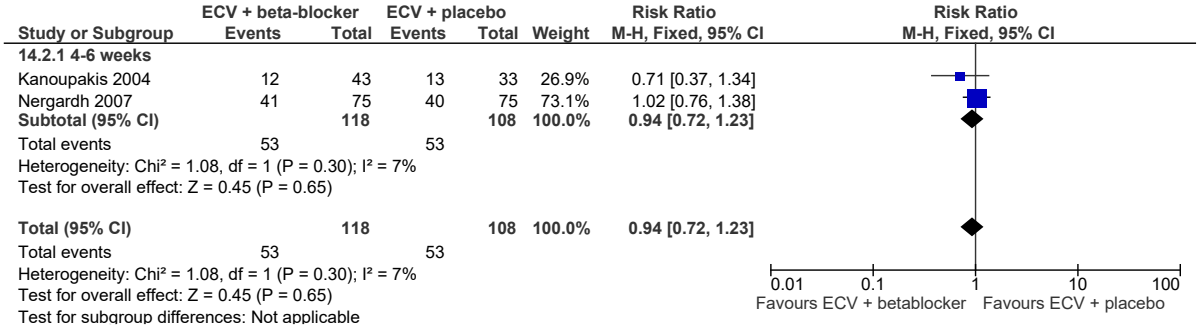


Figure 103: Maintenance of sinus rhythm – 6 months

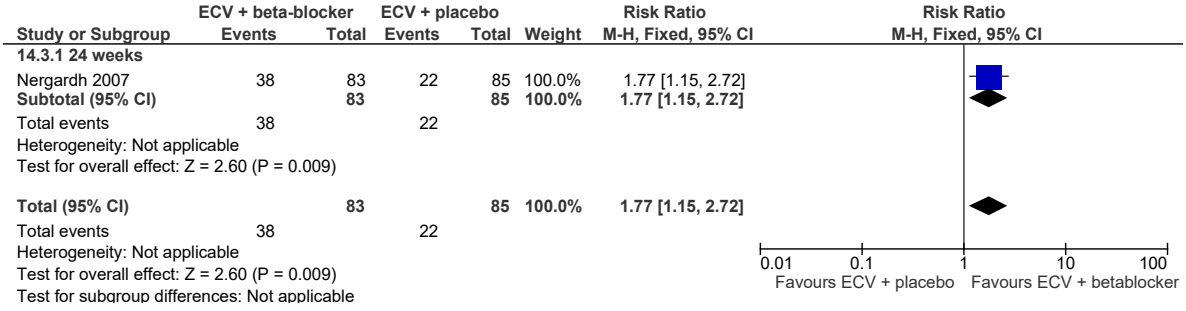
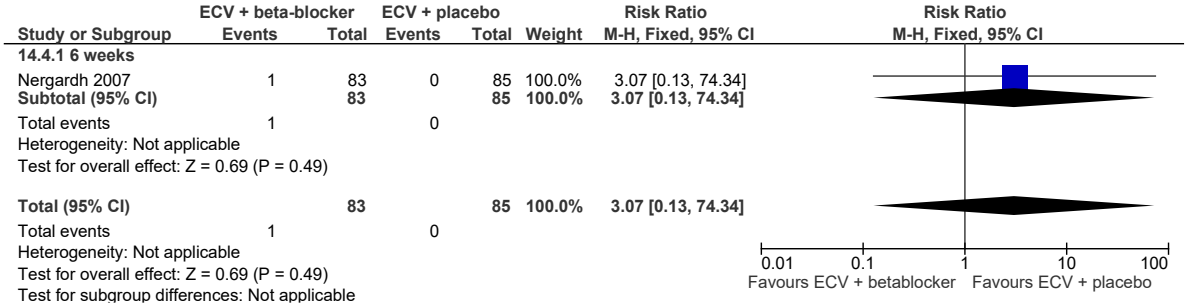


Figure 104: Stroke – 6 weeks



I.9.12 ECV plus diltiazem versus ECV alone

Figure 105: Restoration of sinus rhythm

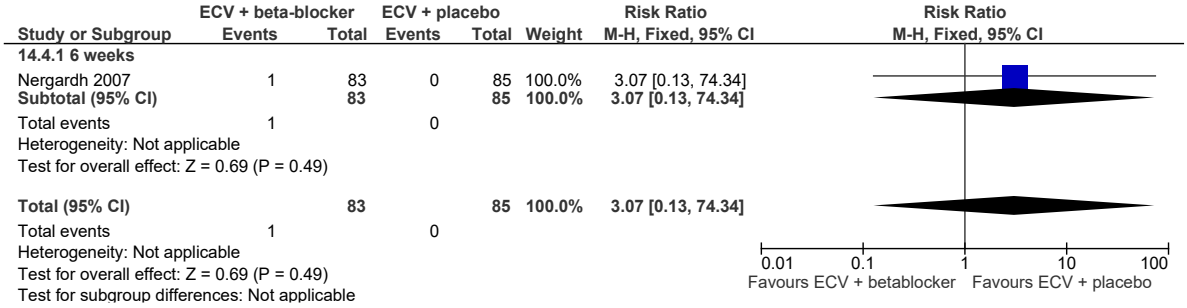
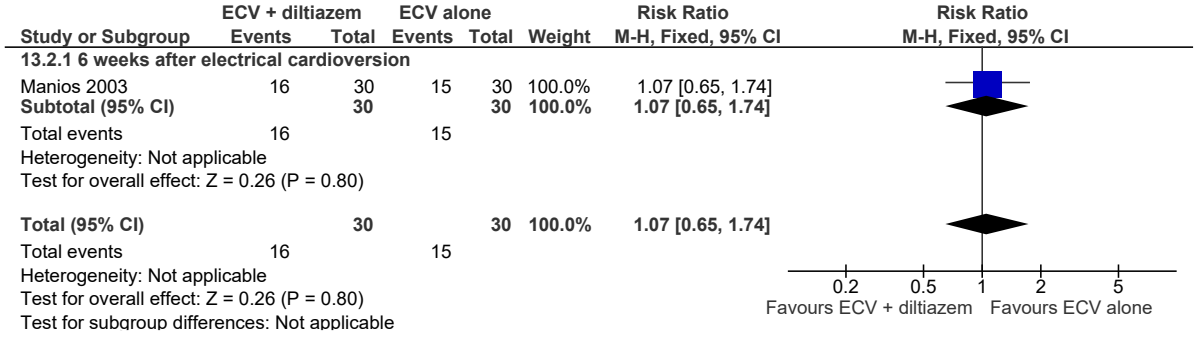


Figure 106: Relapse of AF - 6 weeks



I.9.13 ECV plus amiodarone versus ECV plus digoxin

Figure 107: Restoration of sinus rhythm - immediate

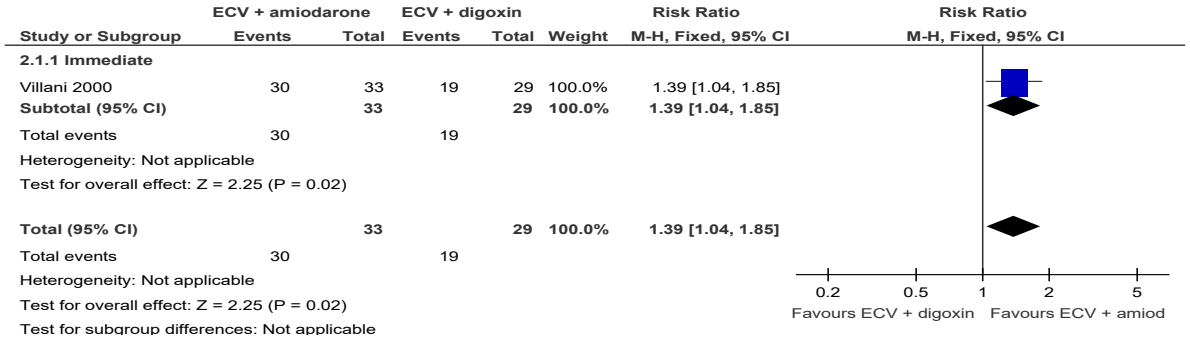
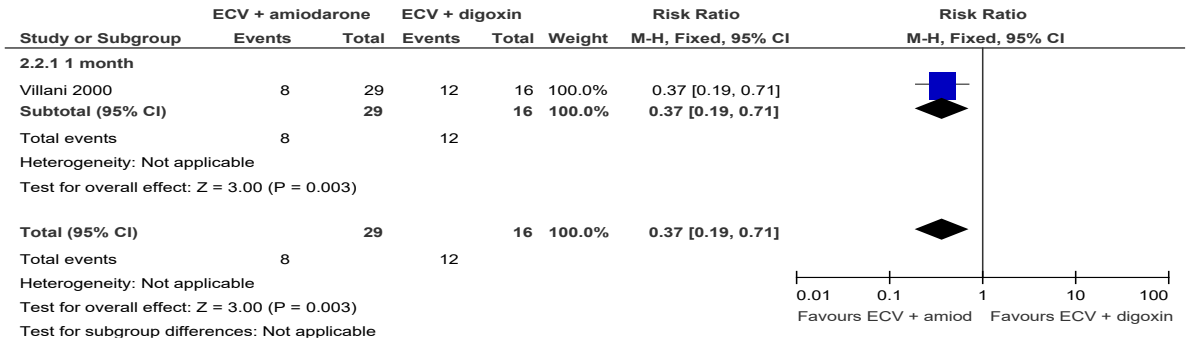


Figure 108: Recurrence of AF – 1 month



I.9.14 ECV plus amiodarone versus ECV plus diltiazem

Figure 109: Restoration of sinus rhythm - immediate

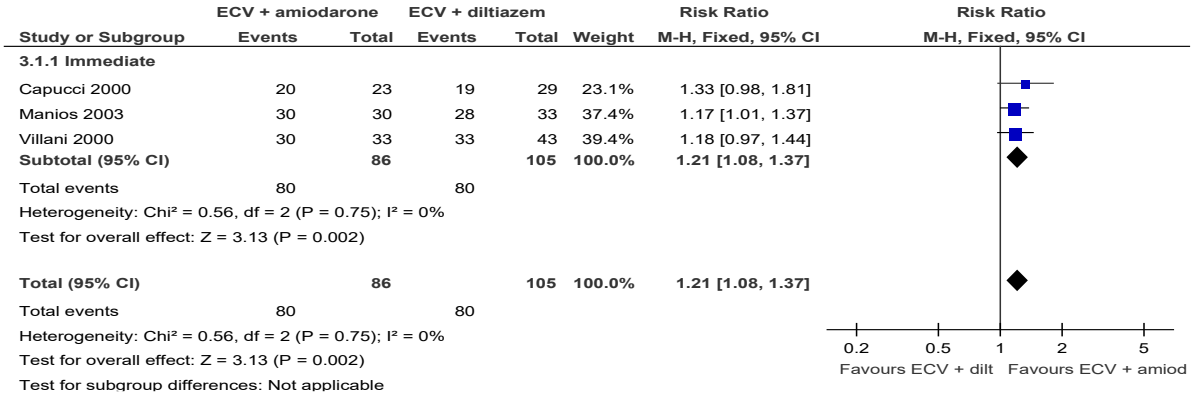
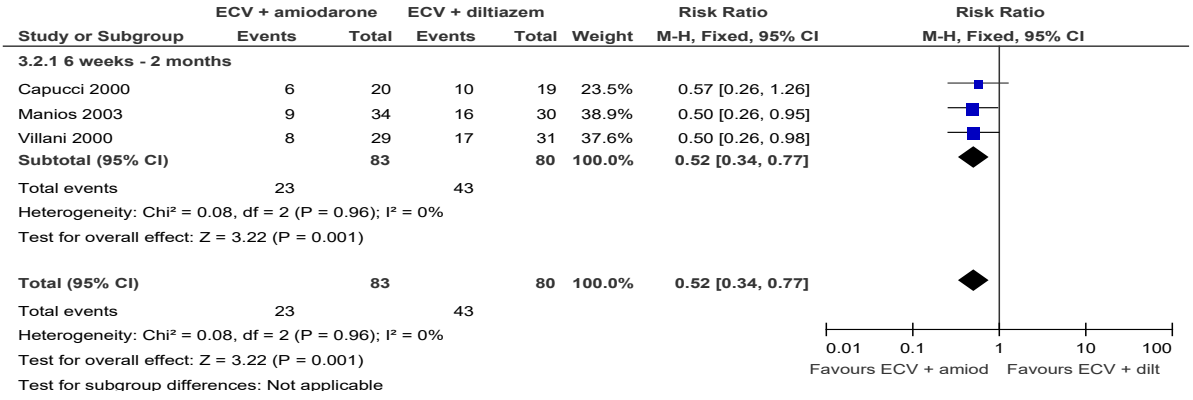


Figure 110: Recurrence of AF – 6 weeks to 2 months



I.9.15 ECV plus amiodarone versus ECV plus dronedarone

Figure 111: Restoration so sinus rhythm - immediately

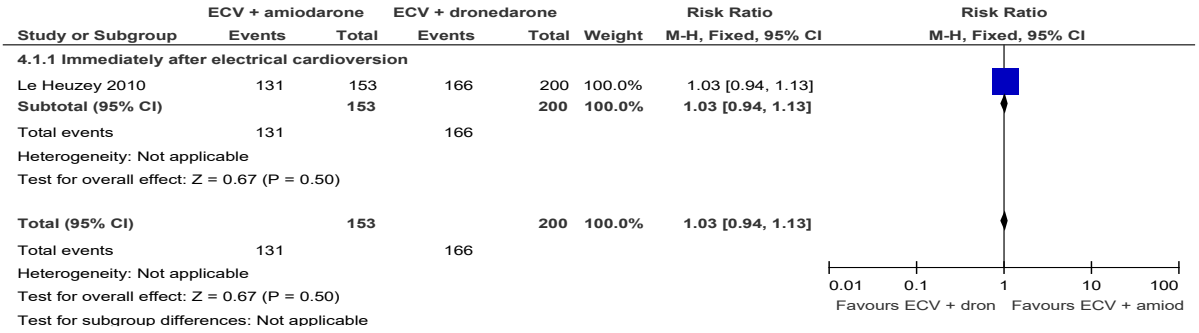


Figure 112: Recurrence of AF – 12 months

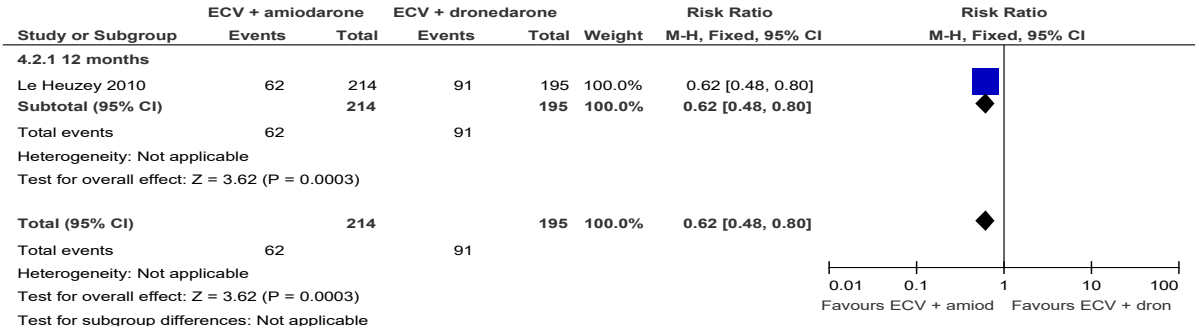


Figure 113: Heart failure – 12 months

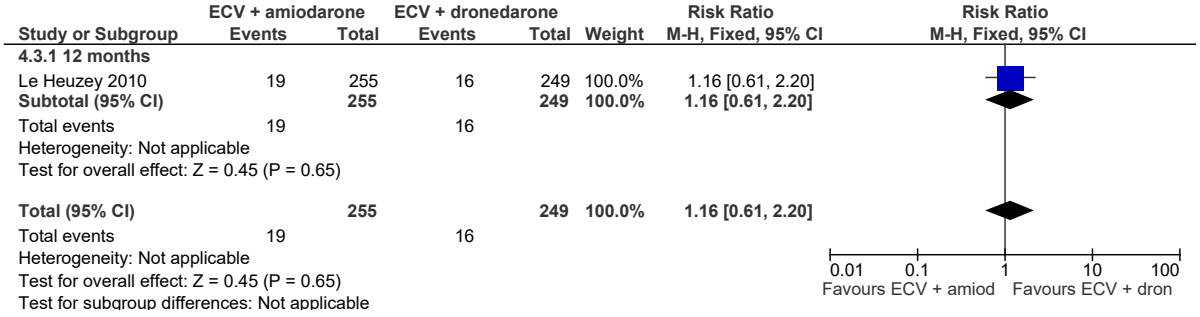
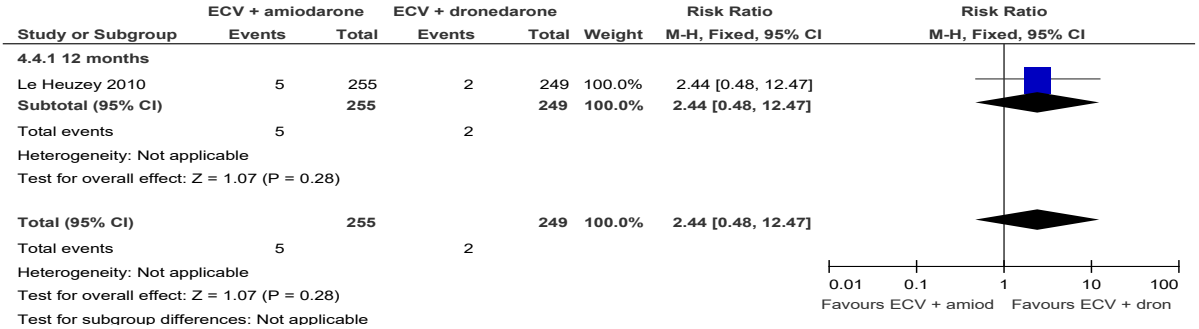
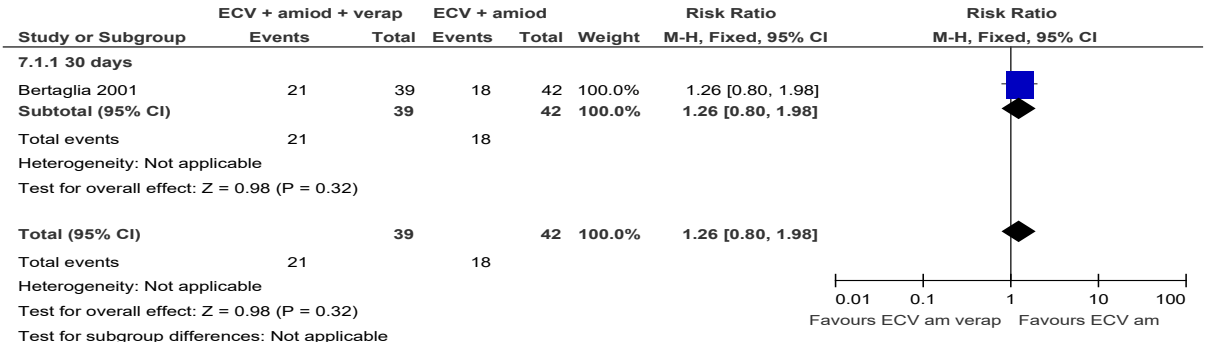


Figure 114: Mortality – 12 months



I.9.16 ECV plus amiodarone plus verapamil versus ECV plus amiodarone

Figure 115: AF relapse – 30 days



I.9.17 ECV plus propafenone plus verapamil versus ECV plus propafenone

Figure 116: Restoration of sinus rhythm - immediate

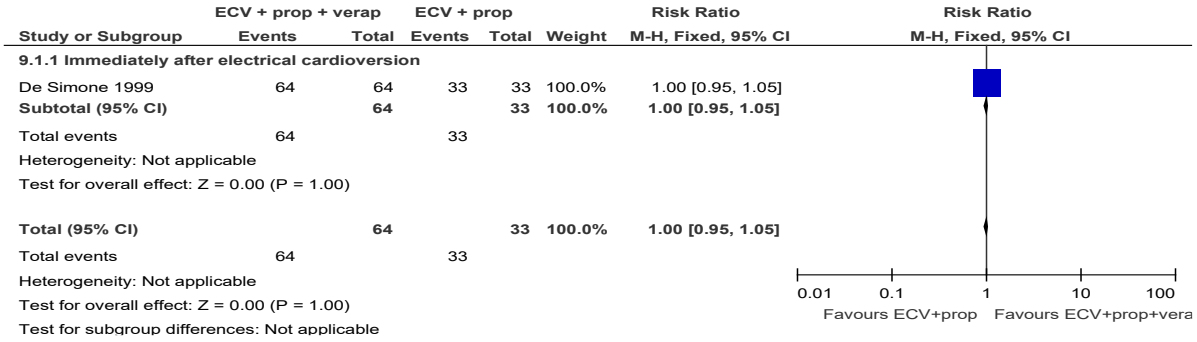
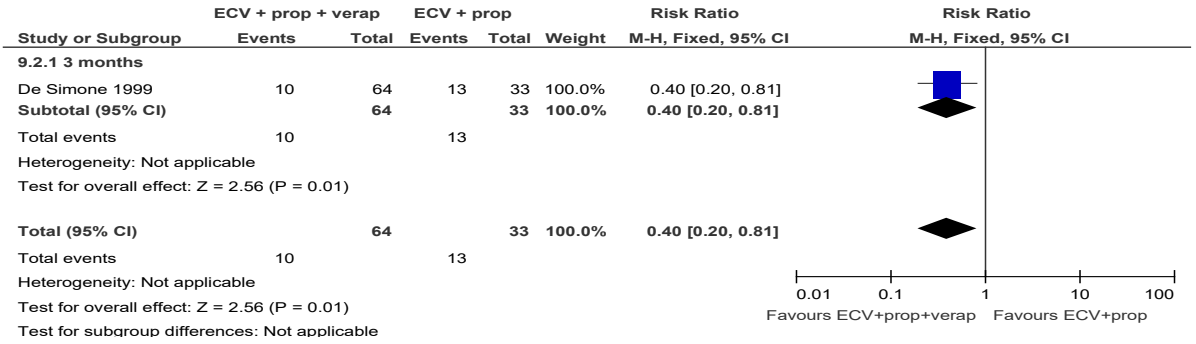
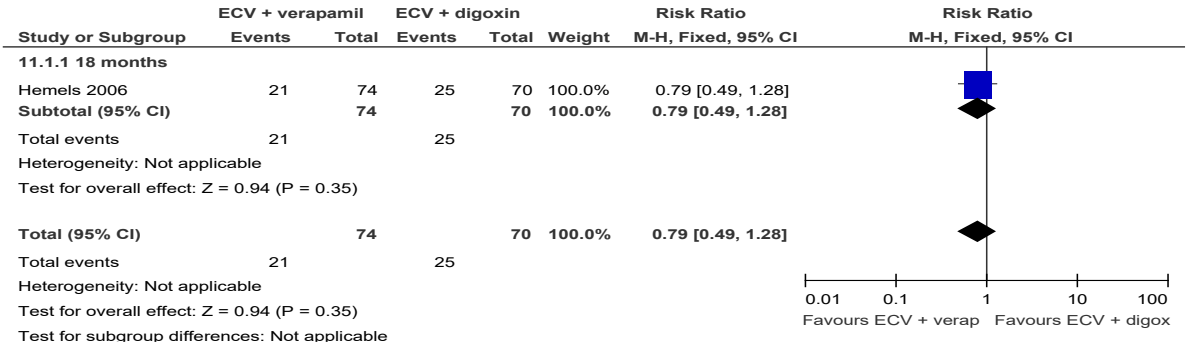


Figure 117: Recurrence of AF- 3 months



I.9.18 ECV plus verapamil versus ECV plus digoxin

Figure 118: Recurrence of AF -18 months



I.10 Maintenance of sinus rhythm

Figure 119: Mortality – individual anti-arrhythmics

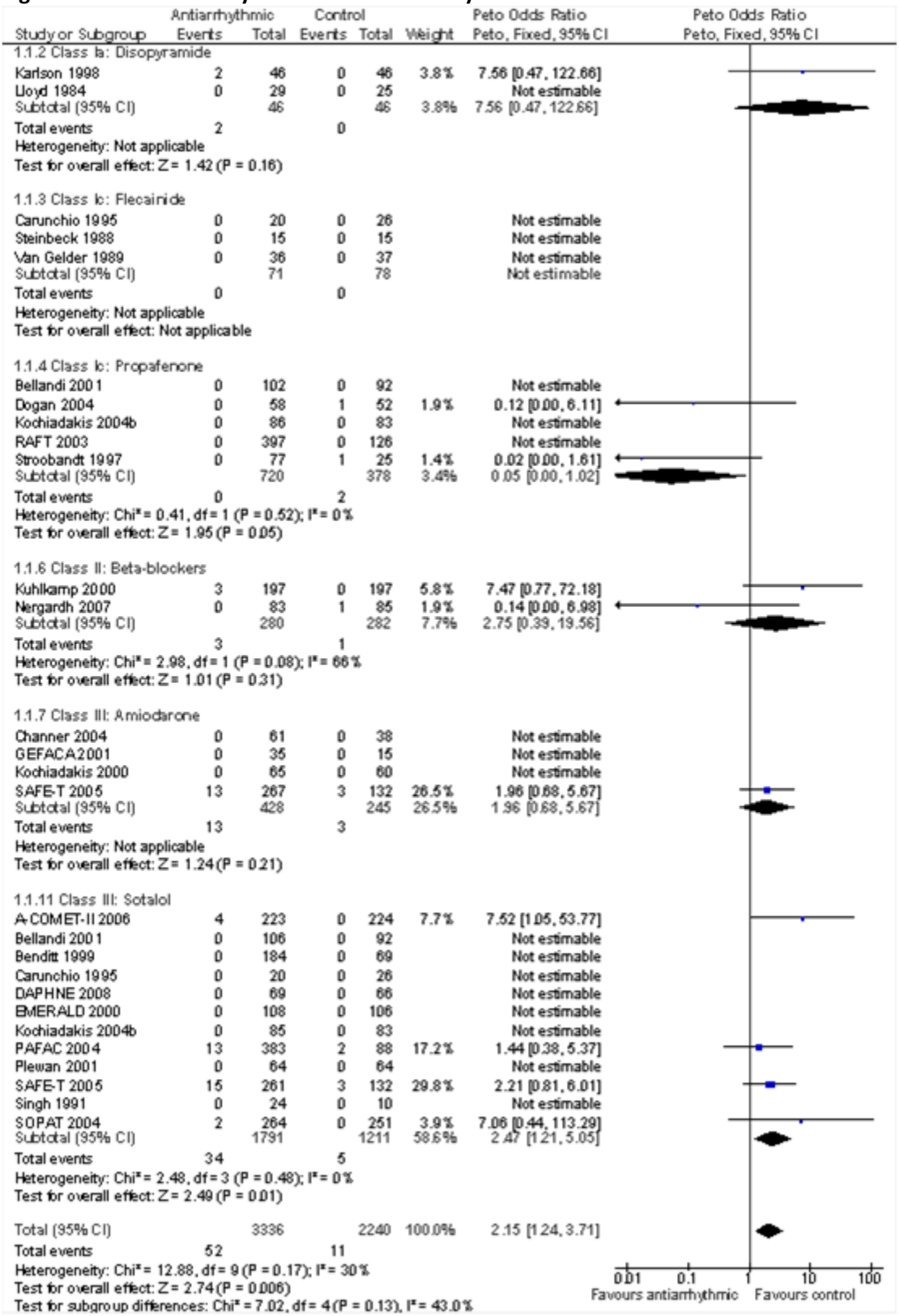


Figure 120: Mortality – comparing antiarrhythmic

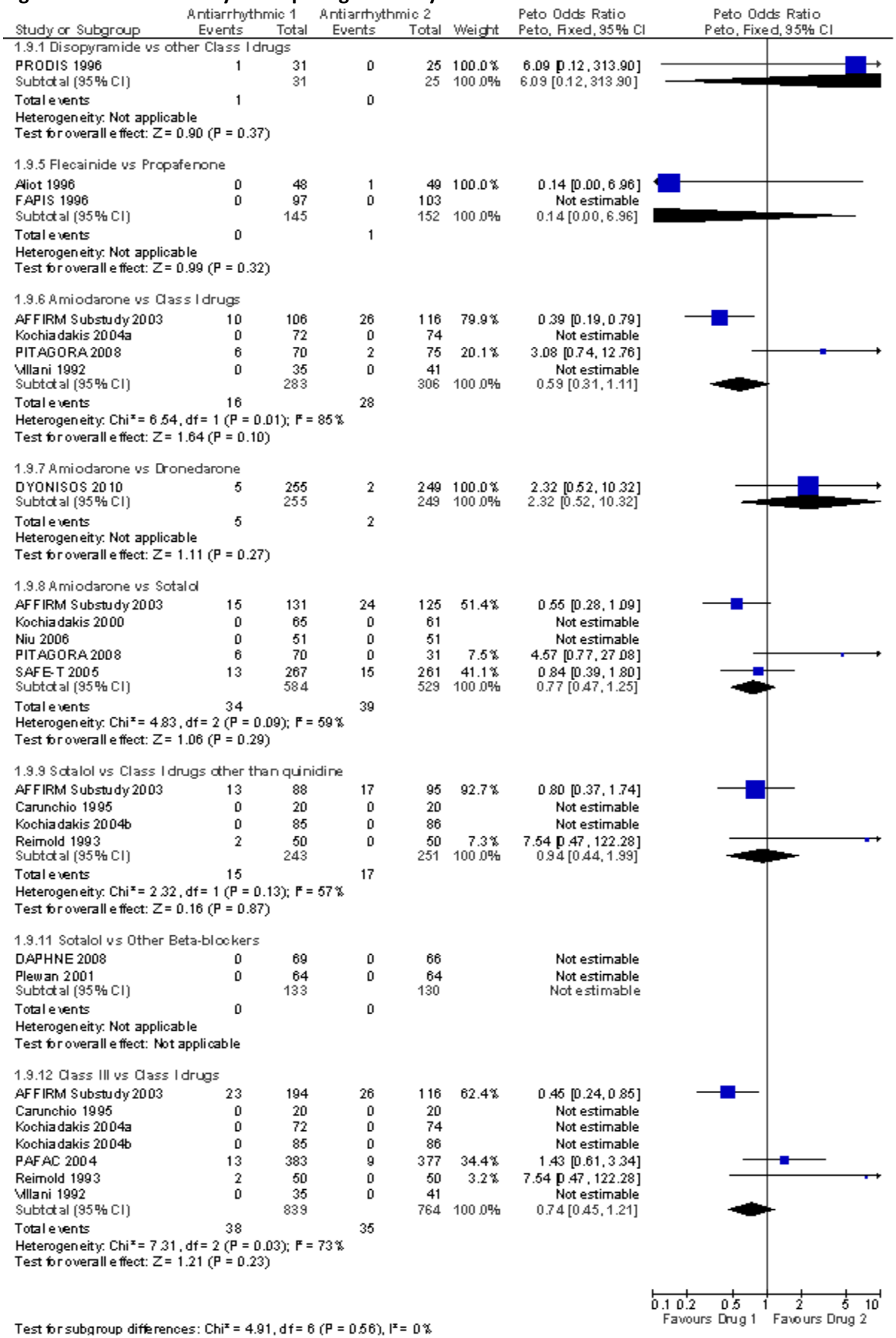


Figure 121: Withdrawals due to adverse events – individual anti-arrhythmics

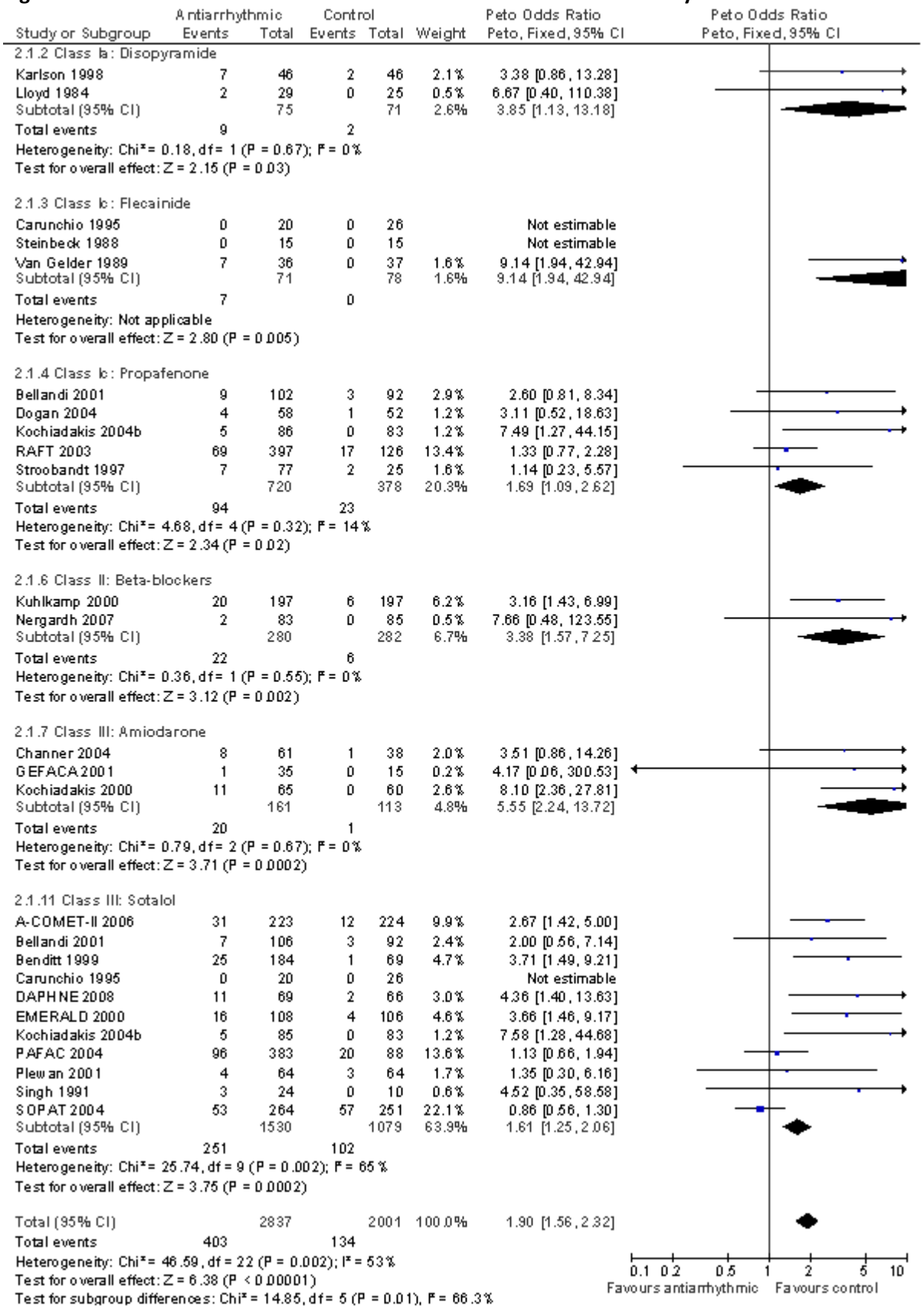


Figure 122: Withdrawals due to adverse events – comparing anti-arrhythmics

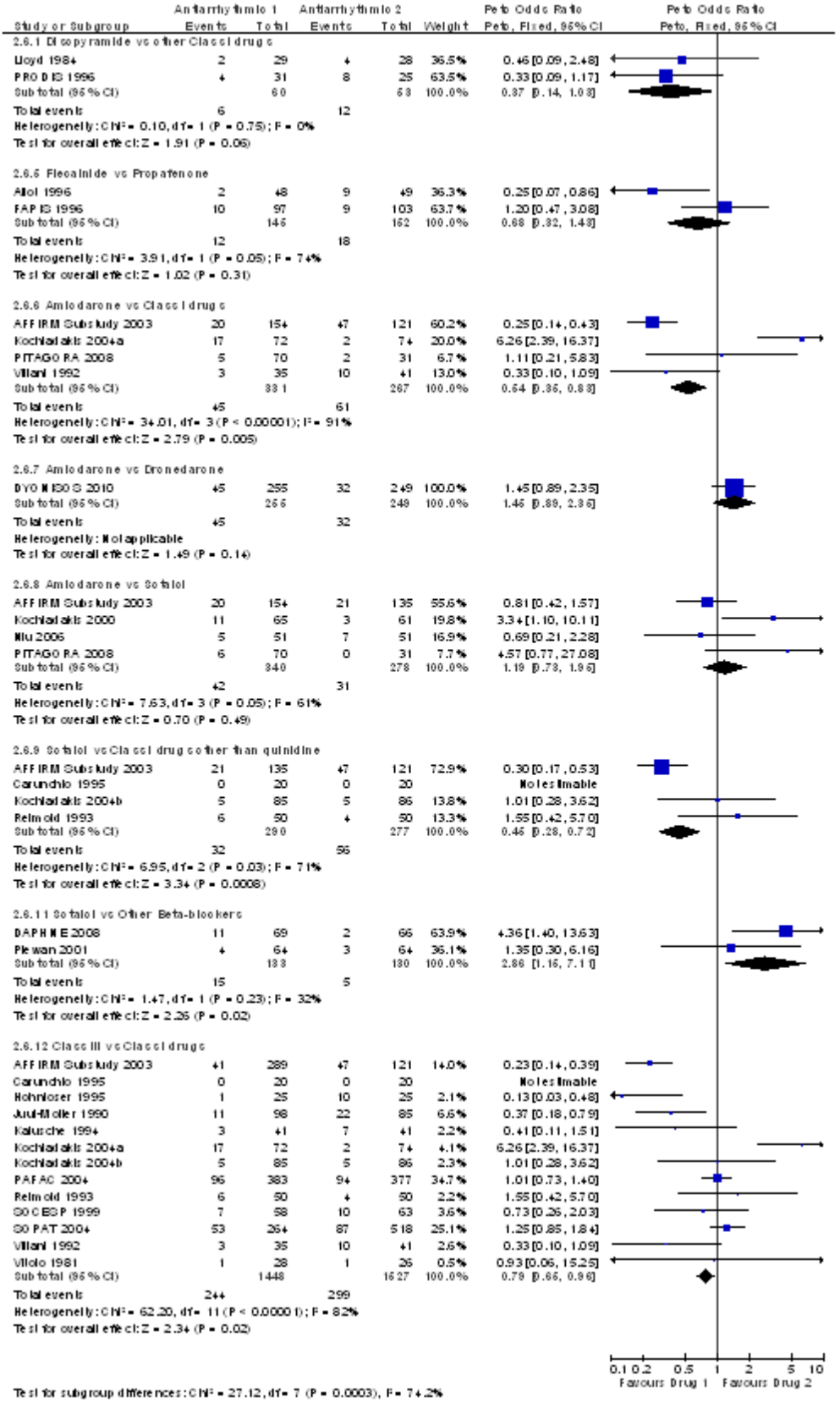


Figure 123: AF recurrence – individual anti-arrhythmics

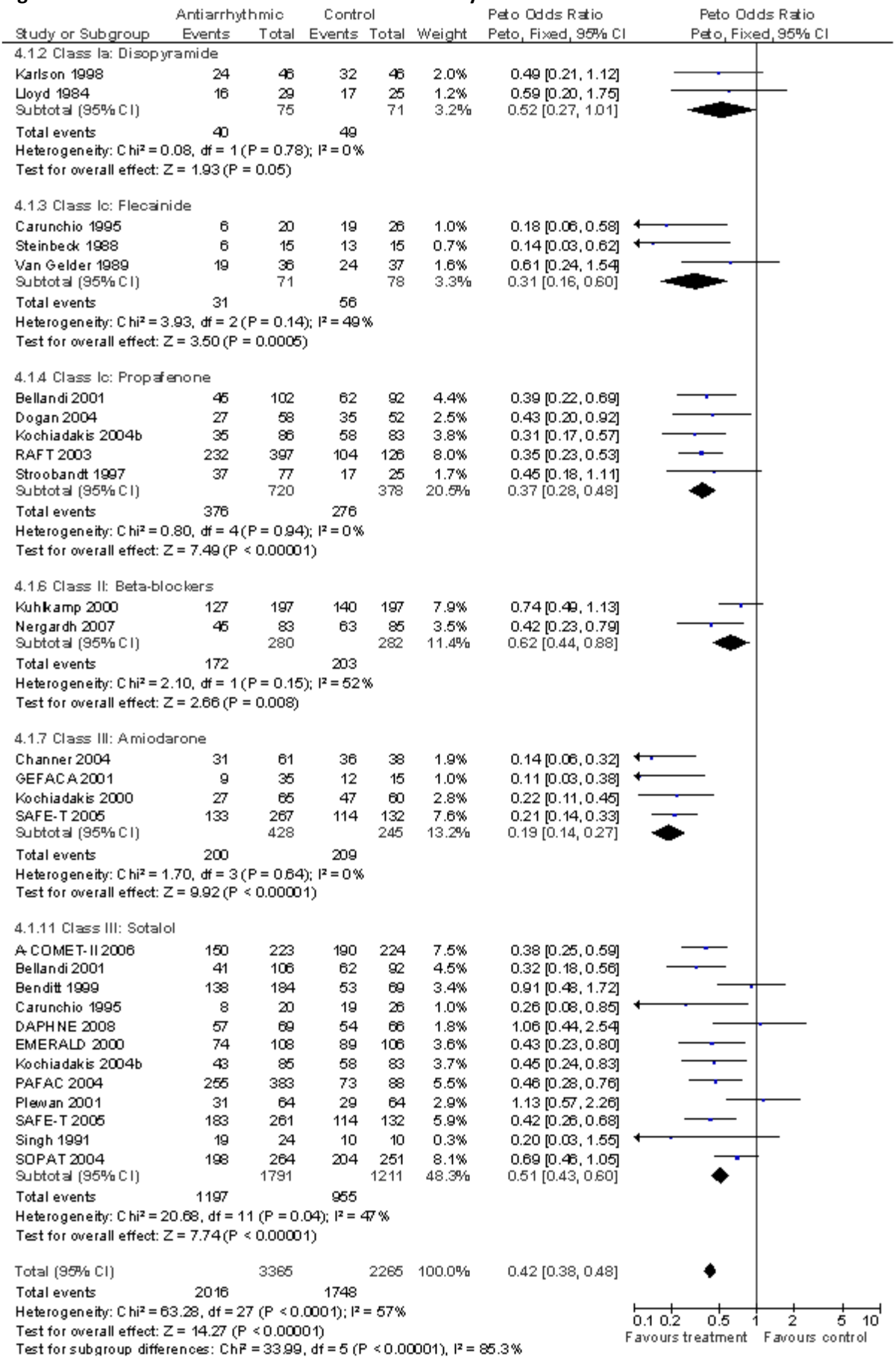
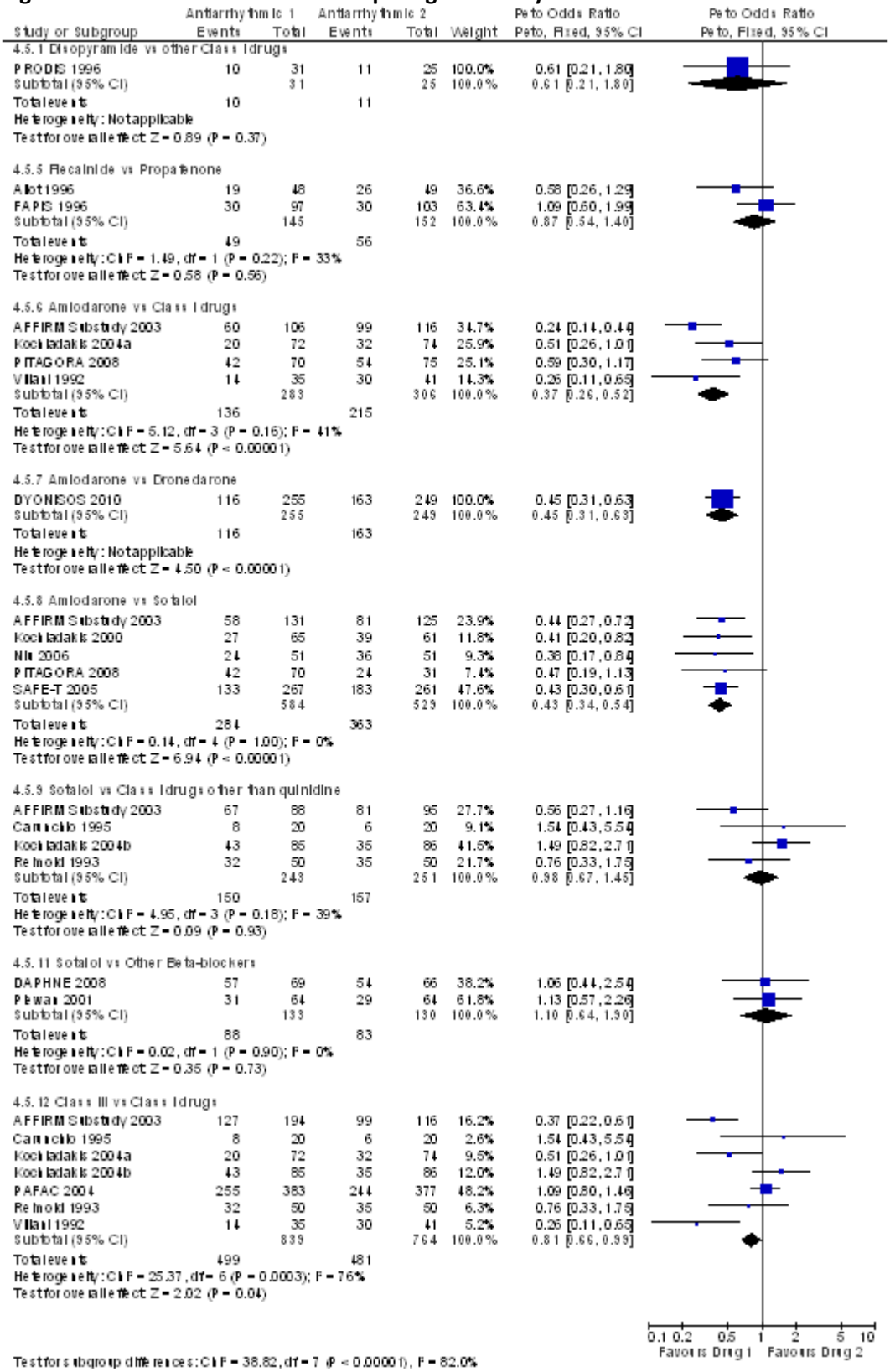


Figure 124: AF recurrence – comparing anti-arrhythmics



I.11 Catheter ablation versus medical therapies

Figure 125: SF-36 – mental component

Study or Subgroup	Catheter ablation Mean	SD	Total	Medical therapies Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Cosedis 2012	51.1	9.2	146	50.9	8	148	77.4%	0.20 [-1.77, 2.17]
Wilber 2010	8.5	12.4	90	1.6	8.3	39	22.6%	6.90 [3.25, 10.55]
Total (95% CI)			**236**			**187**	**100.0%**	**1.71 [-0.02, 3.45]**

Heterogeneity: Chi² = 10.00, df = 1 (P = 0.002); I² = 90%
Test for overall effect: Z = 1.93 (P = 0.05)

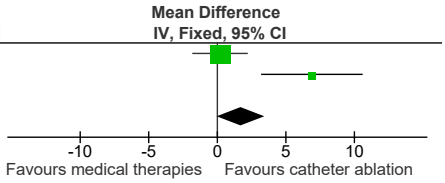


Figure 126: SF-36 – mental component (4 years follow- up)

Study or Subgroup	Catheter ablation Mean	SD	Total	Medical therapies Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pappone 2011	52.9	9	99	42.5	10	87	100.0%	10.40 [7.65, 13.15]
Total (95% CI)			**99**			**87**	**100.0%**	**10.40 [7.65, 13.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 7.41 (P < 0.00001)

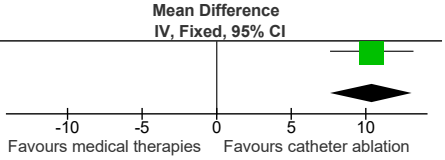


Figure 127: SF-36 – physical component

Study or Subgroup	Catheter ablation Mean	SD	Total	Medical therapies Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Cosedis 2012	50	8.8	146	47.9	8.9	148	60.5%	2.10 [0.08, 4.12]
Wilber 2010	7	8	90	0	6	39	39.5%	7.00 [4.49, 9.51]
Total (95% CI)			**236**			**187**	**100.0%**	**4.03 [2.46, 5.61]**

Heterogeneity: Chi² = 8.89, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 5.02 (P < 0.00001)

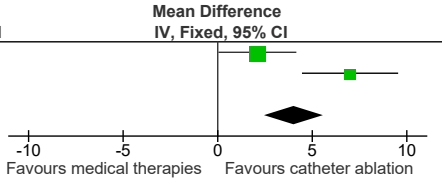


Figure 128: SF-36 – physical component (4 years follow-up)

Study or Subgroup	Catheter ablation Mean	SD	Total	Medical therapies Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pappone 2011	52.3	9	99	44.1	7	87	100.0%	8.20 [5.90, 10.50]
Total (95% CI)			**99**			**87**	**100.0%**	**8.20 [5.90, 10.50]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.98 (P < 0.00001)

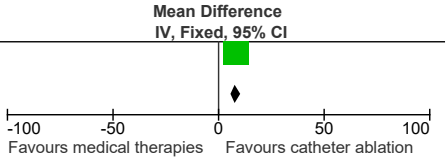
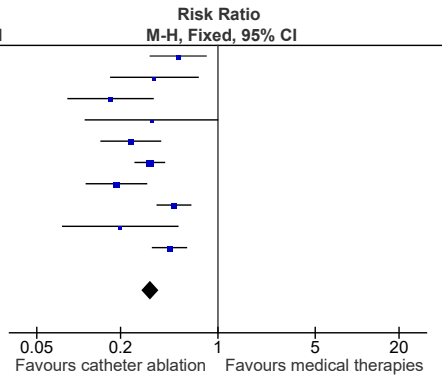


Figure 129: Recurrence of AF

Study or Subgroup	Catheter ablation Events	Total	Medical therapies Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cosedis 2012	22	146	43	148	8.7%	0.52 [0.33, 0.82]
Forleo 2009	7	35	20	35	4.1%	0.35 [0.17, 0.72]
Jaïs 2008	7	53	46	59	8.9%	0.17 [0.08, 0.34]
Krittayaphong 2003	3	15	9	15	1.8%	0.33 [0.11, 0.99]
Oral 2006 (1)	14	77	53	69	11.4%	0.24 [0.14, 0.39]
Packer 2013	49	163	76	82	20.6%	0.32 [0.25, 0.41]
Pappone 2006	14	99	75	99	15.3%	0.19 [0.11, 0.31]
Stabile 2006	30	68	63	69	12.8%	0.48 [0.37, 0.64]
Wazni 2005	4	32	22	35	4.3%	0.20 [0.08, 0.51]
Wilber 2010	38	103	46	56	12.2%	0.45 [0.34, 0.59]
Total (95% CI)		**791**		**667**	**100.0%**	**0.33 [0.29, 0.38]**
Total events	188		453			

Heterogeneity: Chi² = 27.28, df = 9 (P = 0.001); I² = 67%
Test for overall effect: Z = 16.13 (P < 0.00001)



(1) Patients in the control group received amiodarone and transthoracic cardioversion.

Figure 130: Recurrence of AF (4 years follow-up)

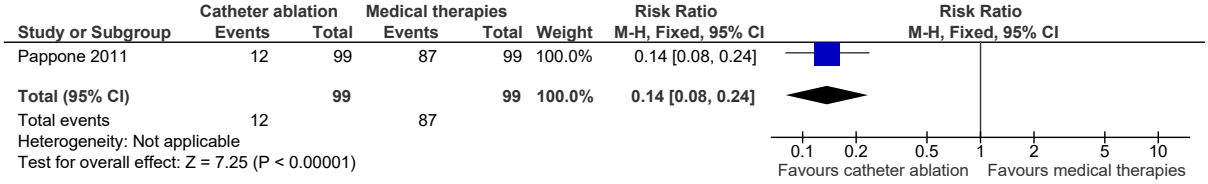


Figure 131: Mortality

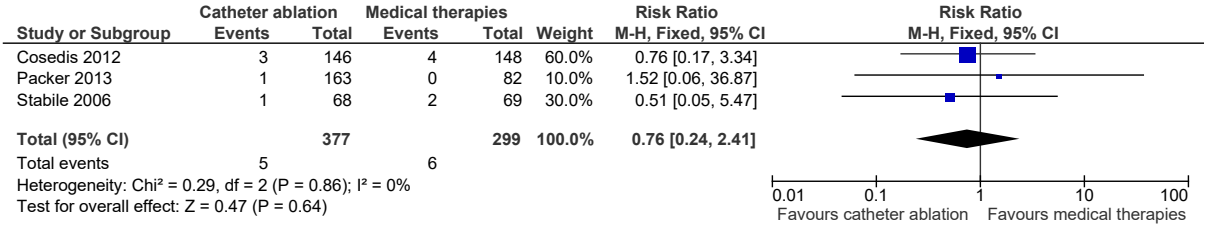
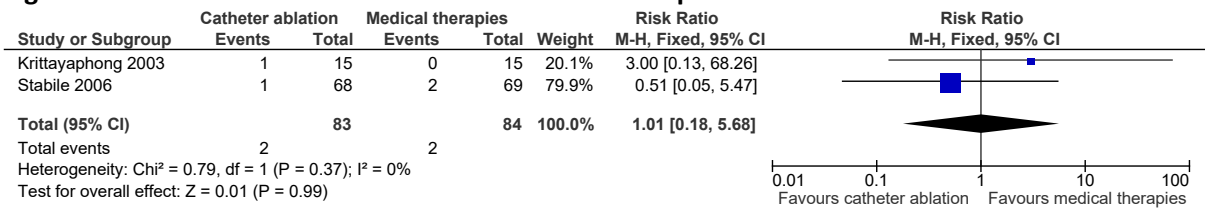


Figure 132: Fatal or non-fatal thromboembolic complications



Chen HS, Wen JM, Wu SN, Liu JP. Catheter ablation for paroxysmal and persistent atrial fibrillation (Review).Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD007101. DOI: 10.1002/14651858.CD007101.pub2 Copyright Cochrane Collaboration, reproduced with permission.

Figure 133: Stroke

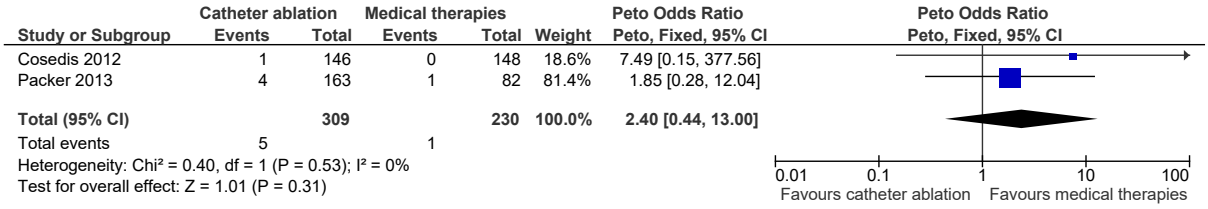


Figure 134: Hospitalisation for heart failure

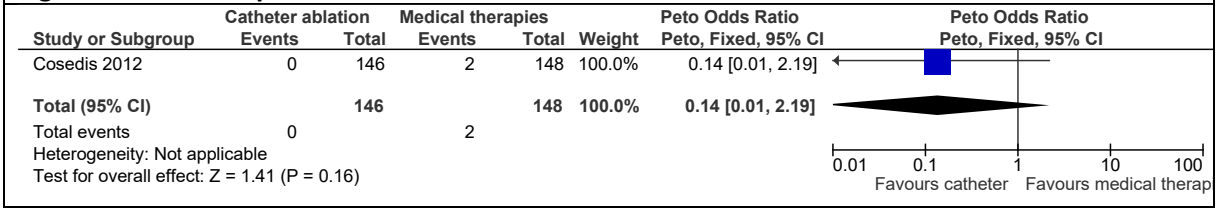
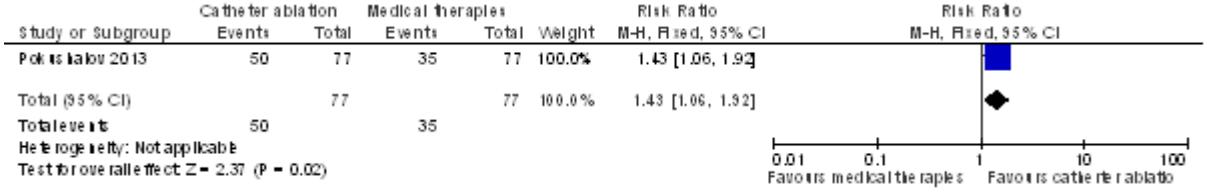


Figure 135: AF free at 3 years



I.12 Catheter ablation - patients with advanced heart failure

Figure 136: SF-36 – mental component

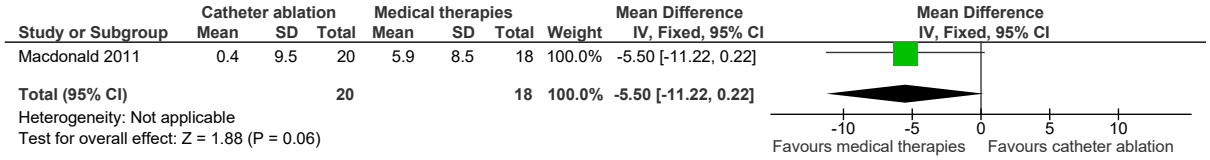


Figure 137: SF-36 – physical component

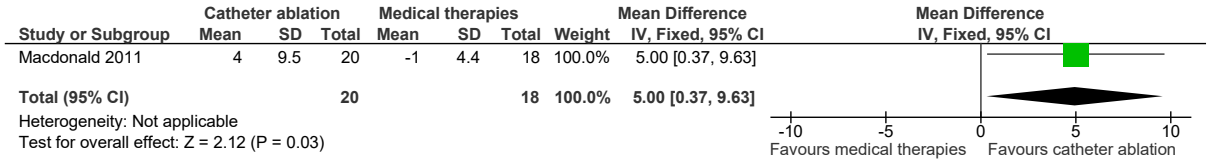


Figure 138: Maintenance of sinus rhythm

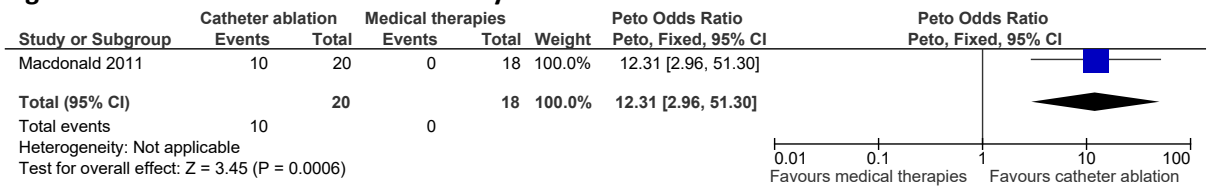


Figure 139: Fatal or non-fatal embolic complications

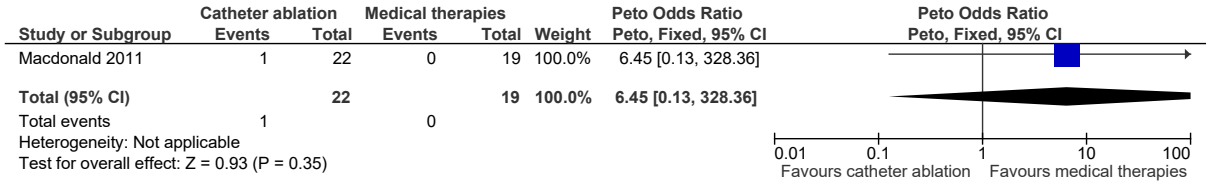
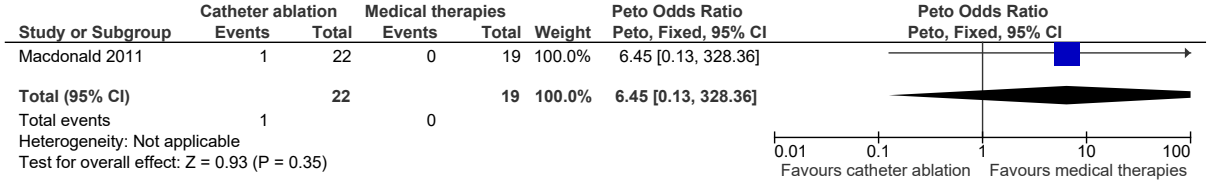


Figure 140: Hospitalisation (cardiovascular)



I.13 Left atrial catheter versus surgical ablation

Figure 141: All cause mortality (30 days)

Study or Subgroup	Surgical ablation Events	Total	Catheter ablation Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
BOERSMA 2012	0	61	1	63	100.0%	0.14 [0.00, 7.04]
Total (95% CI)		**61**		**63**	**100.0%**	**0.14 [0.00, 7.04]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

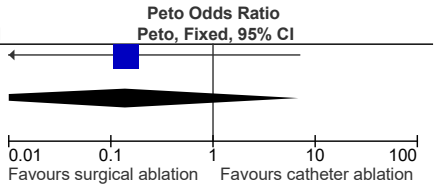


Figure 142: Freedom from left atrial arrhythmia

Study or Subgroup	Surgical ablation Events	Total	Catheter ablation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BOERSMA 2012	40	61	23	63	100.0%	1.80 [1.24, 2.61]
Total (95% CI)		**61**		**63**	**100.0%**	**1.80 [1.24, 2.61]**
Total events	40		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.08 (P = 0.002)

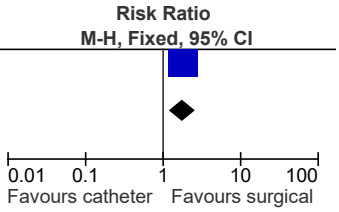


Figure 143: Stroke or thromboembolic complications

Study or Subgroup	Surgical ablation Events	Total	Catheter ablation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BOERSMA 2012	1	61	3	63	100.0%	0.34 [0.04, 3.22]
Total (95% CI)		**61**		**63**	**100.0%**	**0.34 [0.04, 3.22]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)

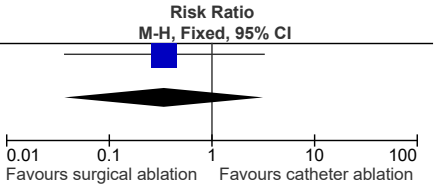
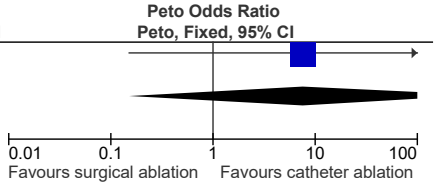


Figure 144: Major bleeding

Study or Subgroup	Surgical ablation Events	Total	Catheter ablation Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
BOERSMA 2012	1	61	0	63	100.0%	7.64 [0.15, 384.99]
Total (95% CI)		**61**		**63**	**100.0%**	**7.64 [0.15, 384.99]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)

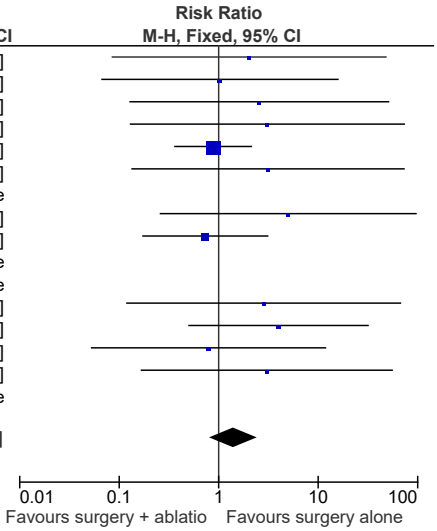


I.14 Left atrial surgical ablation

Figure 145: All cause mortality reported at 30 days

Study or Subgroup	Surgery + ablation Events	Total	Surgery alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abreu 2005	1	42	0	28	2.9%	2.02 [0.09, 47.97]
Akpinar 2003	1	33	1	34	4.8%	1.03 [0.07, 15.80]
Albrecht 2009	2	40	0	20	3.2%	2.56 [0.13, 50.95]
Blomstrom 2007	1	34	0	35	2.4%	3.09 [0.13, 73.21]
Budera 2012	9	116	9	102	46.2%	0.88 [0.36, 2.13]
Chevalier 2009	1	21	0	22	2.4%	3.14 [0.13, 72.96]
de Lima 2004	0	20	0	10		Not estimable
Deneke 2002	2	15	0	15	2.4%	5.00 [0.26, 96.13]
Doukas 2005	3	49	4	48	19.5%	0.73 [0.17, 3.11]
Jessurun 2003	0	25	0	10		Not estimable
Johansson 2012 (1)	0	30	0	35		Not estimable
Jonsson 2012	1	35	0	33	2.5%	2.83 [0.12, 67.19]
Khargi 2001	4	15	1	15	4.8%	4.00 [0.50, 31.74]
Schuetz 2003	1	24	1	19	5.4%	0.79 [0.05, 11.85]
Srivastava 2008	4	120	0	40	3.6%	3.05 [0.17, 55.43]
von Oppell 2009	0	24	0	25		Not estimable
Total (95% CI)		**643**		**491**	**100.0%**	**1.42 [0.82, 2.47]**
Total events	30		16			

Heterogeneity: Chi² = 4.94, df = 11 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)



(1) No data for Johansson as this is the same trial as the Blomstrom paper.

Figure 146: All cause mortality (longest endpoint)

Study or Subgroup	Surgery + ablation Events	Total	Surgery alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abreu 2005	2	41	2	28	7.2%	0.68 [0.10, 4.57]
Akpinar 2003	1	32	2	33	6.0%	0.52 [0.05, 5.41]
Albrecht 2009	2	38	0	20	2.0%	2.69 [0.14, 53.52]
Blomstrom 2007	1	33	0	35	1.5%	3.18 [0.13, 75.33]
Budera 2012	18	111	16	92	52.9%	0.93 [0.50, 1.72]
Chevalier 2009	0	20	0	22		Not estimable
de Lima 2004	1	20	0	10	2.0%	1.57 [0.07, 35.46]
Deneke 2002	2	13	1	15	2.8%	2.31 [0.24, 22.62]
Doukas 2005	0	45	0	44		Not estimable
Jessurun 2003	0	25	0	10		Not estimable
Johansson 2012	0	30	0	35		Not estimable
Jonsson 2012	2	35	2	33	6.2%	0.94 [0.14, 6.31]
Khargi 2001	4	15	1	15	3.0%	4.00 [0.50, 31.74]
Schuetz 2003	0	23	0	18		Not estimable
Srivastava 2008	7	116	2	40	9.0%	1.21 [0.26, 5.57]
von Oppell 2009	0	24	2	25	7.4%	0.21 [0.01, 4.12]
Total (95% CI)		**621**		**475**	**100.0%**	**1.07 [0.69, 1.68]**
Total events	40		28			

Heterogeneity: Chi² = 4.85, df = 10 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)

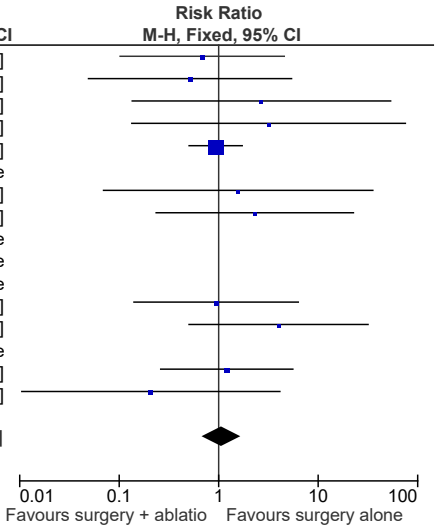


Figure 147: All cause mortality overall at 12months; van Bruegel

Study or Subgroup	Surgery + ablation Events	Total	Surgery alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
van Breugel 2010	2	65	5	67	100.0%	0.41 [0.08, 2.05]
Total (95% CI)		**65**		**67**	**100.0%**	**0.41 [0.08, 2.05]**
Total events	2		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)

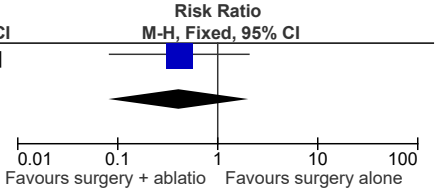


Figure 148: Sinus rhythm at longest endpoint

Study or Subgroup	Surgery + ablation Events	Total	Surgery alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abreu 2005	31	39	7	26	6.5%	2.95 [1.54, 5.67]
Akpinar 2003	10	31	1	32	1.2%	10.32 [1.40, 75.92]
Albrecht 2009	31	36	6	20	6.2%	2.87 [1.45, 5.68]
Blomstrom 2007	22	30	15	35	9.2%	1.71 [1.10, 2.65]
Budera 2012	65	93	30	76	11.2%	1.77 [1.30, 2.41]
Chevalier 2009	12	20	1	22	1.2%	13.20 [1.88, 92.60]
de Lima 2004	16	19	4	10	5.3%	2.11 [0.96, 4.61]
Deneke 2002	9	11	3	14	3.6%	3.82 [1.35, 10.81]
Doukas 2005	20	45	2	44	2.2%	9.78 [2.43, 39.37]
Jessurun 2003	22	25	2	10	2.7%	4.40 [1.26, 15.33]
Johansson 2012	22	30	16	35	9.5%	1.60 [1.05, 2.44]
Jonsson 2012	22	31	12	33	8.3%	1.95 [1.18, 3.23]
Khargi 2001	9	11	4	14	4.6%	2.86 [1.20, 6.86]
Schuetz 2003	17	23	3	18	3.5%	4.43 [1.53, 12.82]
Srivastava 2008	75	109	8	38	6.8%	3.27 [1.74, 6.13]
van Breugel 2010	36	63	26	62	10.4%	1.36 [0.95, 1.96]
von Oppell 2009	18	24	9	23	7.6%	1.92 [1.10, 3.35]
Total (95% CI)		**640**		**512**	**100.0%**	**2.34 [1.86, 2.94]**
Total events	437		149			

Heterogeneity: Tau² = 0.10; Chi² = 32.11, df = 16 (P = 0.010); I² = 50%
Test for overall effect: Z = 7.32 (P < 0.00001)

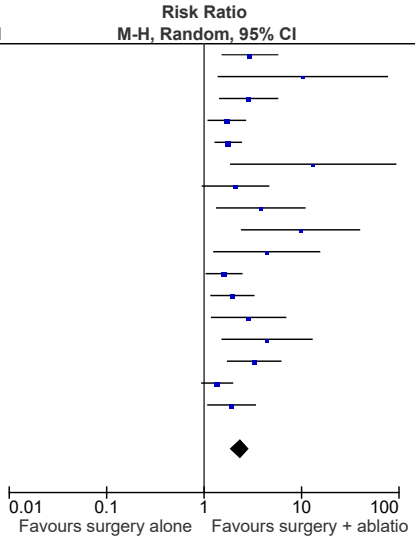


Figure 149: Recurrent AF at longest endpoint

Study or Subgroup	Surgery + ablation Events	Total	Surgery alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abreu 2005	5	39	17	26	13.3%	0.20 [0.08, 0.47]
Albrecht 2009	6	40	14	20	14.4%	0.21 [0.10, 0.47]
de Lima 2004	3	20	5	10	9.1%	0.30 [0.09, 1.01]
Schuetz 2003	3	15	6	9	10.2%	0.30 [0.10, 0.91]
Srivastava 2008	24	116	26	38	20.8%	0.30 [0.20, 0.46]
van Breugel 2010	21	63	26	62	20.1%	0.79 [0.50, 1.25]
von Oppell 2009	4	24	14	23	12.1%	0.27 [0.11, 0.71]
Total (95% CI)		**317**		**188**	**100.0%**	**0.33 [0.21, 0.52]**
Total events	66		108			

Heterogeneity: Tau² = 0.22; Chi² = 16.26, df = 6 (P = 0.01); I² = 63%
Test for overall effect: Z = 4.78 (P < 0.00001)

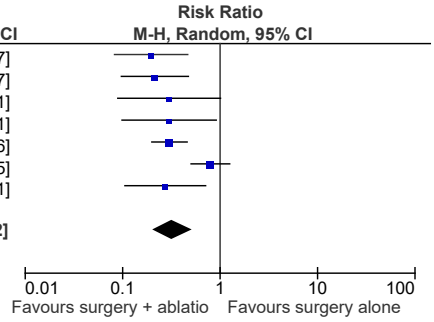


Figure 150: SF-36 bodily pain change scores; von Oppell

Study or Subgroup	Surgery + ablation Mean	SD	Total	Surgery alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
von Oppell 2009	70	4.098	24	76	4.098	23	100.0%	-6.00 [-8.34, -3.66]
Total (95% CI)			**24**			**23**	**100.0%**	**-6.00 [-8.34, -3.66]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.02 (P < 0.00001)

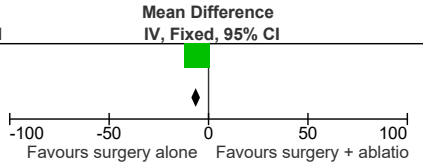


Figure 151: SF-36 role – emotional change scores; von Oppell

Study or Subgroup	Surgery + ablation Mean	SD	Total	Surgery alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
von Oppell 2009	59	5.9814	24	80	5.9814	23	100.0%	-21.00 [-24.42, -17.58]
Total (95% CI)			**24**			**23**	**100.0%**	**-21.00 [-24.42, -17.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 12.03 (P < 0.00001)

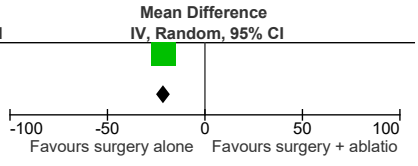


Figure 152: SF-36 mental health change scores; von Oppell

Study or Subgroup	Surgery + ablation Mean	SD	Total	Surgery alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
von Oppell 2009	75	6.7855	24	82	6.7855	23	100.0%	-7.00 [-10.88, -3.12]
Total (95% CI)			**24**			**23**	**100.0%**	**-7.00 [-10.88, -3.12]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.54 (P = 0.0004)

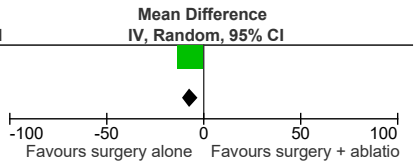


Figure 153: SF-36 physical functioning end scores; van Breugel

Study or Subgroup	Surgery + ablation Mean	SD	Total	Surgery alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
van Breugel 2010	68.42	23.21	63	61.24	23.86	62	100.0%	7.18 [-1.07, 15.43]
Total (95% CI)			**63**			**62**	**100.0%**	**7.18 [-1.07, 15.43]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.71 (P = 0.09)

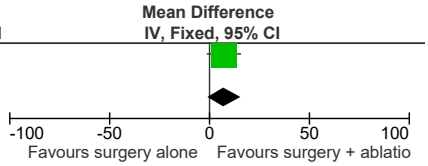


Figure 154: SF-36 mental health end scores; van Breugel

Study or Subgroup	Surgery + ablation Mean	SD	Total	Surgery alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
van Breugel 2010	77.69	13.04	63	73.99	17.46	62	100.0%	3.70 [-1.71, 9.11]
Total (95% CI)			**63**			**62**	**100.0%**	**3.70 [-1.71, 9.11]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)

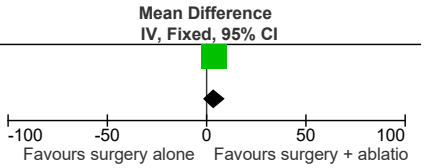


Figure 155: SF-36 physical pain health end scores; van Breugel

Study or Subgroup	Surgery + ablation Mean	SD	Total	Surgery alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
van Breugel 2010	77.74	22.59	63	72.77	21.94	62	100.0%	4.97 [-2.84, 12.78]
Total (95% CI)			**63**			**62**	**100.0%**	**4.97 [-2.84, 12.78]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)

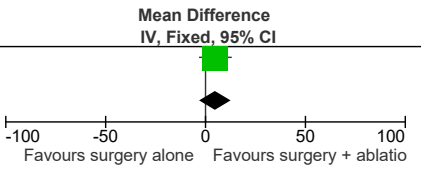


Figure 156: SF-36 vitality end scores; van Breugel

Study or Subgroup	Surgery + ablation Mean	SD	Total	Surgery alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
van Breugel 2010	61.36	16.95	63	59.99	17.8	62	100.0%	1.37 [-4.73, 7.47]
Total (95% CI)			**63**			**62**	**100.0%**	**1.37 [-4.73, 7.47]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

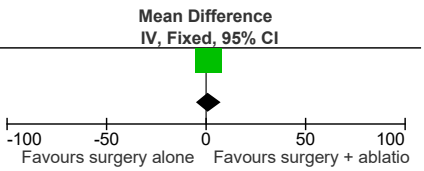


Figure 157: SF-36 role limitation due to emotional problems end scores; van Breugel

Study or Subgroup	Surgery + ablation Mean	SD	Total	Surgery alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
van Breugel 2010	72.11	35.71	63	69.52	36.64	62	100.0%	2.59 [-10.10, 15.28]
Total (95% CI)			**63**			**62**	**100.0%**	**2.59 [-10.10, 15.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)

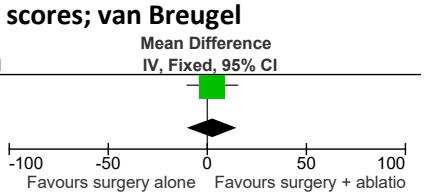


Figure 158: SF-36 role limitation due to social functioning end scores; van Breugel

Study or Subgroup	Surgery + ablation Mean	SD	Total	Surgery alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
van Breugel 2010	80.04	19.34	63	76.21	24.68	62	100.0%	3.83 [-3.95, 11.61]
Total (95% CI)			**63**			**62**	**100.0%**	**3.83 [-3.95, 11.61]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.33)

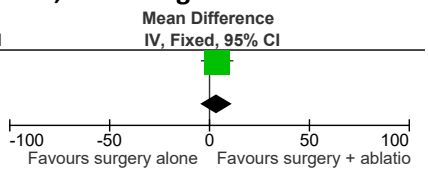


Figure 159: Stroke or thromboembolic complications

Study or Subgroup	Surgery + ablation Events	Total	Surgery alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abreu 2005	0	42	0	28		Not estimable
Akpinar 2003	0	33	2	34	9.4%	0.21 [0.01, 4.13]
Albrecht 2009	4	40	8	20	27.4%	0.25 [0.09, 0.73]
Blomstrom 2007	5	34	2	35	20.7%	2.57 [0.54, 12.38]
Budera 2012	3	111	4	92	21.9%	0.62 [0.14, 2.71]
Chevalier 2009	3	21	0	22	9.8%	7.32 [0.40, 133.66]
Jonsson 2012	1	35	1	33	10.8%	0.94 [0.06, 14.47]
Total (95% CI)		**316**		**264**	**100.0%**	**0.78 [0.27, 2.25]**
Total events	16		17			

Heterogeneity: Tau² = 0.76; Chi² = 9.51, df = 5 (P = 0.09); I² = 47%
Test for overall effect: Z = 0.46 (P = 0.65)

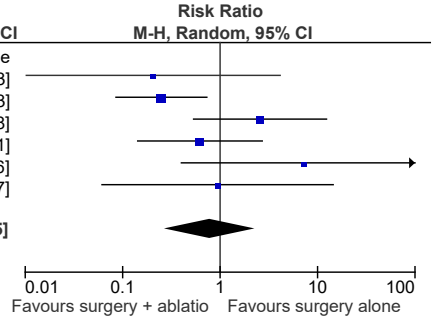
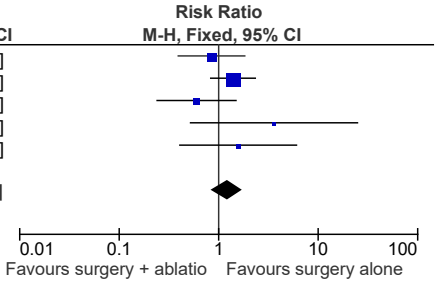


Figure 160: concomitant use of antiarrhythmic drugs

Study or Subgroup	Surgery + ablation Events	Total	Surgery alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blomstrom 2007	8	30	11	35	25.4%	0.85 [0.39, 1.83]
Budera 2012	29	93	17	76	46.7%	1.39 [0.83, 2.34]
de Lima 2004	6	20	5	10	16.6%	0.60 [0.24, 1.49]
Jessurun 2003	9	25	1	10	3.6%	3.60 [0.52, 24.84]
Jonsson 2012	5	35	3	33	7.7%	1.57 [0.41, 6.06]
Total (95% CI)		**203**		**164**	**100.0%**	**1.22 [0.84, 1.75]**
Total events	57		37			

Heterogeneity: Chi² = 4.76, df = 4 (P = 0.31); I² = 16%
Test for overall effect: Z = 1.05 (P = 0.29)



I.15 Pace and ablate

I.15.1 Ablate and pace versus Pharmacological therapies

Figure 161: Ablate and pace versus Pharmacological therapies, outcome: 1.1 Mortality

Study or Subgroup	Abl + Pace Events	Total	Pharmacological therapies Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
WEERASOORIYA 2003	2	49	1	50	100.0%	2.04 [0.19, 21.79]
Total (95% CI)		**49**		**50**	**100.0%**	**2.04 [0.19, 21.79]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)

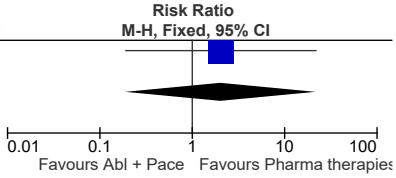


Figure 162: Ablate and pace versus Pharmacological therapies, outcome: 1.2 Living with heart failure questionnaire

Study or Subgroup	Abl + Pace Mean	SD	Total	Pharmacological therapies Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BRIGNOLE 1999	20	16	21	43	22	18	100.0%	-23.00 [-35.25, -10.75]
Total (95% CI)			**21**			**18**	**100.0%**	**-23.00 [-35.25, -10.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.68 (P = 0.0002)

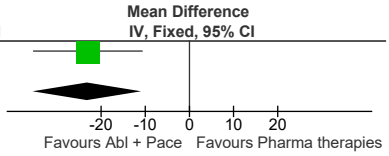


Figure 163: Ablate and pace versus Pharmacological therapies, outcome: 1.3 McMaster Health Index

Study or Subgroup	Abl + Pace Mean	SD	Total	Pharmacological therapies Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 DDDR/MS pacemaker								
MARSHALL 1999	16.1	3.2	37	15.7	3	19	100.0%	0.40 [-1.30, 2.10]
Subtotal (95% CI)			**37**			**19**	**100.0%**	**0.40 [-1.30, 2.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.64)								
1.3.2 VVIR pacemaker								
MARSHALL 1999B	15.6	3.2	29	15.7	3	19	100.0%	-0.10 [-1.88, 1.68]
Subtotal (95% CI)			**29**			**19**	**100.0%**	**-0.10 [-1.88, 1.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.91)								

Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%

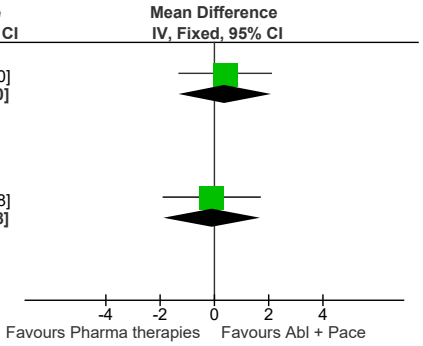


Figure 164: Ablate and pace versus Pharmacological therapies, outcome: 1.4 The Psychological General Well Being Questionnaire

Study or Subgroup	Abl + Pace Mean	SD	Total	Pharmacological therapies Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 DDDR/MS pacemaker								
MARSHALL 1999	77.4	21.6	37	68.5	13.6	19	100.0%	8.90 [-0.36, 18.16]
Subtotal (95% CI)			**37**			**19**	**100.0%**	**8.90 [-0.36, 18.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.88 (P = 0.06)								
1.4.2 VVIR pacemaker								
MARSHALL 1999B	72.4	21	29	68.5	13.6	19	100.0%	3.90 [-5.89, 13.69]
Subtotal (95% CI)			**29**			**19**	**100.0%**	**3.90 [-5.89, 13.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.78 (P = 0.43)								

Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.47), I² = 0%

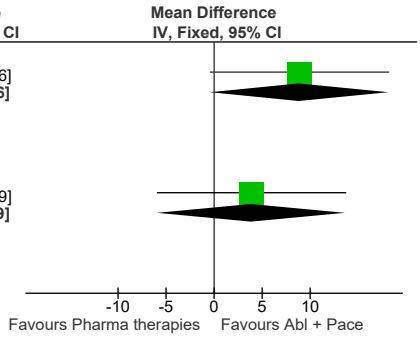


Figure 165: Ablate and pace versus Pharmacological therapies, outcome: 1.5 Assessment of Quality of Life Questionnaire

Study or Subgroup	Abl + Pace Mean	SD	Total	Pharmacological therapies Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
WEERASOORIYA 2003	0.75	0.18	34	0.66	0.18	47	100.0%	0.09 [0.01, 0.17]
Total (95% CI)			**34**			**47**	**100.0%**	**0.09 [0.01, 0.17]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.22 (P = 0.03)

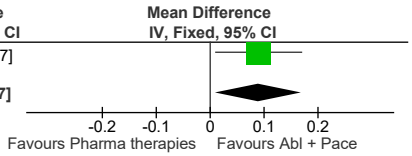


Figure 166: Ablate and pace versus Pharmacological therapies, outcome: 1.6 Sickness Impact Profile

Study or Subgroup	Abl + Pace Mean	SD	Total	Pharmacological therapies Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
WEERASOORIYA 2003	8.89	8.3	34	6.76	4.63	47	100.0%	2.13 [-0.96, 5.22]
Total (95% CI)			**34**			**47**	**100.0%**	**2.13 [-0.96, 5.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)

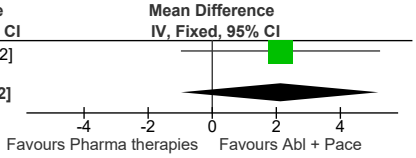


Figure 167: Ablate and pace versus Pharmacological therapies, outcome: -Hospitalisation or electrical cardioversion

Study or Subgroup	Abl + Pace Events	Abl + Pace Total	Pharmacological therapies Events	Pharmacological therapies Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRIGNOLE 1997	1	21	6	18	100.0%	0.14 [0.02, 1.08]
Total (95% CI)		**21**		**18**	**100.0%**	**0.14 [0.02, 1.08]**
Total events	1		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.89 (P = 0.06)

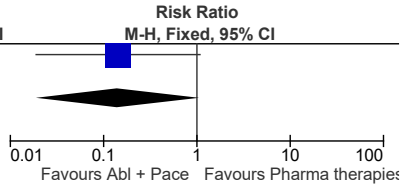
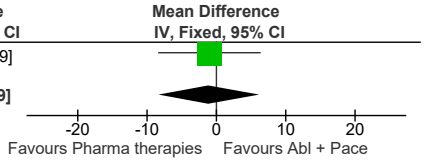


Figure 168: Ablate and pace versus Pharmacological therapies, outcome: - Ejection fraction

Study or Subgroup	Abl + Pace Mean	Abl + Pace SD	Abl + Pace Total	Pharmacological therapies Mean	Pharmacological therapies SD	Pharmacological therapies Total	Weight	Mean Difference IV, Fixed, 95% CI
BRIGNOLE 1997	57	12	19	58	10	16	100.0%	-1.00 [-8.29, 6.29]
Total (95% CI)			**19**			**16**	**100.0%**	**-1.00 [-8.29, 6.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)



I.15.2 Ablate and pace versus Pharmacological therapies (AF and heart failure)

Figure 169: Ablate and pace versus Pharmacological therapies (Heart failure), outcome: 2.1 Mortality

Study or Subgroup	Abl + Pace Events	Abl + Pace Total	Pharmacological Events	Pharmacological Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRIGNOLE 1998	3	32	4	34	100.0%	0.80 [0.19, 3.29]
Total (95% CI)		**32**		**34**	**100.0%**	**0.80 [0.19, 3.29]**
Total events	3		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.75)

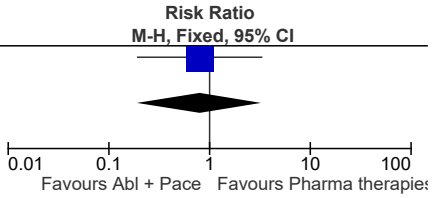


Figure 170: Ablate and pace versus Pharmacological therapies (Heart failure), outcome: 2.2 Living with heart failure questionnaire

Study or Subgroup	Abl + Pace Mean	Abl + Pace SD	Abl + Pace Total	Pharmacological Mean	Pharmacological SD	Pharmacological Total	Weight	Mean Difference IV, Fixed, 95% CI
BRIGNOLE 1998	32	20	28	37	18	26	100.0%	-5.00 [-15.14, 5.14]
Total (95% CI)			**28**			**26**	**100.0%**	**-5.00 [-15.14, 5.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

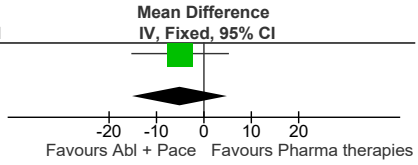
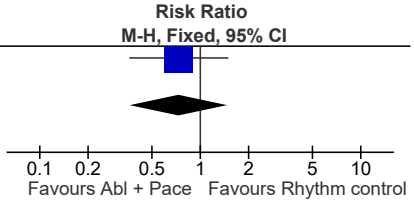


Figure 171: Ablate and pace versus Pharmacological therapies (Heart failure), outcome: 2.3 Hospitalisation or electrical cardioversion

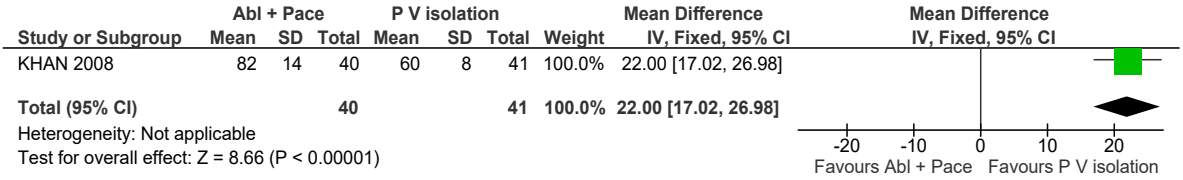
Study or Subgroup	Abl + Pace Events	Abl + Pace Total	Pharmacological Events	Pharmacological Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BRIGNOLE 1998	9	32	13	34	100.0%	0.74 [0.37, 1.48]
Total (95% CI)		**32**		**34**	**100.0%**	**0.74 [0.37, 1.48]**
Total events	9		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)



I.15.3 Ablate and pace versus PV isolation (AF and heart failure)

Figure 172: Ablate and pace versus PV isolation, outcome: 3.1 Living with heart failure



I.15.4 Ablate and pace versus pace and rate control

Figure 173: Ablate and pace versus Pace and rate control, outcome: 4.1 Modified Karolinska Questionnaire

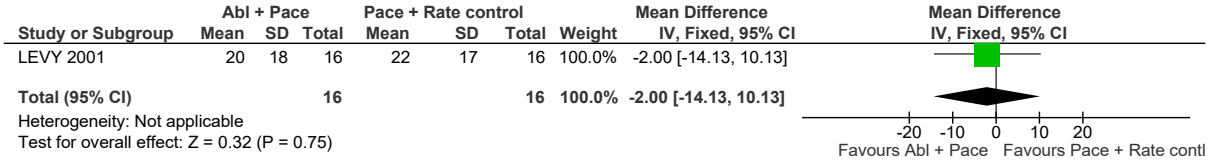
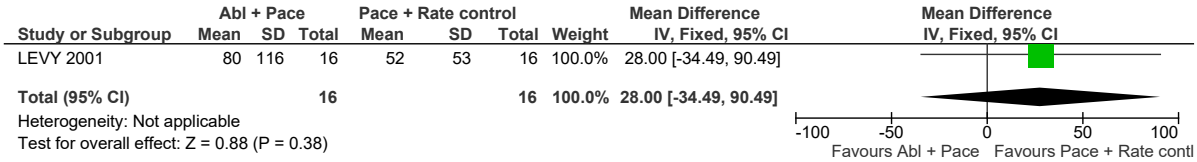


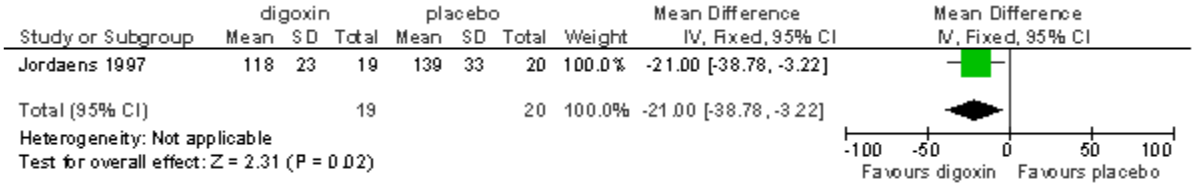
Figure 174: Ablate and pace versus Pace and Rate control, outcome: 4.2 Nottingham Health Profile



I.16 People with acute AF – rate control strategies

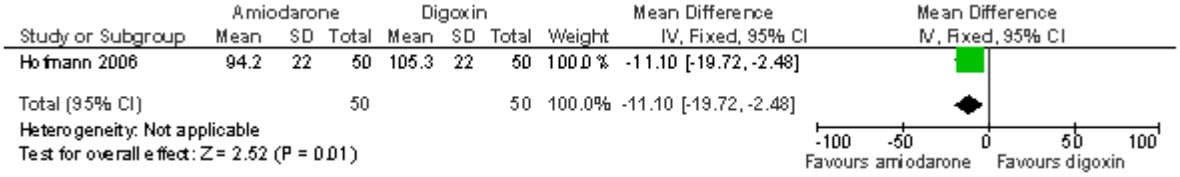
I.16.1 Digoxin versus placebo

Figure 175: Heart rate 30 minutes post treatment



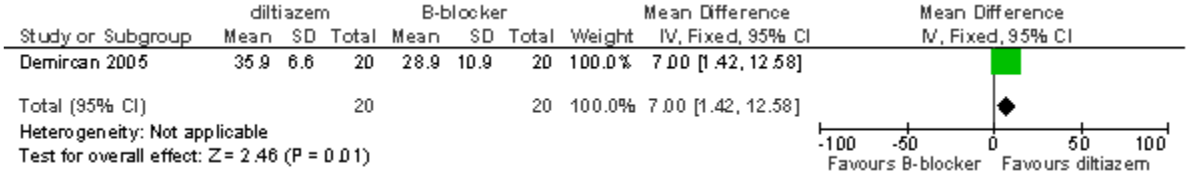
I.16.2 Digoxin versus amiodarone

Figure 176: Mean ventricular rate



I.16.3 Beta-blocker versus calcium channel blocker

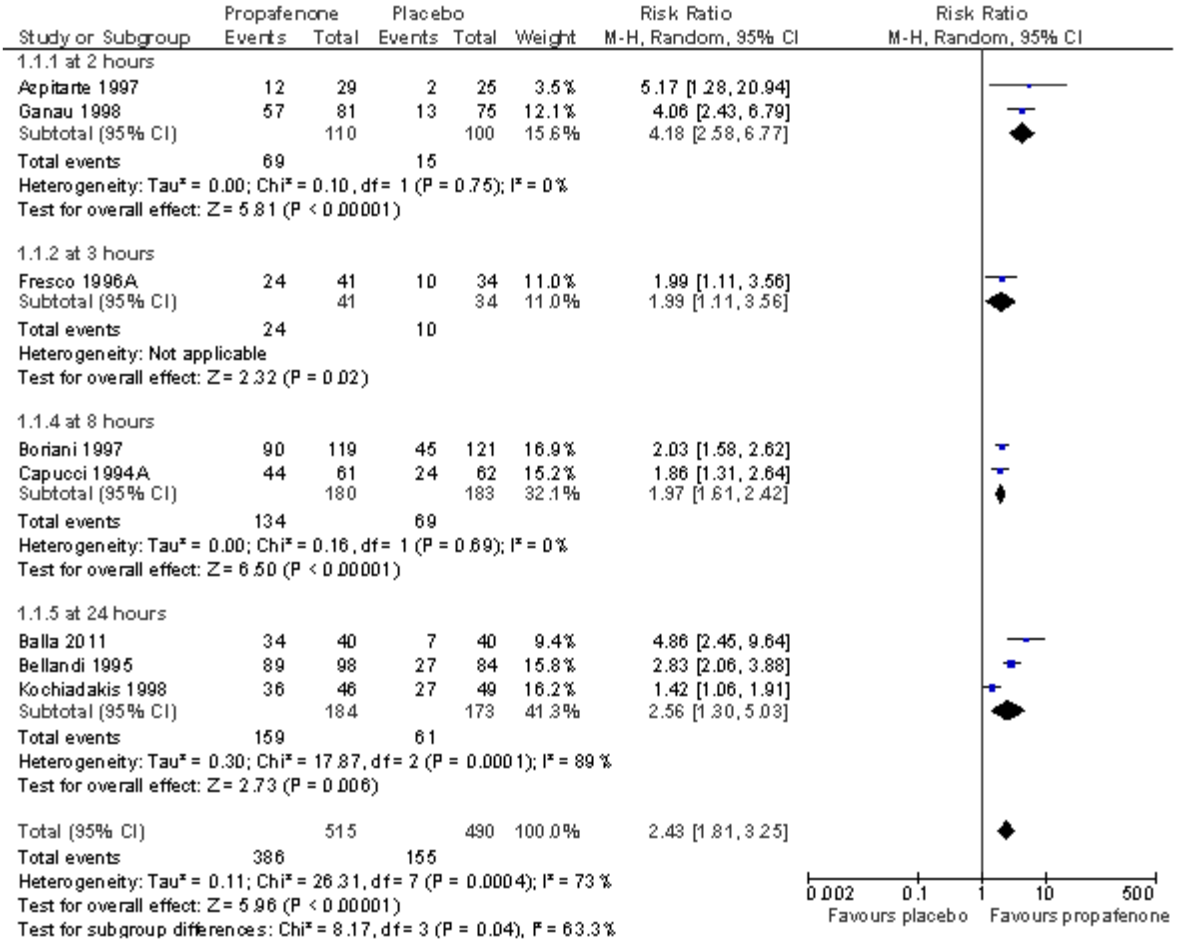
Figure 177: Percentage decrease in VR at 20 minutes



I.17 People with acute AF - restoration of sinus rhythm

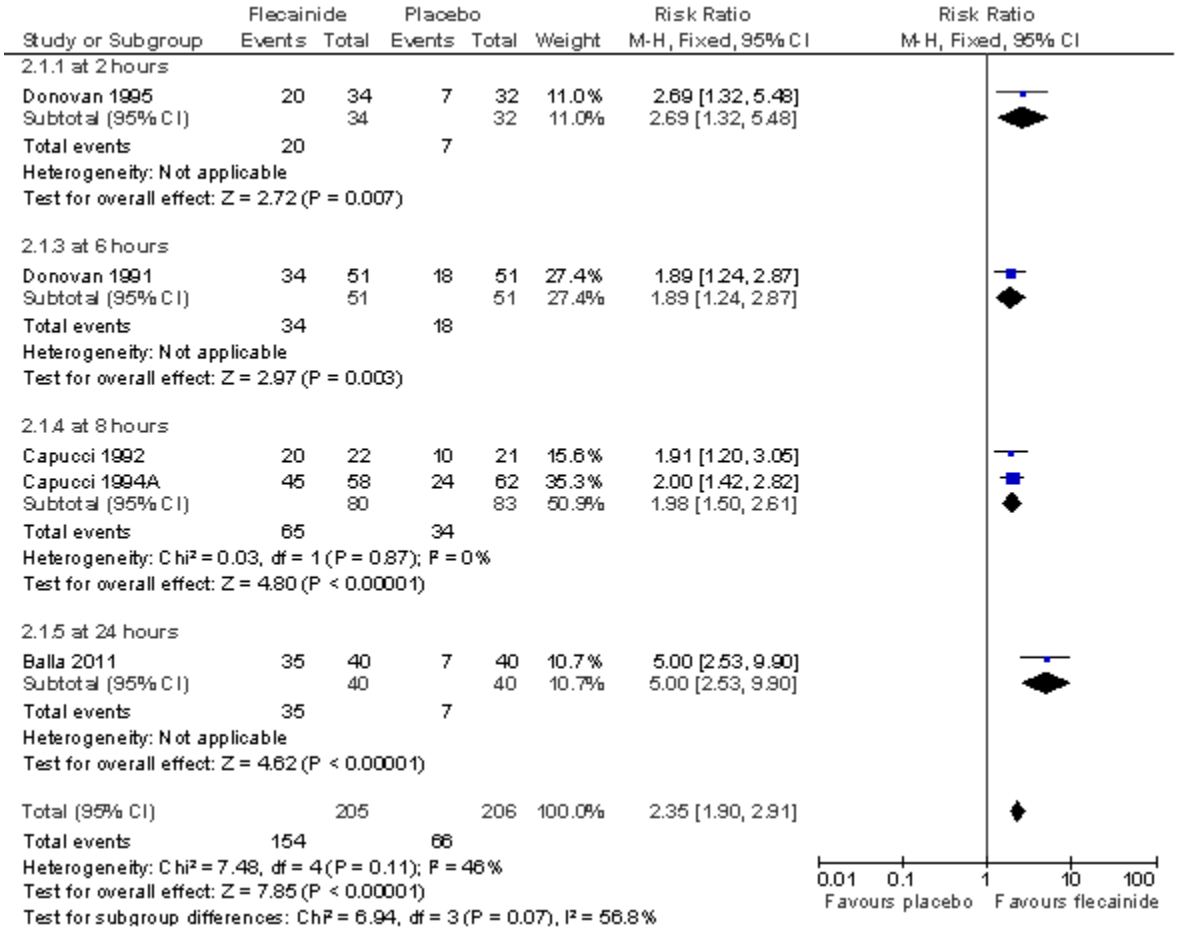
I.17.1 Propafenone versus placebo

Figure 178: Restoration of sinus rhythm-acute AF



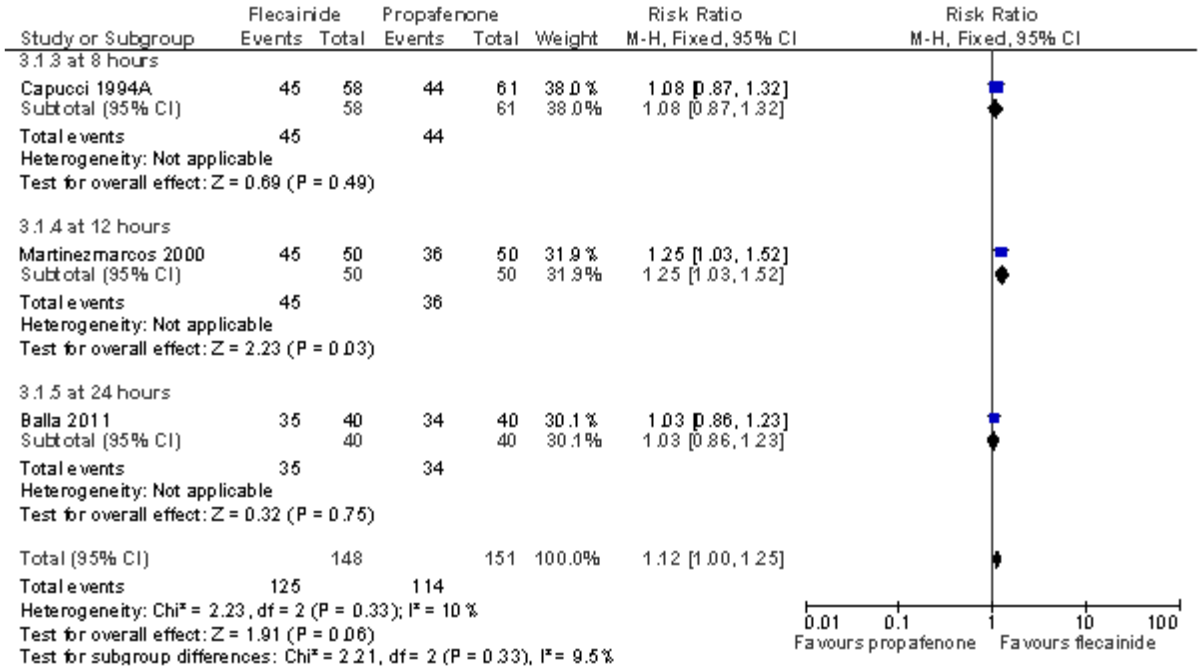
I.17.2 Flecainide versus placebo

Figure 179: Restoration of sinus rhythm-acute AF



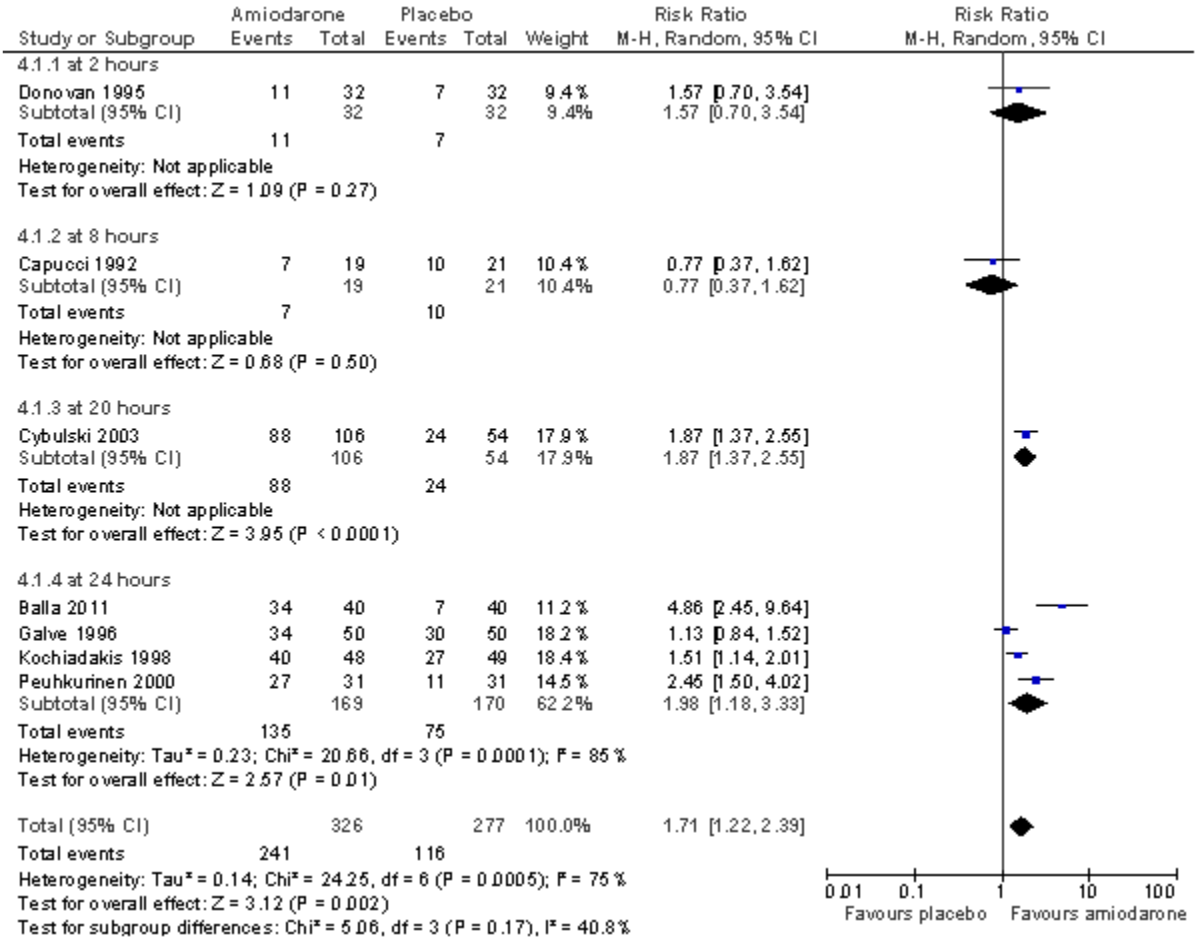
I.17.3 Flecanide versus propafenone

Figure 180: Restoration of sinus rhythm-acute AF



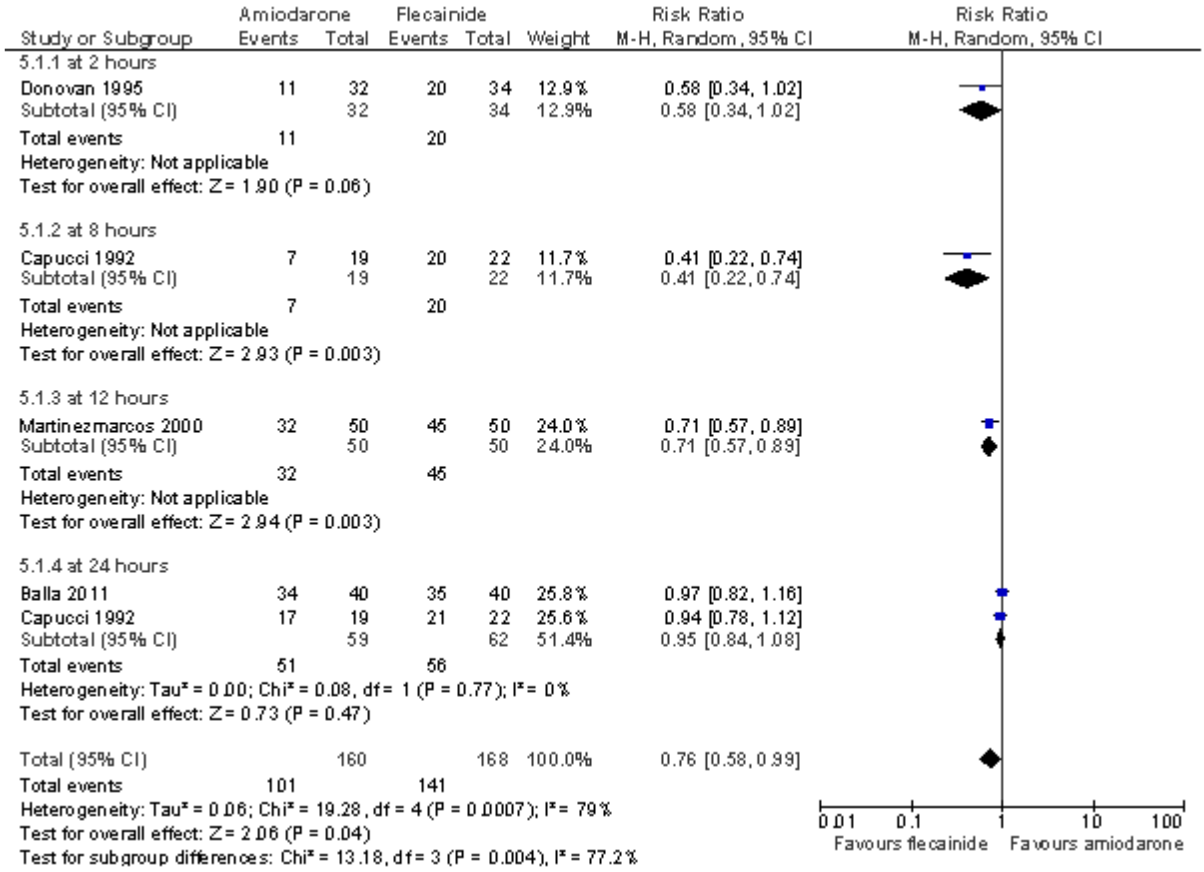
I.17.4 Amiodarone versus placebo

Figure 181: Restoration of sinus rhythm- acute AF



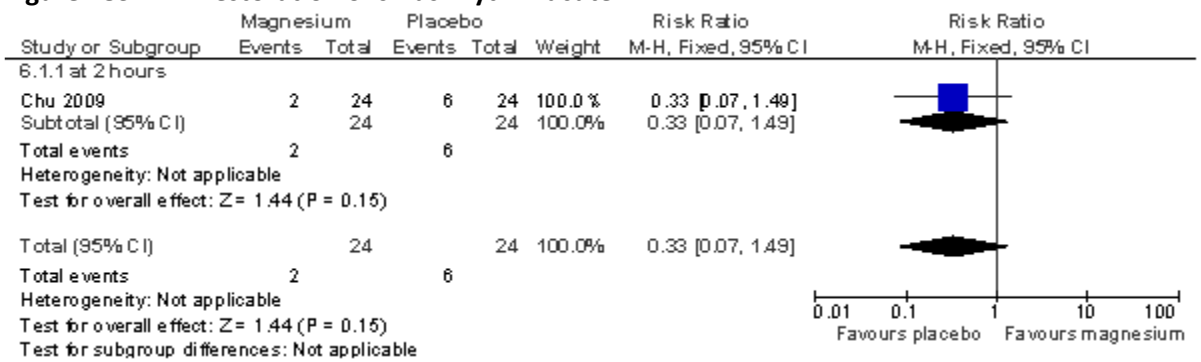
I.17.5 Amiodarone versus flecainide

Figure 182: Restoration of sinus rhythm-acute AF



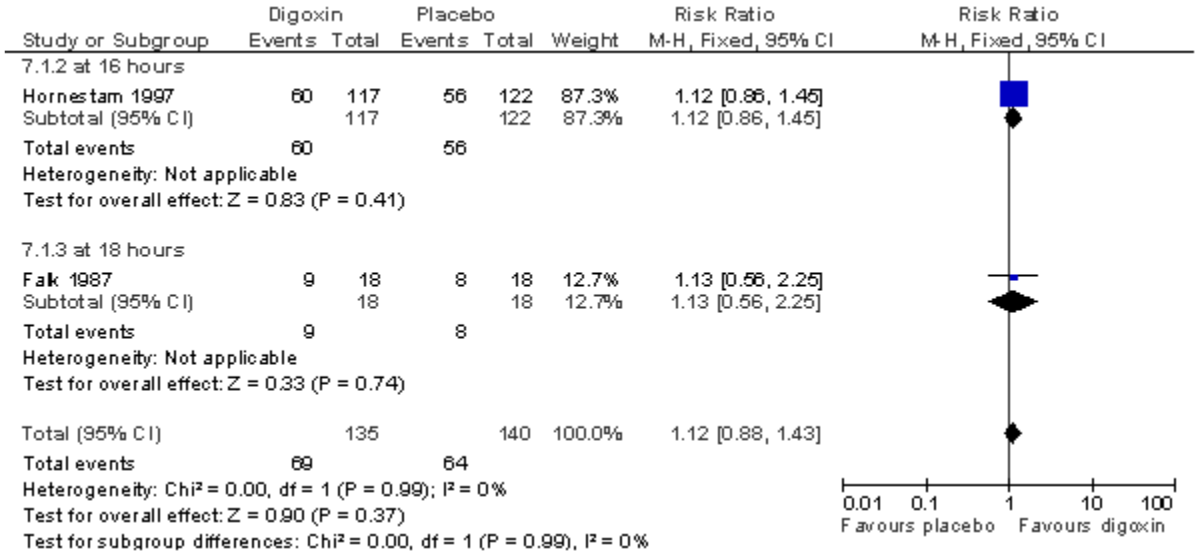
I.17.6 Magnesium versus placebo

Figure 183: Restoration of sinus rhythm-acute AF



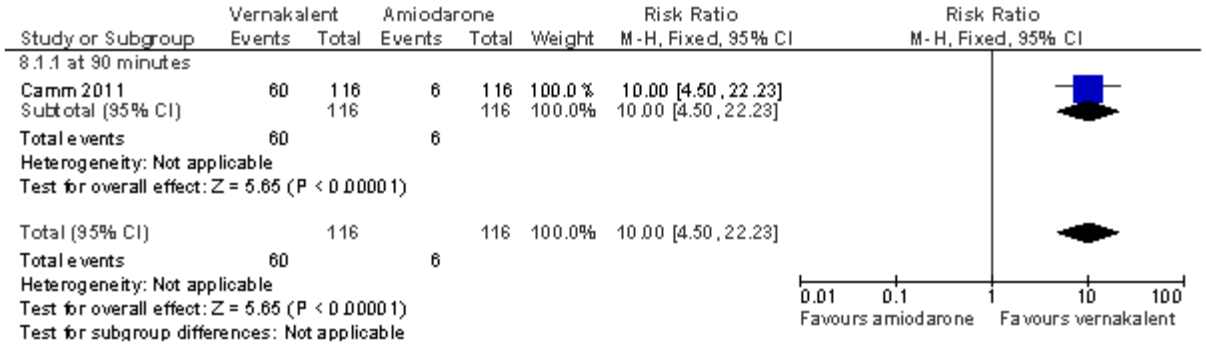
I.17.7 Digoxin versus placebo

Figure 184: Restoration of sinus rhythm-acute AF



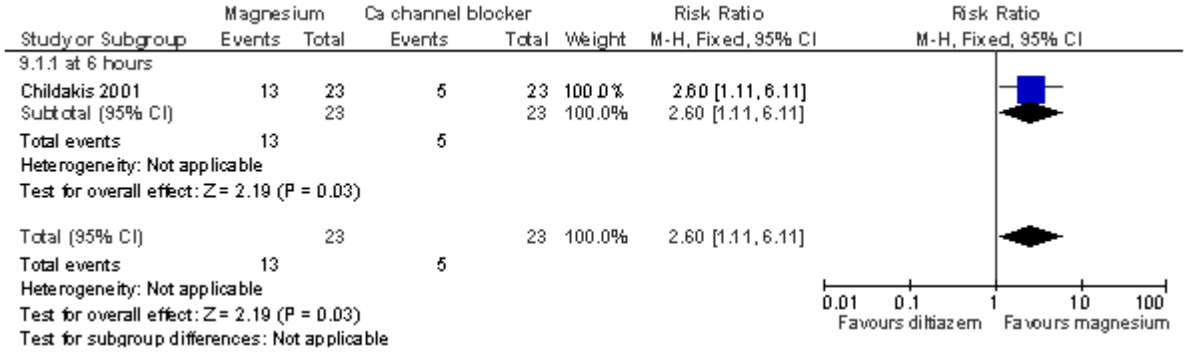
I.17.8 Amiodarone versus vernakalent

Figure 185: Restoration of sinus rhythm-acute AF



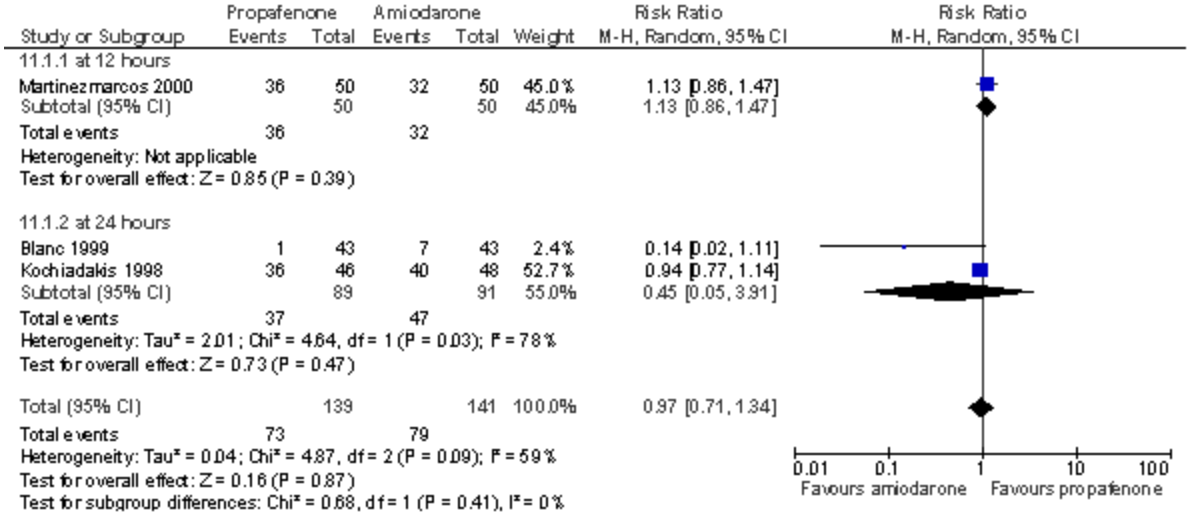
I.17.9 Magnesium versus calcium channel blockers

Figure 186: Restoration of sinus rhythm-acute AF



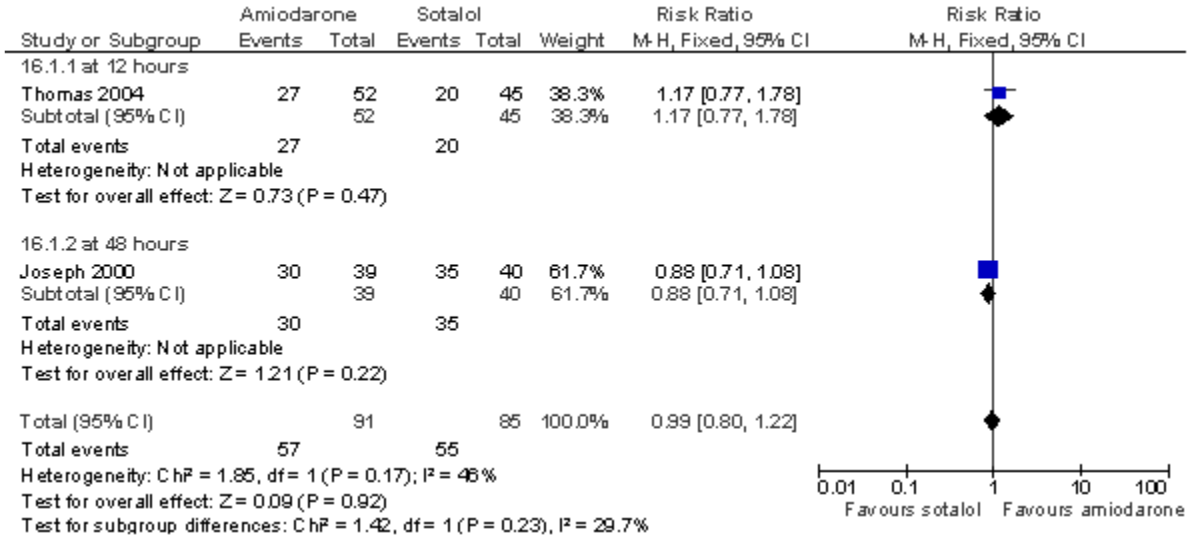
I.17.10 Propafenone versus amiodarone

Figure 187: Restoration of sinus rhythm-acute AF



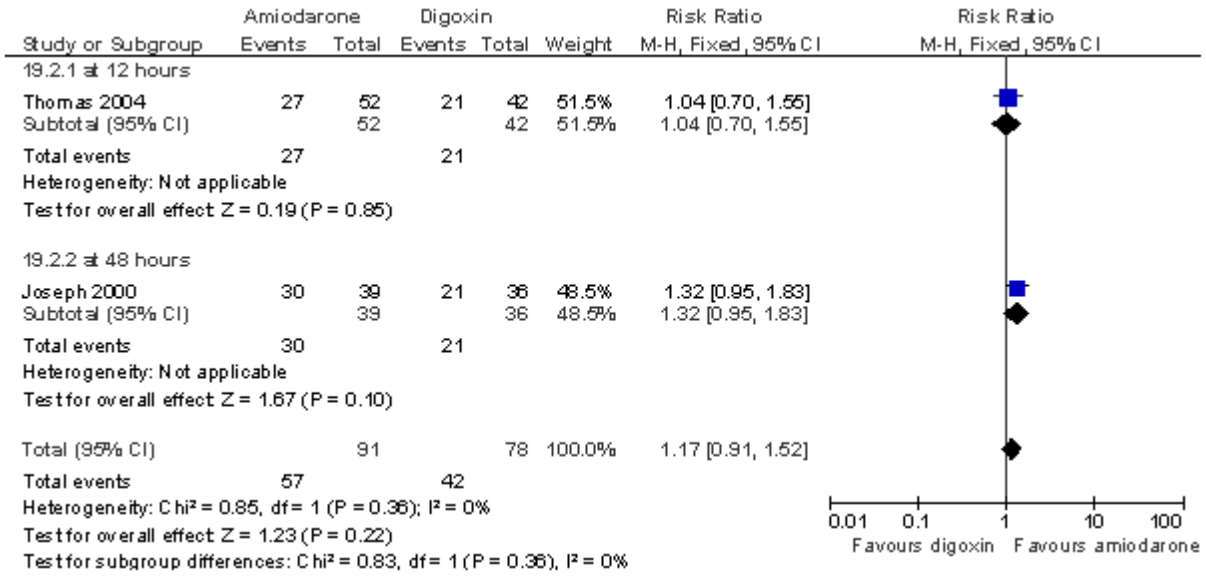
I.17.11 Amiodarone versus sotalol

Figure 188: Restoration of sinus rhythm-acute AF



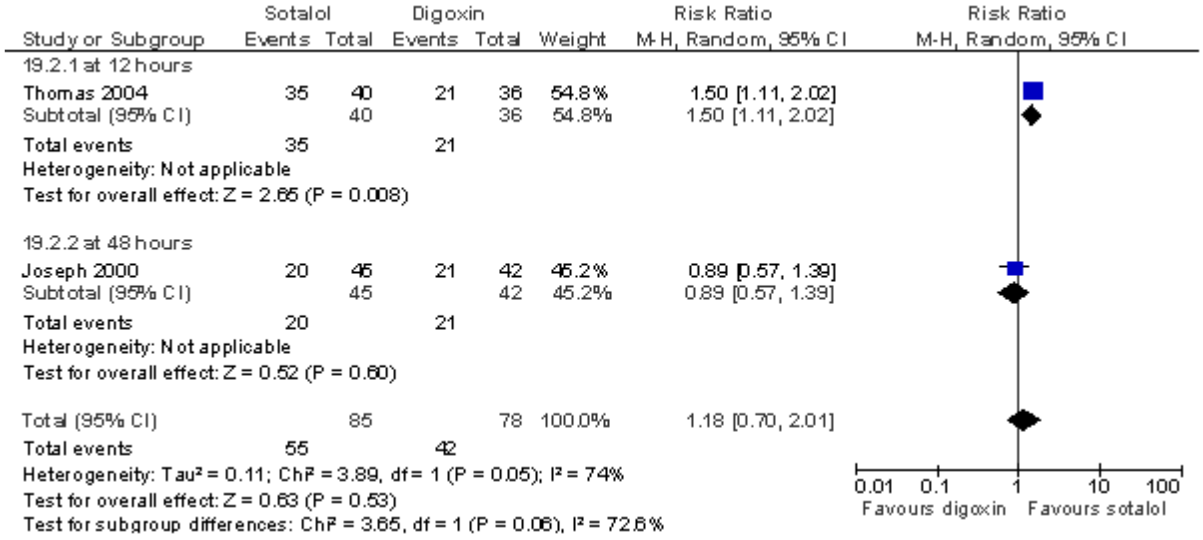
I.17.12 Amiodarone versus digoxin

Figure 189: Restoration of sinus rhythm-acute AF



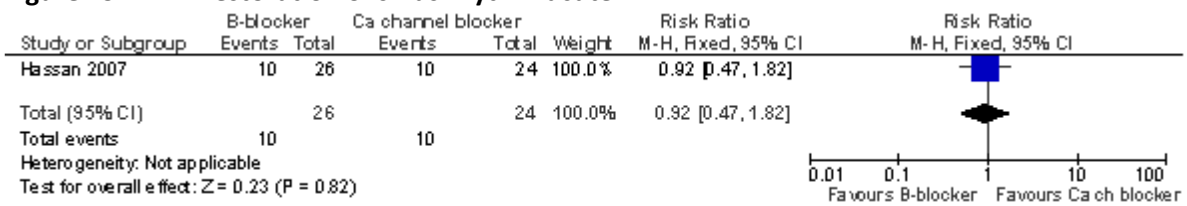
I.17.13 Sotalol versus digoxin

Figure 190: Restoration of sinus rhythm-acute AF



I.17.14 Calcium channel blocker versus beta-blocker

Figure 191: Restoration of sinus rhythm-acute AF



I.17.15 Pharmacological versus electrical cardioversion

Figure 192: Successful cardioversion – within 6 hours

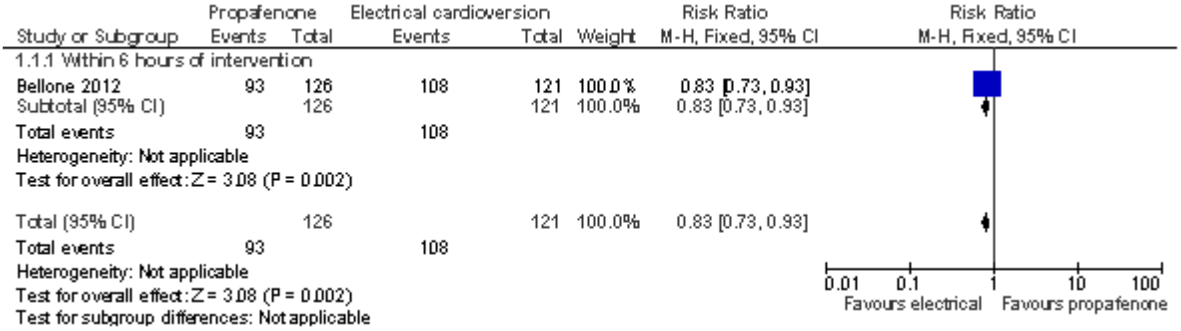
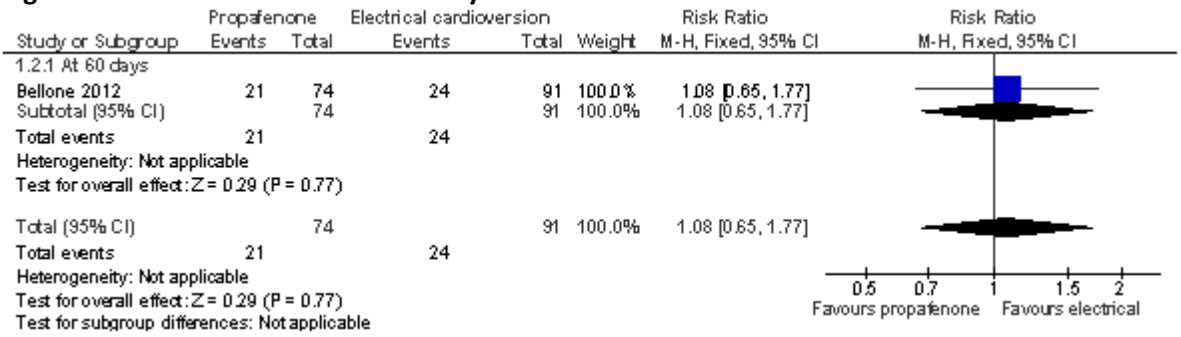


Figure 193: Patients in AF at 60 days



Appendix J: Excluded clinical studies

J.1 Education

Study	Title	Exclusion reason
Batty 2001[78]	Investigation of intervention strategies to increase the appropriate use of antithrombotics in elderly hospital in-patients with atrial fibrillation	Incorrect interventions, Study does not match review question
Bull 2011[145]	P59 Exploring the professional support needs of patients with atrial fibrillation	Incorrect study design –abstract
Fraenkel 2012[343]	A pilot randomised controlled trial of a decision support tool to improve the quality of communication and decision-making in individuals with atrial fibrillation	Inappropriate comparison
Grunau 2011[396]	Patient self-management of warfarin therapy: pragmatic feasibility study in Canadian primary care	Not review population
Hua 2011[477]	Practice nursed-based, individual and video-assisted patient education in oral anticoagulation--protocol of a cluster-randomized controlled trial	Incorrect study design – protocol,
Kaner 2007[504]	Medical communication and technology: a video-based process study of the use of decision aids in primary care consultations	Inappropriate comparison, Unclear methodology, Cochrane excluded due to poor randomisation technique
Khan 2004[520]	The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation	Unclear methodology
Laupacis 1998[576]	A randomized trial of an audiobooklet (AB) decision aid in patients with atrial fibrillation	Incorrect study design, abstract
Malm 2007[634]	Effects of a self-care program on the health-related quality of life of pacemaker patients: a nursing intervention study	Not review population
Smith 2010[824]	Trial of an Educational intervention on patients' knowledge of Atrial fibrillation and anticoagulant therapy, INR control, and outcome of Treatment with warfarin (TREAT)	Incorrect study design, protocol
Stone 1989[837]	Comparison between videotape and personalized patient education for anticoagulant therapy	Not guideline condition

J.2 Referral to specialist care

Study	Title	Exclusion reason
Referral to specialist AF services		
Albert 2010[27]	Influence of dedicated heart failure clinics on delivery of recommended therapies in outpatient cardiology practices: findings from the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF)	Not guideline condition, Incorrect study design
Boodhoo 2004[108]	The safety and effectiveness of a nurse led cardioversion service under sedation	Incorrect study design, Incorrect interventions, Economic study
Botkin 2003[119]	Outpatient cardioversion of atrial arrhythmias: efficacy, safety, and costs	Incorrect interventions, Economic study, Incorrect study design

Study	Title	Exclusion reason
Bowyer 2011[126]	A randomised trial of nurse-led intervention at the time of catheter ablation of atrial fibrillation-effects on quality of life, symptom severity and rehospitalisation	Incorrect study design, Conference abstract
Bungard 2012[147]	Sustained impact of anticoagulant control achieved in an anticoagulation management service after transfer of management to the primary care physician	Incorrect interventions
Burkiewicz 2005[150]	Effect of access to anticoagulation management services on warfarin use in patients with atrial fibrillation	Incorrect interventions
Currie 2004[247]	Introduction of nurse led DC cardioversion service in day surgery unit: prospective audit	Incorrect study design, Audit
Gerber 2012[376]	The health care setting rather than medical speciality impacts on physicians adherence to guideline-conform anticoagulation in outpatients with non-valvular atrial fibrillation: a cross sectional survey	Incorrect study design, Survey
Hendriks 2007[438]	A new disease management program to improve the treatment of patients with atrial fibrillation... 7th Annual Cardiovascular Nursing Spring Meeting of the European Society of Cardiology Council on Cardiovascular Nursing and Allied Professions: changing practice to improve care Manchester, U	Incorrect study design, Conference abstract
Hendriks 2010[440]	An integrated chronic care program for patients with atrial fibrillation: study protocol and methodology for an on-going prospective randomised controlled trial	Incorrect study design, Study protocol and methodology
Hendriks 2010[437]	An integrated chronic care programme for patients with atrial fibrillation	Incorrect study design, Conference abstract
Hendriks 2011[435]	P57 The standard integrated care model in atrial fibrillation: the support for atrial fibrillation clinics being operational or starting up	Incorrect study design, Conference abstract
Hendriks 2012[434]	Cost-effectiveness of a nurse-led integrated chronic care approach versus usual care in patients with atrial fibrillation	Incorrect study design, Conference abstract, Cost effectiveness paper
Hendriks 2013[436]	Erratum: Nurse-led care vs. usual care for patients with atrial fibrillation: Results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation (European Heart Journal (2012) 33 (2692-2699))	Incorrect study design, Corrigendum
Hone 2012[463]	An evaluation of an atrial fibrillation clinic for the follow-up of patients presenting to the emergency department with newly diagnosed or symptomatic arrhythmia	Incorrect study design, Conference abstract
Inglis 2004[481]	A new solution for an old problem? Effects of a nurse-led, multidisciplinary, home-based intervention on readmission and mortality in patients with chronic atrial fibrillation	Not review population
Jackson 2002[485]	A nurse-led atrial fibrillation service	Incorrect study design, Description of a nurse led service
Kellen 1998[515]	Physician specialty is associated with differences in warfarin use for atrial fibrillation	Incorrect study design, Survey
Khoo 2012[523]	Improving atrial fibrillation outcomes through an	Incorrect study design, Conference

Study	Title	Exclusion reason
	interdisciplinary atrial fibrillation clinic: Incidence of cerebrovascular events and emergency room visits	abstract
Kim 2002[525]	A prospective, randomized, controlled trial of an emergency department-based atrial fibrillation treatment strategy with low-molecular-weight heparin	Incorrect interventions, Economic paper
Lau 2011[573]	A new atrial fibrillation clinic in Vancouver: Treatment decisions and patient satisfaction during the first 9 months	Incorrect study design, Conference abstract
Lauck 2011[574]	Improving access and optimizing care: Development of an atrial fibrillation clinic to implement Canadian cardiovascular society guidelines	Incorrect study design, Conference abstract
Martins 2004[652]	Rapid access arrhythmia clinic for the diagnosis and management of new arrhythmias presenting in the community: a prospective, descriptive study	Incorrect study design, Descriptive study
Morgan 2002[676]	Randomised trial of two approaches to screening for atrial fibrillation in UK general practice	Incorrect interventions
Nichol 2008[694]	Quality of anticoagulation monitoring in nonvalvular atrial fibrillation patients: comparison of anticoagulation clinic versus usual care	Incorrect interventions
Poli 2003[751]	Low incidence of haemorrhagic complications of oral anticoagulant therapy in patients with atrial fibrillation in the daily practice of an anticoagulation clinic	Incorrect study design, Cross-sectional study
Poli 2005[752]	Management of oral anticoagulant therapy in the real practice of an anticoagulation clinic: focus on atrial fibrillation	Incorrect study design, Cross-sectional study
Shirley 1996[813]	Multidisciplinary working : the role of a nurse practitioner in managing an anticoagulant service	Incorrect study design, Literature review
Smith 2012[823]	Intensive educational intervention improves time in therapeutic range in atrial fibrillation patients initiating warfarin: Results from the TREAT study	Incorrect study design, Conference abstract, Incorrect interventions
Stewart 2011[835]	Optimizing the management of high risk patients with atrial fibrillation: Promising signs from the standard versus atrial fibrillation specific management study (SAFETY)	Incorrect study design, Conference abstract
Tieleman 2006[860]	Atrial fibrillation (AF) clinic to improve the treatment of patients with atrial fibrillation (AF Clinic)	Incorrect study design, Protocol
Wong 2011[912]	Efficacy and safety of a pharmacist-managed inpatient anticoagulation service for warfarin initiation and titration	Incorrect interventions
Wright 2010[914]	An audit of two methods of anticoagulation monitoring in a general practice	Incorrect interventions

J.3 Stroke risk tools

Reference	Reason for exclusion
Abuassi 2013[11]	Low event rate, only 10 patients with thromboembolic events
Ad 2010[15]	incorrect population - AF patients after catheter ablation

Reference	Reason for exclusion
Agarwal 2012[18]	Non-systematic reviews
Araujo 2013[48]	No relevant outcomes (incidence of AF + stroke/bleeding, no prognostic data/multivariate analysis)
Babberjee 2013[74]	$CHADS_2$ +CKD (grouped by eGFR)
Berisha 2011[89]	No relevant outcomes
Boriani 2011[115]	$CHADS_2$ and CHA_2DS_2-VASc +continuous arrhythmia burden monitoring
Cha 2012A[180]	Low event rate, only 28 patients with thromboembolic events
Chao 2011C[183]	incorrect population - AF patients after catheter ablation
Chao 2012D[184]	Aim is to look at male versus female patients
Chao 2012E[185]	No relevant outcomes (no hazard ratios reported/multivariate analysis)
Chen 2011A[193]	Non-systematic reviews
Coutts 2011[241]	incorrect population - not AF patients
Ederhy 2012[307]	C reactive protein as an add on to existing risk tools
Ertas 2013[316]	Single risk factor - neutrophil/lymphocyte ratio
Feinberg 1999[331]	No relevant outcomes (no hazard ratios reported/multivariate analysis)
Flaker 2012[337]	No relevant outcomes (incidence of AF + stroke, no prognostic data/multivariate analysis)
Gage 2001[362]	Low event rate, only 71 patients with stroke
Guo 2012[404]	Low event rate
Gupta 2012[405]	No relevant outcomes (incidence of AF + stroke, no prognostic data/multivariate analysis)
Hermida 2012[441]	Does not look at stroke (mortality only)
Hijazi 2012[443]	NT-proBNP as an add on to existing risk tools
Hobbs 2011[449]	Low event rate, only 54 patients with thromboembolic events
Holt 2012[462]	No relevant outcomes (incidence of AF + stroke, no prognostic data/multivariate analysis)
Hong 2012[464]	No relevant outcomes (looking at early neurological outcomes)
Hoshino 2013B[470]	No relevant outcomes (no hazard ratios reported/multivariate analysis)
Hughs 2008[479]	Non-systematic reviews

Reference	Reason for exclusion
Jover 2012[497]	Stroke included as a composite endpoint
Keogh 2011[517]	Non-systematic reviews
Komatsu 2010[546]	No relevant outcomes (incidence of AF + stroke, no prognostic data/multivariate analysis)
Komatsu 2011[547]	No relevant outcomes (no hazard ratios reported/multivariate analysis)
Komatsu 2012[548]	Low event rate, less than 100 patients with stroke
Lip 2006A[610]	Low event rate, only 43 patients with stroke
Lip 2007[613]	Single risk factor - C reactive protein and CD 40 ligand
Lip 2010D[608]	Non-systematic reviews
Lip 2010E[612]	Low event rate, only 25 patients with stroke
Masaki 2009[653]	Low event rate, only 23 patients with stroke
Nakagawa 2011B[683]	Patients with CKD and AF, outcomes stratified by estimated glomerular filtration rate.
Olesen 2012[710]	No relevant outcomes (hazard ratios reported/multivariate analysis not reported for risk tool, only individual risk factors)
Olesen 2012A[712]	Looking at vascular disease as a single risk factor
Piccini 2013B[736]	Adding renal dysfunction to $CHADS_2$
Piyasku 2013[742]	No relevant outcomes (event rates when reclassified scores)
Poli 2011[754]	Low event rate, only 32 patients with stroke
Poli 2009[750]	Low event rate
Potpara 2012[758]	Low event rate
Rietbrock 2008[777]	Incorrect study design (case-control)
Roldan 2013A[779]	$CHADS_2$ +CKD
Ruiz 2010[792]	Low event rate
Ruiznodar 2011A[793]	incorrect population - AF patients undergoing percutaneous coronary stenting
Sandhu 2011[797]	No relevant outcomes (no hazard ratios reported/multivariate analysis)
Santos 2013[798]	Non-systematic reviews
Sasahara 2012[799]	Low event rate, only 20 patients with stroke
Stroke 2008[839]	Non-systematic reviews

Reference	Reason for exclusion
Takashima 2012[847]	Low event rate, only 42 patients with stroke
Wang 2003[897]	Low event rate, only 83 patients with stroke
Yarmohammadi 2012[923]	Patients undergoing direct-current cardioversion
Zuo 2013[935]	Incorrect population (patients with arrhythmic symptoms). Aim of study to test risk tools ability to predict new onset AF and ischemic stroke).

J.4 Anticoagulation

Study	Title	Exclusion reason
Antithrombotic therapy		
Aalbers 2010[6]	Rivaroxaban equals warfarin treatment in atrial fibrillation patients at high risk of stroke	Incorrect study design
Adams 2001[16]	Antiplatelet aggregating versus anticoagulant agents in preventing early recurrent stroke among patients with atrial fibrillation	Incorrect interventions
Agarwal 2012[18]	Current trial-associated outcomes with warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis	Cochrane review used
Alhusban 2011[29]	Secondary prevention of stroke in the elderly: a review of the evidence	Incorrect study design
Al Khatib 2013 [25]	Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial	Incorrect comparison (apixaban v warfarin)
Altman 1994[33]	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	Not guideline condition
Andersen 2008[34]	Warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation: a meta-analysis	Cochrane review used
Anon 2006[3]	Warfarin prevents more stroke than clopidogrel and aspirin in afib	Incorrect study design, Not guideline condition
Anon 2006[2]	ACTIVE-W: warfarin beats clopidogrel/aspirin in atrial fibrillation	Incorrect study design
Anon 2012[5]	Optimal warfarin management for the prevention of thromboembolic events in patients with atrial fibrillation: a systematic review of the clinical evidence	Not guideline condition
Ansara 2010[41]	Aspirin dosing for the prevention and treatment of ischemic stroke: an indication-specific review of the	Incorrect study design

Study	Title	Exclusion reason
	literature	
Antithrombotic 2002[43]	Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients	Not guideline condition
Assiri 2013 [55]	Mixed treatment comparison meta-analysis of aspirin, warfarin, and new anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation	MTA
Astellas 2009[57]	A study evaluating safety and tolerability of YM150 compared to warfarin in subjects with atrial fibrillation (OPAL-2)	Not a journal paper
Astellas pharma inc 2007[56]	Direct factor Xa inhibitor YM150 for prevention of stroke in subjects with non-valvular atrial fibrillation	Not a journal paper
Baker 2012[69]	Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation	Incorrect interventions
Bayer 2006[79]	A study comparing once daily oral rivaroxaban with adjusted-dose oral warfarin for the prevention of stroke in subjects with non-valvular atrial fibrillation	Not a journal paper
Bayer 2007[80]	Efficacy and safety of rivaroxaban for the prevention of stroke and embolism in subjects with non-valvular atrial fibrillation	Not a journal paper
Berge 2002[88]	Anticoagulants versus antiplatelet agents for acute ischaemic stroke	Not guideline condition
Bover 2009[124]	Long-term follow-up of atrial fibrillation patients in the NASPEAF study. Prospective evaluation of different antiplatelet treatments	Incorrect study design
Bovio 2011[125]	Dabigatran etexilate: a novel oral thrombin inhibitor for thromboembolic disease	Incorrect study design
Boysen 1990[127]	Effect of warfarin contra aspirin and placebo in chronic atrial fibrillation	Incorrect study design
Bristol-myers 2006[138]	Apixaban for the prevention of stroke in subjects with atrial fibrillation	Not a journal paper
Bristol-myers 2007[139]	A phase III study of apixaban in patients with atrial fibrillation (AVERROES)	Not a journal paper
Bruins 2013[141]	Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation	Cochrane- no new studies
Camm 2009[158]	The RE-LY study: Randomized Evaluation of Long-term anticoagulant therapy: Dabigatran vs. warfarin	Incorrect interventions

Study	Title	Exclusion reason
Capadanno 2013[164]	Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: a meta-analysis of 50,578 patients	meta-analysis- no new studies
Chesebro 1996[198]	Bleeding during antithrombotic therapy in patients with atrial fibrillation	Not guideline condition
Chung 2011[213]	Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation	Incorrect interventions
Connolly 2009[231]	Dabigatran versus warfarin in patients with atrial fibrillation	Incorrect interventions
Connolly 2011[230]	Net clinical benefit of adding clopidogrel to aspirin therapy in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable	Inappropriate comparison, Incorrect study design
Cooper 2006[235]	Mixed comparison of stroke prevention treatments in individuals with non-rheumatic atrial fibrillation	Incorrect study design, Mixed treatment comparison
Cooper 2009[234]	Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation	Incorrect study design
Daiichi Sankyo co ltd 2008[255]	A Phase 3, randomised, double-blind, double-dummy, parallel group, multi-center, multi-national study for evaluation of efficacy and safety of DU-176b versus warfarin in subjects with atrial fibrillation - Effective anticoagulation with factor Xa next Generation in Atrial Fibrillation (ENG	Not a journal paper
Daiichi sankyo inc 2007[256]	A study to assess the safety of a potential new drug in comparison to standard practice of dosing with warfarin for non-valvular atrial fibrillation	Not a journal paper
Daiichi Sankyo inc 2008[257]	ENGAGE - AF TIMI - 48. Global study to assess the safety and effectiveness of DU-176b vs standard practice of dosing with warfarin in patients with atrial fibrillation	Not a journal paper
Dentali 2007[274]	Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials	Systematic review
Dentali 2012[275]	Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature	Incorrect interventions

Study	Title	Exclusion reason
Desai 2006[277]	Pacing and Clinical Electrophysiology	Not a journal paper
Desilvey 2006[280]	Clopidogrel plus aspirin vs oral anticoagulation for atrial fibrillation: the ACTIVE W trial	Incorrect study design
Diener 2010[287]	Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial	Incorrect interventions
Downes 2003[298]	A comparison of warfarin and aspirin for stroke prevention in octogenarians in atrial fibrillation study	Incorrect study design
Dunn 2011[300]	Apixaban reduced stroke and systemic embolism compared with aspirin in adults with AF for whom VKA therapy was unsuitable	abstract
Easton 2012[302]	Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial	Incorrect interventions
Ebell 2005[303]	Choosing between warfarin (Coumadin) and aspirin therapy for patients with atrial fibrillation	Incorrect study design
Edvardsson 2001[309]	The effect of a fix low-dose combination of warfarin and aspirin on the stroke incidence in patients with chronic atrial fibrillation and a low-medium risk (for the Swedish atrial fibrillation trial)	Incorrect study design, Abstract
Edvardsson 2003[308]	Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation	Incorrect intervention
Ehlers 2013[311]	Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin: a systematic review and meta-analysis	systematic review (studies included)
Eikelboom 2011[313]	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	Incorrect interventions
Eikelboom 2013A[312]	Balancing the benefits and risks of 2 doses of dabigatran compared with warfarin in atrial fibrillation	Intra-class comparison
Esprit study group 2007[317]	Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial	Not guideline condition
Ezekowitz 1995[319]	Silent cerebral infarction in patients with	Incorrect study design

Study	Title	Exclusion reason
	non-rheumatic atrial fibrillation. The Veterans Affairs Stroke Prevention in non-rheumatic Atrial Fibrillation Investigators	
Ezekowitz 2007[322]	Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study)	Incorrect interventions
Ezekowitz 2009[320]	Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran	Incorrect interventions
Feinberg 1994[330]	Warfarin vs aspirin in atrial fibrillation: SPAF II study results	Incorrect study design
Ferreira 2013[333]	Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial	warfarin v dabigatran (intra-class comparison)
Flaker 2012[337]	Bleeding During Treatment With Aspirin Versus Apixaban in Patients With Atrial Fibrillation Unsuitable for Warfarin: The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin k Antagonist Treatment (AVERROES) Tr	data already included Connolly 2011B
Flaker 2012[335]	Efficacy and safety of dabigatran compared to warfarin in patients with paroxysmal, persistent, and permanent atrial fibrillation: Results from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study	Incorrect study design
Fox 2011[342]	Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment	Incorrect interventions
Garcia 2013[371]	Apixaban versus warfarin in patients with atrial fibrillation according to prior warfarin use: Results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial	Sub study of excluded intra-class comparison
Granger 2011[390]	Apixaban versus warfarin in patients with atrial fibrillation	Incorrect interventions
Granger 2012[389]	Apixaban reduced stroke and systemic embolism compared with warfarin in atrial fibrillation	Incorrect interventions
Green 1997[392]	Anticoagulation in chronic nonvalvular atrial fibrillation: a critical appraisal and meta-analysis	Cochrane review used
Gullov 1993[400]	The AFASK 2 study: atrial fibrillation,	Incorrect study design

Study	Title	Exclusion reason
	aspirin- and anticoagulant- therapy	
Gullov 1997[403]	Fixed low-dose warfarin alone or combined with aspirin and aspirin alone versus adjusted-dose warfarin for stroke prevention in atrial fibrillation. Second Copenhagen atrial fibrillation, aspirin and anticoagulation study (AFASAK 2)	Incorrect study design
Gullov 1998[402]	The AFASAK 2 study - the 2nd Copenhagen atrial fibrillation, aspirin and anticoagulant therapy study	Incorrect study design
Gullov 1998[401]	Fixed mini dose 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	Incorrect interventions
Handjani 1995[416]	Safety and antithrombotic effects of fixed low-dose warfarin-aspirin combination in rheumatic mitral stenosis associated with atrial fibrillation	mitral stenosis
Hankey 2012[418]	Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF	Incorrect interventions
Harenberg 2012[419]	Comparison of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with atrial fibrillation using network meta-analysis	Incorrect interventions
Harrington 2013[420]	Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation	economic model (intra-class comparison)
Hart 1998[422]	Prevention of stroke in patients with nonvalvular atrial fibrillation	Incorrect study design
Hart 1999[421]	Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis	Cochrane reviews used
Hart 2007[425]	Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation	Cochrane reviews used
Hart 2007[424]	Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation	Incorrect study design
Hellemons 1999[431]	Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation: the PATAF trial study design	Incorrect study design
Hohnloser 2013[459]	The effects of apixaban on hospitalizations in patients with different types of atrial fibrillation: insights from the AVERROES trial	post hoc analysis of included study

Study	Title	Exclusion reason
Hori 2012[467]	Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study -	Incorrect interventions
Hori 2013[466]	Dabigatran versus warfarin: effects on ischemic and haemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation	intervention not relevant (dabigatran v warfarin)
Kansal 2012[508]	Dabigatran versus rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation in Canada. Comparative efficacy and cost-effectiveness	Incorrect interventions
Katona 2006[511]	The Belgian Improvement Study in Oral Anticoagulant Therapy: a randomized clinical trial	Incorrect study design
Koudstaal 2008[555]	Antiplatelet therapy for preventing stroke in patients with non-rheumatic atrial fibrillation and a history of stroke or transient ischemic attacks	Cochrane - withdrawn
Krishnan 2005[557]	Warfarin therapy and systolic hypertension in men with atrial fibrillation	Incorrect study design, Post hoc study
Lancaster 1991[567]	The impact of long-term warfarin therapy on quality of life. Evidence from a randomized trial. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators	Incorrect study design
Lane 2013[568]	Combined anticoagulation and antiplatelet therapy for high-risk patients with atrial fibrillation: a systematic review	Cochrane- no new studies
Laupacis 1994[575]	Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: Analysis of pooled data from five randomized controlled trials	Incorrect study design
Lavitola 2010[577]	Warfarin or aspirin in embolism prevention in patients with mitral valvulopathy and atrial fibrillation	mitral valvulopathy
Lee 2013[581]	New oral anticoagulants versus warfarin for stroke prevention in atrial fibrillation: development of coverage decision frameworks	conference abstract
Lechat 2001[580]	Anticoagulant (fluindione)-aspirin combination in patients with high-risk atrial fibrillation. A randomized trial (Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontane; FFAACS)	Anticoagulant not listed in protocol
Lengyel 2004[587]	Warfarin or acenocoumarol is better in the anticoagulant treatment of chronic atrial fibrillation? A SPORTIF-III sub study	Not in English
Liddell 2003[596]	Clopidogrel and warfarin: absence of	Short follow-up

Study	Title	Exclusion reason
	interaction in patients receiving long-term anticoagulant therapy for non-valvular atrial fibrillation	
Lip 2000[604]	Antiplatelet agents versus control or anticoagulation for heart failure in sinus rhythm	Not guideline condition
Lip 2001[601]	Anticoagulation for heart failure in sinus rhythm	Not guideline condition
Lip 2001[602]	A randomised controlled trial of warfarin versus aspirin for stroke prevention in the management of atrial fibrillation in an elderly (aged > 75) primary care population	Not a journal paper
Lip 2002[603]	Anticoagulation for heart failure in sinus rhythm: a Cochrane systematic review	Not guideline condition
Lip 2006[606]	Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis	Cochrane reviews used
Lip 2008[609]	Stroke prevention	Incorrect study design
Lip 2009[614]	Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety, and tolerability study of four doses of AZD0837 vs. vitamin K antagonists	Not guideline condition
Lip 2011[615]	Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a Phase II study of AZD0837 in patients who are appropriate for but unable or unwilling to take vitamin K antagonist therapy	Incorrect interventions
Lip 2012[611]	Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation	Not guideline condition
Lip 2012[616]	Anticoagulation versus placebo for heart failure in sinus rhythm	Not guideline condition
Li-saw-hee 2000[595]	Effects of fixed low-dose warfarin, aspirin-warfarin combination therapy, and dose-adjusted warfarin on thrombogenesis in chronic atrial fibrillation	No relevant outcomes
Logan 1992[621]	Warfarin compared to aspirin in atrial fibrillation: design and patient characteristics of the Stroke Prevention in Atrial Fibrillation (SPAF) II Study	Incorrect study design
Lopes 2010[624]	Apixaban for reduction in stroke and other ThromboemboLic events in atrial	Incorrect interventions

Study	Title	Exclusion reason
	fibrillation (ARISTOTLE) trial: design and rationale	
Lopes 2012[623]	Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial	Incorrect interventions
Lorenzo 2004[626]	Short term prevention of thromboembolic complications in patients with atrial fibrillation with aspirin plus clopidogrel	Inappropriate length of follow-up
Mak 2012[633]	Coronary and mortality risk of novel oral antithrombotic agents: a meta-analysis of large randomised trials	Incorrect interventions
Mant 1998[643]	Re: CJ Green, DC Hadorn, K Bassett, A Kazanjian, Anticoagulation in chronic nonvalvular atrial fibrillation: a critical appraisal and meta-analysis. 1997;13:811-5	Incorrect study design
Mant 2002[640]	RCT of warfarin versus aspirin for stroke prevention in the management of atrial fibrillation in an elderly (aged 75 or over) primary care population	Incorrect study design
Mant 2003[642]	Protocol for Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA): a randomised controlled trial of warfarin versus aspirin for stroke prevention in the management of atrial fibrillation in an elderly primary care population [ISRCTN89345269]	Methods paper
Mant 2007[638]	BAFTA: a randomised controlled trial of warfarin versus aspirin for stroke prevention in atrial fibrillation in a primary care population aged over 75	Incorrect study design, Abstract
Mant 2008[639]	Is warfarin a safe alternative to aspirin in elderly patients with atrial fibrillation?	Not guideline condition
Mantha 2012[644]	An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation	Not guideline condition
Matchar 1994[655]	Medical treatment for stroke prevention	Incorrect study design
Mcbride 1990[662]	Preliminary report of the stroke prevention in atrial fibrillation study	Preliminary report
Mcbride 1996[663]	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	Incorrect interventions
Mcbride 2004[661]	A safety and efficacy trial evaluating the use of SanOrg34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation	Not a journal paper

Study	Title	Exclusion reason
Miller 2012[669]	Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation	Incorrect interventions
Morilla 2012 [678]	A meta-analysis on the efficacy of dabigatran versus warfarin among patients with atrial fibrillation	meta-analysis- no new studies
Neutel 1998[691]	A randomized crossover study to compare the efficacy and tolerability of Barr warfarin sodium to the currently available Coumadin	Incorrect interventions
Ntaios 2012[700]	Non-vitamin-k-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials	Not guideline condition
Ogawa 2011[704]	Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study-	Incorrect interventions
Olsson 2010[715]	Safety and tolerability of an immediate-release formulation of the oral direct thrombin inhibitor AZD0837 in the prevention of stroke and systemic embolism in patients with atrial fibrillation	Incorrect interventions
Patel 2011[725]	Rivaroxaban versus warfarin in nonvalvular atrial fibrillation	Incorrect interventions
Perez 2002[729]	The role of combined antiplatelet plus moderate level of anticoagulation for prevention of embolism in atrial fibrillation. A national randomized, multicentre trial	Incorrect study design
Perez-gomez 2006[730]	Combined antiplatelet plus moderate anticoagulant therapy in the elderly with atrial fibrillation	Not guideline condition
Pullicino 2013[764]	Stroke in heart failure in sinus rhythm: the warfarin versus aspirin in reduced cardiac ejection fraction trial	post hoc study without comparison
Rash 2006[766]	A randomised controlled trial of warfarin and aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO)	Incorrect study design, Abstract
Rasmussen 2012[768]	Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis	Incorrect interventions
Reynolds 2004[775]	Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and meta-analysis	Cochrane review used

Study	Title	Exclusion reason
Rocket 2010[778]	Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study	Incorrect interventions
Roskell 2010[785]	Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate	Incorrect study design
Ruff 2010[791]	Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective anticoagulation with factor Xa next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48)	Study design and rationale
Segal 2000[807]	Prevention of thromboembolism in atrial fibrillation. A meta-analysis of trials of anticoagulants and antiplatelet drugs	Cochrane review used
Segal 2006[808]	Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter	Cochrane - withdrawn
Sharma 2001[810]	SPORTIFF III:- Efficacy and safety study of oral thrombin inhibitor H376/95 compared with warfarin in prevention of stroke and systemic embolic event in patients with atrial fibrillation	Not a journal paper
Shen 2002[812]	Efficacy and safety study of the oral direct thrombin inhibitor H376/95 compared with dose-adjusted warfarin (coumadin) in the prevention of stroke and systemic embolic events in patients with atrial fibrillation (SPORTIF V)	Not a journal paper
Singer 1992[815]	The effect of aspirin on the risk of stroke in non-rheumatic atrial fibrillation: the BAATAF Study	Incorrect study design, Abstract
Tahir 2013 [846]	The new oral anti-coagulants and the phase 3 clinical trials - a systematic review of the literature	meta-analysis- no new studies
Taylor 2001[850]	Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation	Cochrane review used
Testa 2012[853]	Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation	Incorrect interventions
Turpie 1993[869]	A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement	45% AF population, Not guideline condition

Study	Title	Exclusion reason
Uchino 2012[870]	Dabigatran association with higher risk of acute coronary events: meta-analysis of non-inferiority randomised controlled trials	Not guideline condition, Incorrect study design
Van 1994[881]	The 'European atrial fibrillation study': Secondary prevention of thromboembolic complications with oral anticoagulants or acetylsalicylic acid in patients with non-rheumatic atrial fibrillation	Not in English
Van Diepen 2013 [874]	Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF	intra-class comparison (warfarin v rivaroxaban)
Van walraven 2002[884]	Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis	Cochrane reviews used
Weibert 2000[904]	A randomized, crossover comparison of warfarin products in the treatment of chronic atrial fibrillation	Sub-study of included RCT
Weitz 2010[905]	Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation	Incorrect interventions
White 2007[907]	Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V	Incorrect study design
Yamaguchi 1999[918]	Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a prospective randomized multicentre trial	Not guideline condition
Yamashita 2012[921]	Randomized, multicentre, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation	Incorrect interventions
Yigit 2000[924]	The Turkish atrial fibrillation study	Not in English

J.5 Bleeding risk

Reference	Reason for exclusion
Burgess 2013 [149]	Population – not correct population
Gomes 2013 [386]	No relevant outcomes
Iwasaki 2012 [484]	Abstract
Kooiman 2012[550]	Abstract
Loewen 2011[620]	Systematic review

Reference	Reason for exclusion
Nakamora 2012 [684]	Abstract
Omran 2012 [716]	Population – not correct population
Poli 2011a[755]	No relevant outcomes
Poli 2007 [753]	No relevant outcomes
Ruiz 2012 [794]	Population – not correct population

J.6 Monitoring

Reference	Reason for exclusion
Ad 2009 [14]	Intervention and comparison do not match protocol (comparison of devices to monitor heart rhythm)
Baker 2009 [68]	Intervention does not match protocol (study of speciality clinic vs usual care)
Baker 2011 [67]	Intervention does not match protocol (assessment of patient knowledge)
Beyth 2000 [94]	Population does not match protocol (not all AF)
Borgman 2012 [111]	Population does not match protocol (not all AF)
Boriani 2011 [115]	Incorrect study design and intervention does not match protocol (no comparison group; pacemaker)
Boriani 2012 [117]	Intervention does not match protocol (implantable cardiac defibrillator)
Capucci 2005 [173]	Study does not answer question (predicting factors predisposing to adverse events)
Conti 2012 [232]	Intervention and comparison do not match protocol (intense observation vs standard care in the acute setting)
Decker 2008 [269]	Intervention and comparison do not match protocol (intense observation vs standard care in the acute setting)
Dolan 2008 [290]	Systematic review is not relevant to review question (anticoagulation control)
Garwood 2008 [372]	Population does not match protocol (not all AF)
Hanke 2009 [417]	Study does not answer question
Holden 2000 [460]	Population does not match protocol (not all AF)
Ip 2009 [483]	Intervention does not match protocol (implantable cardiac defibrillator)
Kamalvand 1997 [501]	Intervention does not match protocol (transtelephonic device)
Liu 2010 [617]	Intervention does not match protocol (transtelephonic device)
Matchar 2002 [656]	Intervention and comparison do not match protocol (anticoagulation control v usual care)
Mitra 2005 [671]	Comparison does not match protocol (clinician monitoring vs computer aided dosing)
Nichol 2008 [694]	Intervention and comparison do not match protocol (anticoagulation control v usual care)
Pengo 2006 [728]	Incorrect study design (no comparison group)
Tran 2013[865]	Comparison does not match protocol
Ziegler 2006 [931]	Intervention does not match protocol (pacemaker)
Ziegler 2010 [930]	Population does not match protocol (not all AF)
Ziegler 2012 [932]	Study does not answer question (comparison of defibrillators)

J.7 Left Atrial Appendage Occlusion

Study1	Title	Exclusion reason
Fountain 2006[341]	The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) trial	Incorrect study design
Healey 2005[429]	Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke	Population does not match protocol, Under 20% with AF
Kar 2011[509]	Left atrial appendage closure and the PROTECT AF trial: Results at 1500 patient-years of follow-up	Not a randomised study, Follow-up paper of Holmes paper without any usable data.
Mccabe 2009[664]	Left atrial appendage occlusion in non-valvular atrial fibrillation	Incorrect study design
Nagpal 2009[682]	Concurrent prophylactic left atrial appendage exclusion: results from a randomized controlled trial pilot study	Population does not match protocol, Only 8 out of 43 study population had AF
National horizon scanning centre (nhsc) 2009[687]	WATCHMAN left atrial appendage (LAA) closure device for non-valvular atrial fibrillation (AF)	Incorrect study design

J.8 Rate versus rhythm control strategies

Reference	Reason for exclusions
Anon 2002[4]	Conference presentation
Anthony 2004[42]	Systematic review
Boman 1983[106]	Not question of interest
Caldeira 2011[155]	Systematic review
Caldeira 2012[156]	Systematic review
Carlsson 2000[174]	Review used as background
Chen 2011[191]	Systematic review
Chen 2012[192]	Systematic review
Chung 2005[212]	Not outcome of interest
Cordina 2005[238]	Systematic review
de Denus 2005[263]	Systematic review
Fernandes 2004[332]	Review used as background
Flaker 2005[336]	Not question of interest
Hagens 2003[410]	Discussion paper
Hu 2006[476]	Post-op patients
Kellen 2006[516]	Not question of interest
Madrid 2003[631]	Not question of interest
Mead 2005[666]	Systematic
Nilsson 2010[696]	Non-RCT
Okcun 2004 [705]	No useable outcomes
Okcun 2009[706]	Not intervention of interest
Szulc 2006[844]	Duplicate of Opolski; does not add any information
Testa 2005[854]	Systematic review

Reference	Reason for exclusions
Vora 2004[895]	Population did not match protocol (rheumatic AF)
Yildiz 2008[925]	Population did not match protocol (AF and hypertension)

J.9 Rate control strategies

Study1	Exclusion reason
Anderson 1986[35]	Study design inappropriate
Ang 1990[40]	Study design inappropriate
Aronow 1979[51]	Study design inappropriate
Aronow 1979[52]	Not relevant to review question or unclear PICO
Aronow 1980[50]	Study design inappropriate
Atarashi 2002[58]	Not relevant to review question or unclear PICO
Atwood 1987[61]	cross over trial
Atwood 1999[60]	Study design inappropriate
Balser 1998[73]	Not relevant to review question or unclear PICO
Bianconi 1998[96]	Study design inappropriate
Bianconi 2000[95]	Not relevant to review question or unclear PICO
Blevins 1987[100]	Incorrect study design
Botto 1998[120]	Within class comparison
Boudonas 1995[123]	Mix of population - not all AF
Brodsky 1994[140]	No useable outcomes
Byrd 1984[152]	Study design inappropriate
Channer 1994[181]	Study design inappropriate
Chatterjee 2013[187]	Systematic review (re-run search)
Cheng 2010[197]	Not relevant to review question or unclear PICO
Christiansen 2010[209]	Not relevant to review question or unclear PICO
Chu 2009[210]	Not relevant to review question or unclear PICO
Collvinent 2013[222]	Systematic review (with non-randomised and randomised studies)
Connolly 2011[228]	Not relevant to review question or unclear PICO
Cotter 1999[240]	Study design inappropriate
Dabrowski 2010[251]	Randomised controlled trial: open label
Dahlstrom 1992[254]	Study design inappropriate
Das 1988[260]	Study design inappropriate
Davy 2008	Intervention does not match protocol (dronedarone)
Delle karth 2001[270]	Not relevant to review question or unclear PICO
Deng 2010[273]	Incorrect interventions, not relevant to review question or unclear PICO
Dias 1991[285]	Study designs inappropriate, Incorrect sample size
Dibianco 1984[286]	Cross over trial
Ellenbogen 1991[314]	Randomised controlled trial: open label
Farshi 1999[328]	Incorrect study design

Study1	Exclusion reason
Fauchier 2009[329]	Incorrect study design
Fragakis 2009[344]	Not relevant to review question or unclear PICO
Freemantle 2011[348]	Not relevant to review question or unclear PICO
Fung 2002[357]	Inappropriate comparison
Goldenberg 1994[385]	Methods are not adequate/unclear
Gonzalez 1981[387]	Not relevant to review question or unclear PICO
Groenveld 2011[393]	Incorrect interventions
Halley 1980[412]	Randomised controlled trial: open label
Hays 1994[428]	Incorrect interventions
Heywood 1995[442]	Study designs inappropriate
Hnatkova 1996[447]	Not relevant to review question or unclear PICO
Hohnloser 2009[457]	Not relevant to review question or unclear PICO
Hohnloser 2009[451]	Not relevant to review question or unclear PICO
Hou 1995[471]	Randomised controlled trial: open label
Hsieh 1998[474]	Not relevant to review question or unclear PICO
James 1989[486]	cross over trial
Joglar 2001[488]	Methods are not adequate/unclear
Kochiadakis 2001[537]	Study design inappropriate
Kochiadakis 2005[542]	No relevant outcomes
Koh 1995[543]	Study design inappropriate
Lang 1983[570]	Incorrect study design
Lawson-matthew 1995[578]	Incorrect interventions, cross over trial
Lee 1997[582]	Incorrect interventions
Lewis 1987[590]	Study design inappropriate
Lewis 1988[591]	Incorrect study design
Lewis 1988[592]	Study design inappropriate
Lewis 1989[593]	Study design inappropriate
Lin 1986[600]	Study design inappropriate
Lundstrom 1990[629]	Not relevant to review question or unclear PICO
Maragno 1988[645]	Incorrect study design
Martinez 2005[650]	Study design inappropriate
Masood 2010[654]	Inappropriate comparison
Mocini 1991[673]	Incorrect study design
Molajo 1984[674]	Not relevant to review question or unclear PICO
Morganroth 1985[677]	Incorrect interventions
Murgatroyd 1999[680]	Systematic review: study designs inappropriate
Olshansky 2004[714]	Incorrect study design
Page 2011[721]	Not relevant to review question or unclear PICO
Panidis 1983[722]	Study design inappropriate
Phillips 1997[735]	Study design inappropriate
Platia 1989[743]	Randomised controlled trial: open label
Pomfret 1988[756]	Study design inappropriate
Roth 1986[786]	Incorrect study design

Study1	Exclusion reason
Schreck 1997[804]	Randomised controlled trial: open label
Segal 2000[806]	Study design inappropriate
Simpson 2001[814]	Study design inappropriate
Singh 1991[819]	Randomised controlled trial: open label
Siu 2009[821]	Randomised controlled trial: open label
Skanes 2012[822]	Not relevant to review question or unclear PICO
Steinberg 1986[833]	Incorrect interventions
Sung 1995[843]	Not relevant to review question or unclear PICO
Tamariz 2004[848]	Not relevant to review question or unclear PICO
Tommaso 1983[863]	cross over trial
Tsuneda 2006[868]	Study design inappropriate
Ulimoen 2013[872]	Study design inappropriate
Van gelder 2006[880]	Not relevant to review question or unclear PICO
Van gelder 2006[877]	Inappropriate comparison
Van gelder 2010[878]	Not relevant to review question or unclear PICO
Veloso 2005[886]	Incorrect study design
Wattanasuwan 2001[899]	Randomised controlled trial: open label
Waxman 1981[900]	Not review population, not relevant to review question or unclear PICO
Wong 1990[911]	Study design inappropriate
Zirak 2012[933]	Not relevant to review question
Zoble 1987 [934]	Data unable to be meta-analysed

J.10 Rhythm control strategies - restoration of sinus rhythm

Study	Exclusion reason
Abi-mansour 1998[8]	Intervention does not match protocol
Abrams 1985[9]	Population does not match protocol
Ahmed 2010[22]	Inappropriate comparison, Incorrect interventions
Aizawa 2010[23]	Not a randomised study
Alatawi 2005[26]	Inappropriate comparison
Aliot 1996[30]	No useable outcomes
Andrade 2010[36]	Review paper
Anon 1997[1]	Drug/ intervention not available/ licensed in the UK
Aragon 2013 [47]	Conference abstract
Asher 2002[53]	Intervention does not match protocol
Atarashi 2007[59]	No useable outcomes
Atwood 2007[62]	No useable outcomes, Inappropriate comparison
Baldi 1992[70]	No useable outcomes
Baroffio 1995[75]	Crossover study
Bash 2012[77]	Review paper
Bechtel 2003[82]	Intervention does not match protocol
Bertaglia 2002[91]	Incorrect interventions, All had initial cardioversion, then more or no more
Bertini 1990[93]	Population does not match protocol

Study	Exclusion reason
Borgeat 1991[110]	Intervention does not match protocol
Boriani 1998[112]	Population does not match protocol
Boriani 2002[116]	Review paper
Boriani 2004[114]	abstract only
Botto 1994[121]	Incorrect study design
Botto 1997[122]	Inappropriate comparison
Budeus 2006[144]	Intervention does not match protocol
Bunch 2011[146]	Review paper
Burgess 2006[148]	Intervention does not match protocol
Butler 1993[151]	Intervention does not match protocol
Cagli 2006[154]	Intervention does not match protocol
Camm 1990[159]	Incorrect study design
Campbell 1985[162]	Intervention does not match protocol
Capucci 1994[167]	Intervention does not match protocol
Capucci 1995[165]	Review paper
Capucci 1999[169]	No useable outcomes
Carlsson 2001[175]	Intervention does not match protocol
Channer 1994[181]	Crossover study
Chapman 1993[186]	Population does not match protocol
Chen 2012[190]	Non-English language publication
Chevalier 2003[199]	Review paper
Chhetri 1969[201]	Population does not match protocol
Chimienti 1996[204]	No useable outcomes
Choi 2010[205]	Incorrect study design
Ciccone 1985[214]	Population does not match protocol
Claessens 1972[215]	Population does not match protocol
Cobbe 1995[219]	Population does not match protocol
Cochrane 1994[220]	No useable outcomes
Coleman 2004[221]	Intervention does not match protocol
Conde 2013 [223]	Study not randomised
Connolly 1987[227]	Population does not match protocol
Cordina 2005[238]	Review paper
Cotter 1999[240]	No useable outcomes
Dale 2006[258]	Review paper
De ferrari 2012[264]	Inappropriate comparison, Review
Demir 2011[271]	Intervention does not match protocol
Desai 1997[278]	Review paper
Dorian 1996[295]	open label study, Population does not match protocol
Elliott 2008[315]	Intervention does not match protocol, Comparison does not match protocol
Ezekowitz 2012[321]	Intervention does not match protocol
Falk 1987[323]	No useable outcomes
Falk 1997[325]	Intervention does not match protocol

Study	Exclusion reason
Fogari 2008[339]	Intervention does not match protocol
Forney 2000[340]	No useable outcomes, numbers in groups not known
Fragakis 2012[345]	Drug/ intervention not available/ licensed in the UK
Frick 1999[354]	No useable outcomes
Frost 1997[355]	Intervention does not match protocol
Geller 2009[375]	Intervention does not match protocol
Gitt 2013 [381]	Study design does not match protocol (cohort, not comparable)
Goette 2007[382]	Intervention does not match protocol
Goette 2012[383]	Intervention does not match protocol
Grover 2013 [395]	Conference abstract
Halinen 1995[411]	Intervention does not match protocol
Hilleman 2002[444]	Review paper
Hillestad 1972[446]	Intervention does not match protocol
Ho 2007[448]	Review paper
Hohnloser 1991[455]	Intervention does not match protocol
Hohnloser 1995[456]	Intervention does not match protocol
Hohnloser 1996[454]	Intervention does not match protocol
Hohnloser 2004[458]	Intervention does not match protocol
Hohnloser 2004[452]	Intervention does not match protocol
Hopson 1996[465]	Open label study, Population does not match protocol
Hornestam 1999[469]	No useable outcomes
Jong 1995[492]	Not guideline condition, Only 7/87 had AF (mainly atrial flutter); not reported separately
Kafkas 2007[500]	Intervention does not match protocol
Kanoupakis 2003[506]	Incorrect interventions, Inappropriate comparison
Kerin 1996[518]	Intervention does not match protocol
Kochiadakis 1998[536]	Intervention does not match protocol
Kochiadakis 2007[539]	Intervention does not match protocol
Komatsu 2009[545]	Intervention does not match protocol
Kondili 1990[549]	Incorrect study design
Kosior 2009[554]	Intervention does not match protocol
Kumagai 2000[559]	Drug/ intervention not available/ licensed in the UK, Intervention does not match protocol
Letelier 2003[588]	Review paper
Lombardi 2006[622]	Intervention does not match protocol
Mattioli 1998[657]	Intervention does not match protocol
Mazzone 2000[658]	Intervention does not match protocol
Mcalister 2004[659]	Population does not match protocol
Miller 2000[670]	Systematic review: study designs inappropriate
Negreva 2012 [689]	Intervention does not match protocol
Nichol 2002[693]	Review paper
Okishige 2000[707]	Intervention does not match protocol
Patten 2004[727]	Intervention does not match protocol
Podda 2012[745]	Systematic review is not relevant to review question or unclear PICO

Study	Exclusion reason
Poulin 2013 [759]	Health economic paper
Pritchett 1991[760]	Population does not match protocol
Pritchett 2000[761]	Intervention does not match protocol
Reisinger 1998[771]	Population does not match protocol
Rienstra 2006[776]	No useable outcomes
Romano 2001[783]	Non-English language publication
Ronaszeki 2011[784]	Intervention does not match protocol
Roy 2004[790]	Intervention does not match protocol
Roy 2008[789]	Drug/ intervention not available/ licensed in the UK
Shariff 2013 [809]	Post hoc analysis of included AFFIRM study
Stambler 1996[830]	Intervention does not match protocol
Stern 1982[834]	Crossover study
Sullivan 2013[842]	Systematic review is not relevant to review question or unclear PICO
Taha 2013 [845]	Conference abstract
Tejan-sie 2003[851]	Intervention does not match protocol, Comparison does not match protocol
Toivonen 1986[862]	Intervention does not match protocol
Tsaknakis 1999[866]	Non-English language publication
Vardas 2000[885]	Population does not match protocol
Vijayalakshmi 2006[889]	Open label study
Volgman 1998[892]	Intervention does not match protocol
Vos 1998[896]	Intervention does not match protocol
Whitbeck 2013 [906]	Further analysis of study of study already included
Xanthos 2007[916]	Inappropriate comparison
Yamase 2012[919]	Drug/ intervention not available/ licensed in the UK
Yamashita 2006[922]	Intervention does not match protocol

J.11 Rhythm control strategies - maintenance of sinus rhythm

Study	Exclusion reason
Almroth 2009[31]	Intervention does not match protocol (atorvastatin)
Benditt 1999[86]	Comparison does not match protocol (within class)
Boissel 1981[104]	Intervention does not match protocol (quinidine)
Bollmann 2008[105]	Intervention does not match protocol (candesartan)
Bosi 1990[118]	No useable outcomes and does not match review question
Bradley 2005[128]	Review paper
Buckley 2007[142]	No useable outcomes and does not match review question (prophylaxis)

Byrne-quinn 1970[153]	Intervention does not match protocol (quinidine)
Chimienti 1993[203]	Population does not match protocol (supraventricular arrhythmias)
Chimienti 1996[204]	Population does not match protocol (not all AF)
Chouty 1988[206]	Not a randomised study
Chun 1995[211]	Not a randomised study
Connolly 1989[225]	Crossover study
Connolly 2008[224]	Intervention does not match protocol (dronedarone)
Cook 2010[233]	Review paper
Coplen 1990[236]	Intervention does not match protocol (quinidine)
Crijns 1996[245]	Intervention does not match protocol (disopyramide)
Dagres 2011[253]	Intervention does not match protocol (dronedarone)
Dan 1997[259]	No useable outcomes and does not match review question
De paola 1999[266]	Intervention does not match protocol (quinidine)
De simone 2003[268]	No useable outcomes and does not match review question
Doyle 2009[299]	Systematic review is not relevant to review question or unclear PICO
Duray 2011[301]	Intervention does not match protocol (dronedarone)
Fogari 2012[338]	Intervention does not match protocol (telmisartan/ ramipril)
Frick 2000[353]	Intervention does not match protocol (magnesium)
Grecu 2007[391]	Intervention does not match protocol (ace inhibitor)
Gullestad 1993[399]	Population does not match protocol (not all AF)
Hillestad 1971[445]	Intervention does not match protocol (quinidine)
Hohnloser 2009[457]	Intervention does not match protocol (dronedarone)
Howard 1995[472]	Review paper
Howard 1999[473]	Intervention does not match protocol (ibutilide)

Huang 2011[478]	No useable outcomes and does not match review question
Innes 1997[482]	Intervention does not match protocol (quinidine)
Jong 2006[493]	Comparison does not match protocol (same drug, different doses)
Juul-moller 1990[499]	Intervention does not match protocol (quinidine)
Kanna 2007[505]	Non- randomised study
Katritsis 2003[512]	Comparison does not match protocol (within class)
Kaufman 2004[513]	No useable outcomes and does not match review question
Kirchhof 2012[527]	Intervention does not match protocol (comparison of short vs. long term therapy)
Kochiadakis 2000[531]	Non-English language publication (Greek)
Kochiadakis 2001[532]	Review paper
Komatsu 2003[544]	Non-English language publication (Japanese)
Kosior 2001[552]	Crossover study, Not a randomised study
Kosior 2002[551]	Crossover study
Kosior 2006[553]	No useable outcomes and does not match review question
Kowey 2009[556]	Drug/intervention not available/ licensed in the UK
Lafuente-lafuente 2006[562]	Review paper
Le heuzey 2010[579]	Intervention does not match protocol
Madrid 2004[632]	Intervention does not match protocol (angiotensin II receptor blockers)
Normand 1976[698]	Intervention does not match protocol (quinidine)
Piccini 2009[737]	Review paper
Roy 2000[787] Singh 2007[817]	Crossover study Intervention does not match protocol (dronedarone)

Sodermark 1975[825]	Intervention does not match protocol (quinidine)
Sticherling 2005[836]	Comparison does not match protocol (dose length study)
Torp-pedersen 2011[864]	Intervention does not match protocol (vernakalent)
Xia 2009[917]	Intervention does not match protocol (rosuvastatin)
Yin 2006[926]	Intervention does not match protocol (angiotensin II receptor blocker)
Zehender 1992[927]	Intervention does not match protocol (quinidine)

J.12 Left atrial catheter ablation

Reference	Reason for exclusion
Andrade 2011[37]	Systematic review with non RCTs included
Andrew 2011[38]	Systematic review - comparison does not match protocol
Arentz 2007[49]	Comparison does not match protocol
Bai2012[66]	Comparison does not match protocol
Bertaglia 2007[92]	Study design only
Bonanno 2010[107]	Systematic review – superseded by included Cochrane review by Cheng 2012
Bordignon 2013[109]	Unable to obtain. Cancelled as comparing types of ablation
Chen 2013[195]	Conference abstract
Dacosta 2006[250]	Population does not match protocol (atrial flutter)
Dagres 2011[252]	Systematic review with non RCTs included
Di Biase 2011a[283]	Abstract
Jones 2013[490]	Outcome does not match protocol (exercise)
Jones 2013A[491]	Editorial
Kay 1998[514]	Not a RCT
Khan 2008[519]	Comparator does not match protocol (pace and ablate)
Kirkutis 2004[528]	Population does not match protocol (chronic AF patients) and outcomes do not match protocol (heart rate control)
Koch 2012[530]	Comparator does not match protocol (comparison of catheter modes)
Lan 2009[566]	Not a RCT
Lau 1995[572]	Population does not match protocol (supraventricular tachycardia)
Lin 2013[599]	Exclude- all new studies previously excluded in chapter
Liu 2008[618]	Not a RCT
Malmborg 2013[635]	Comparator does not match protocol (comparison of catheter modes)
Marrouche 2007[647]	Comparator does not match protocol (comparison of

Reference	Reason for exclusion
	catheter modes)
Marrouche 2009[646]	Study design only
Martinek 2013[649]	Conference abstract
Miyazaki 2010[672]	Comparator does not match protocol (all patients had ablation)
Natale 2000[685]	Population does not match protocol (atrial flutter)
Nielsen 2012[695]	Abstract
Oral 2003a[718]	Comparator does not match protocol (comparison of catheter type)
Reynolds 2010[774]	Outcomes does not match protocol (on graph without SDs)
Reynolds 2012[773]	Not an RCT
Terasawa2009[852]	Systematic review (superseded by Cochrane Chen 2012)
Van Dijk 2013[875]	Conference abstract
Viganego 2010[888]	Not an RCT

J.13 Left atrial surgical ablation

Reference	Reason for exclusion
Cheng 2010 [196]	Systematic review with non RCTs included
Cui 2008 [246]	Comparator does not match protocol (different types of surgery)
Gasparini 2006 [373]	Intervention does not match protocol (not ablation)
Hassantash 2008 [427]	Protocol only
Jons 2009 [494]	Study design does not match protocol
Kumagai 2013 [560]	Comparator does not match protocol
Lim 2012 [598]	Comparator does not match protocol (different types of ablation)
Pires 2010 [740]	Comparator does not match protocol (different types of surgery)
Scherer 2006 [803]	Comparator does not match protocol
Pokushalov 2012 [747]	Comparator does not match protocol
Pokushalov 2013 [746]	Comparator does not match protocol (different types of ablation)
Wazni 2003 [901]	Intervention does not match protocol (catheter ablation)
Zhou 2011 [929]	Systematic review with non RCTs included

J.14 Pace and ablate

Reference	Reason for exclusions
Badheka 2013[64]	Post hoc analysis of AFFIRM study
Bagherzadeh 2011[65]	Abstract
Bradley 2007[129]	Meta-analysis with no relevant outcomes
Brignole 2011[137]	AV junction ablation and CRT device implantation plus optimised echo-guided CRT verses AV junction ablation and CRT device implantation plus RV apical pacing
Brignole 2002 [133]	AV junction ablation plus antiarrhythmic therapy vs AV junction ablation without antiarrhythmic therapy

Reference	Reason for exclusions
Brignole 2002 [135]	Review
Brignole 2003 [136]	Discussion
Dong 2010 [291]	Non-RCT
Ganesan 2012 [370]	Abstract
Gerstenfeld 2001 [378]	No AV ablation
Gillis 1999 [380]	DDI rate 30 bpm mode or DDIR lower rate 70 bpm mode followed by possible ablation
Hamdan 2006 [415]	Protocol
Hsieh 2005[475]	Non-RCT
Lampe 2012[564]	Non-RCT
Lee 1998[583]	AV junction ablation versus AV junction modification
Morady 1993[675]	Compares two types of ablation
Natale 1999[686]	Non-RCT
Opolski 2004[717]	AV junction group not reported separately
Proclemer 1999[763]	AV junction ablation versus modulation
Sonne 2009[827]	Non-RCT
Ueng 2001[871]	Non-RCT
Wang 2013[898]	Compares types of pacing
Wilton 2011[910]	Post-hoc analysis
Wood 2000[913]	SR (relevant outcomes not reported)

J.15 Acute

These are included in the rate and rhythm exclusion lists (see Section J.9 and J.10).

Appendix K: Excluded economic studies

K.1 Education

There were no excluded studies for this review

K.2 Referral

Reference	Reason for exclusion
Boodhoo 2004[108]	This UK study was **not applicable** due to incorrect interventions (nurse led sedation of cardioversion compared to normal care) and has **very serious limitations** due to lack of detail regarding costing.
Taylor 1996[849]	This UK economic evaluation was **not applicable** due to incorrect intervention (anticoagulation services) and population (not AF specific).

K.3 Stroke risk tools

Reference	Reason for exclusion
Thomson 2000[857]	This UK study evaluated criteria for warfarin initiation using a markov model. However the study did not evaluate the risk scores specifically and did not give sources for cost estimates or method. It was excluded on the account that findings would be superseded by the NCGC economic

Reference	Reason for exclusion
	analysis.

K.4 Anticoagulation

Reference	Reason for exclusion
Abdelhafiz 2003 [7]	This CCA compared the cost of warfarin and associated monitoring to the cost of stroke, using an observational study (n=402) from a UK societal perspective (included productivity loss). It was **selectively excluded** on the account the included studies also considered quality of life within the same analysis and more relevant comparators within the same analysis.
Andrikopoulos 2013[39]	This Greek CUA compared dabigatran (outside of the review question) to anticoagulation, dual antiplatelet, and single antiplatelet, without presenting results for no therapy or by risk strata. This study therefore was less applicable than the included studies and economic modelling undertaken for the guideline and **selectively excluded.**
Boccuzzi 2009[102]	This cost impact study was based on retrospective observational registry data from a USA insurer prospective. It was **not applicable** as it did not compare warfarin to another comparator.
Caro 1997[177]	This CCA was based on a decision analytic model (not detailed but stated was not Markov in design) and compared no prophylaxis, warfarin and aspirin from a USA insurer perspective. It was **selectively excluded** on the account the included studies also considered quality of life within the same analysis and evidence from the UK NHS perspective was available.
Coyle 2013[244]	This study was **not applicable** due to the intervention of comparison being outside of the review protocol (i.e. a new agent of anticoagulation).
Davidson 2011[261]	This CCA was based on Swedish registry data and compared no prophylaxis, warfarin and acetyl-salicylic acid from a Swedish societal perspective. It was **selectively excluded** on the account the included studies also considered quality of life within the same analysis, and evidence from the UK NHS perspective was available.
Davidson 2013[262]	This study was judged to **not be applicable** due to the intervention of comparison being outside of the review protocol (i.e. a new agent of anticoagulation).
Desbiens 2002[279]	This CUA was based on a Markov model comparing anticoagulation with warfarin to no anticoagulation scenarios of anticoagulation with warfarin, from a USA insurer perspective and lifetime horizon. It was **selectively excluded** on the account the included studies also considered more comparators within the same analysis and evidence from the UK NHS perspective was available.
Eckman 1995[305]	This study was partially applicable (due to the dated costs) and judged to have potentially serious limitations. However, developers felt this study was superseded by other available evidence in terms of its applicability and/or methodological quality, and therefore this study was **selectively excluded.**
Fragoulakis 2011[346]	This study was judged to **not be applicable** due to the intervention of comparison being outside of the review protocol (i.e. a new agent of anticoagulation).
Freeman 2011[347]	This CUA was based on a Markov model comparing dabigatran to warfarin, from a USA insurer perspective with lifetime horizon and informed by the findings of the RE-LY trial. This study was **not applicable** as warfarin was compared only to a novel agent, which was not a strategy of interest in this review.
Gage 1995. [361]	This CUA was based on a Markov model comparing warfarin, aspirin and no

Reference	Reason for exclusion
	therapy. The costs were pre 1994 and used a Medicare USA perspective. This study was **selectively excluded** due to the availability of more applicable evidence.
Gerson 2004[377]	This CUA was based on a Markov model comparing anticoagulation with continued warfarin to six other bridging strategies including lower dose or hold warfarin, low molecular heparin, and unfractionated heparin, before colonoscopy, and was undertaken from a USA insurer perspective with 10 year horizon. It was assessed to be **not applicable** to the review question, as it compared anticoagulation strategies for bridging rather than for long term control.
Ghatte 2011[379]	This cost impact study was based on retrospective observational registry data from a USA insurer prospective. It was assessed to be **not applicable** to the review question as it did not compare warfarin to another comparator.
Gustaffson 1992[406]	This CEA compared warfarin to aspirin, with the main outcome measure of cost of strokes saved. It took a Swedish payer perspective and presented results for the population rather than per patient. It was **selectively excluded** on the account the included studies also considered quality of life within the same analysis and evidence from the UK NHS perspective was available.
Gonzalezjuanatey 2012[388]	This study was judged to **not be applicable** due to the intervention of comparison being outside of the review protocol (i.e. a new agent of anticoagulation).
Hallinen 2000[413]	This costing study was conducted within a retrospective cohort study estimating the cost of warfarin and impact of INR from a Finnish provider perspective. It was **selectively excluded** on the account the included studies also considered quality of life within the same analysis and evidence from the UK NHS perspective was available.
Kamel 2012[503]	This CUA (based on a Markov model comparing dabigatran to warfarin, from a USA insurer perspective with lifetime horizon and informed by the findings of the RE-LY trial). This study was **not applicable** as warfarin was compared only to a novel agent, which was not a strategy of interest in this review.
Lamy 2012[565]	This CCA was based on the findings of the ACTIVE-A trial and compared the costs of clopidogrel and aspirin to aspirin monotherapy, from a Canadian Provider perspective. It was **selectively excluded** on the account the included studies also considered quality of life and more comparators within the same analysis (see Shah 2011).
Lee 2012O[584]	This study was judged to **not be applicable** due to the intervention of comparison being outside of the review protocol (i.e. a new agent of anticoagulation).
Leigh 2007[586]	This CUA (based on a semi Markov model comparing anticoagulation with warfarin to ximelagatran, from a USA insurer perspective and lifetime horizon) was assessed to be **not applicable** to the review question due to inappropriate comparators.
Lightowlers 1998[597]	This CEA, based on the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) compared warfarin to no anticoagulation to estimate the incremental life years gained free from stroke from a UK NHS perspective. It was **selectively excluded** on the account the included studies also considered quality of life and more relevant comparators within the same analysis.
Mercaldi 2011[668]	This cost impact study was based on retrospective observational registry data from a USA insurer prospective. It was assessed to be **not applicable** to the review question as it did not compare warfarin to another comparator.
O'Brien 2005A[701]	This USA CUA compared ximelagatran to warfarin and aspirin using a Markov model. This study was **selectively excluded** due to the availability of more applicable evidence (i.e. Kensal 2012) and evidence with a wider range of

Reference	Reason for exclusion
	comparators (Shah 2011).
Pink 2011[739]	Discrete event simulation model extrapolating the findings of the RE-LY was undertaken using an NHS perspective. This study was **not applicable** as warfarin was compared only to a novel agent, which was not a strategy of interest in this review.
Quinn 2007[765]	This CUA was based on a probabilistic Markov model comparing warfarin to aspirin or placebo in AF patients with haemodialysis, and from a USA insurer perspective. It was assessed to be **partially applicable** to the review question, however was **selectively excluded** as the included studies had a more applicable population.
Song 2012[826]	This cost impact study was based on retrospective observational registry data from a USA insurer prospective. It was assessed to be **not applicable** to the review question as it did not compare warfarin to another comparator.
Sorensen 2009[828]	This CUA (based on a Markov model comparing 4 scenarios of anticoagulation with warfarin, from a USA insurer perspective and lifetime horizon was assessed to be **not applicable** to the review question, as it did not compare warfarin to any other comparator in isolation (to note this study did compare warfarin to warfarin plus aspirin)
Sorenson 2011[829]	This CUA based on a Markov model comparing dabigatran to warfarin, from a Canadian provider perspective with lifetime horizon and informed by the findings of the RE-LY trial. This study was **not applicable** as warfarin was compared only to a novel agent, which was not a strategy of interest in this review..
Thomson 2000[857]	This CUA was based on a Markov model comparing the cost effectiveness of warfarin to no treatment for different subgroups of patients with AF, assumed to be from NHS perspective (although no source for cost data was reported). It was **selectively excluded** on the account the included studies had more relevant comparators within the same analysis and more detailed reporting of costing method.
Tilden 2011[861]	This study was judged to **not be applicable** due to the intervention of comparison being outside of the review protocol (i.e. a new agent of anticoagulation).
Valiya 2005[873]	This Australian CUA compared ximelagatran to warfarin and aspirin using a Markov model. This study was **selectively excluded** due to the availability of more applicable evidence (i.e. Kensal 2012) and evidence with a wider range of comparators (Shah 2011).
Zhao 2011[928]	This study was judged to **not be applicable** due to the intervention of comparison being outside of the review protocol (i.e. a new agent of anticoagulation).

K.5 Bleeding risk

Reference	Reason for exclusion
Thomson 2000[857]	This UK study evaluated criteria for warfarin initiation using a markov model. However the study did not evaluate the risk scores specifically and did not give sources for cost estimates or method. It was excluded on the account that findings would be superseded by the NCGC economic analysis.

K.6 Monitoring

Reference	*Reason for exclusion*
Kamel 2010[502]	Cost-effectiveness of outpatient cardiac monitoring to detect atrial fibrillation after ischemic stroke. Excluded as **intervention not applicable** to the review question.
Papers regarding specific methods of quality control for anticoagulation	
Anderson 2004[35]	Cost analysis of a managed care decentralized outpatient pharmacy anticoagulation service. Excluded as **not applicable** to the review question.
Geitona 2008[374]	Cost-minimisation analysis of oral anticoagulant therapy monitoring methods: the case for prothrombin time self-monitoring. Excluded as not applicable to the review question. Excluded as **intervention not applicable** to the review question.
Jowett 2009[498]	The cost-effectiveness of computer-assisted anticoagulant dosage: results from the European Action on Anticoagulation (EAA) multicentre study. Excluded as **intervention not applicable** to the review question.
Leey 2009[585]	Cost-effectiveness of genotype-guided warfarin therapy for anticoagulation in elderly patients with atrial fibrillation. Excluded as **intervention not applicable** to the review question.
Menzin 2005[667]	Quality of anticoagulation control and costs of monitoring warfarin therapy among patients with atrial fibrillation in clinic settings: a multi-site managed-care study. Excluded as **intervention not applicable** to the review question.
Patrick 2009[726]	Cost-effectiveness of genotype-guided warfarin dosing for patients with atrial fibrillation. Excluded as **intervention not applicable** to the review question.
Regier 2006[769]	Cost-effectiveness of self-managed versus physician-managed oral anticoagulation therapy. Excluded as **intervention not applicable** to the review question.

K.7 Left atrial appendage occlusion

There were no excluded studies for this review

K.8 Rate versus rhythm

Reference	Reason for exclusion
Catherwood 1999[179]	This is a decision analytic analysis of eight strategies for treating patients with persistent AF in a USA setting. It was considered partially applicable because it was a USA setting and because two of the strategies were rate control (aspirin with rate control agent and warfarin with rate control agent). However, as both the rate control strategies were dominated no further details of these strategies (costs or QALYs) were reported in the study results. For this reason the study was **excluded** as having very serious limitations for this comparison.
Pietrasik 2007 [738]	This is a cost minimisation analysis of rhythm and rate control strategies in persistent AF patients. It was considered partially applicable because the setting was Poland. However this evidence was felt superseded by that of Hagens, 2004, who conducted a cost effectiveness analysis and therefore **selectively excluded.**
Poulin 2013[759]	This is a cost analysis of rhythm and rate control strategies in AF patients with congestive heart failure, and considered partially applicable because the setting was Canada. This evidence was felt superseded by the cost effectiveness analysis by Perez 2004, and therefore **selectively excluded.**

K.9 Rate control strategies

There were no excluded studies for this review

K.10 Rhythm control strategies

K.10.1 Restoration of sinus rhythm

Reference	Reason for exclusion
Catherwood 1999[179]	A cost utility analysis assesses strategies of both anticoagulation and antiarrhythmic use which are not consistent with current practice and had assumptions contrary to findings in subsequent randomised trials. Therefore it was excluded on the account of having **very serious limitations.**
Eckman 1999[304]	A cost utility analysis assesses strategies of both anticoagulation and antiarrhythmic use which are not consistent with current practice and had assumptions contrary to findings in subsequent randomised trials. Therefore it was excluded on the account of having **very serious limitations.**
de Paola, 2003[265].	A comparison of chemical vs. electrical cardioversion with cost effectiveness presented as cost per patient converted to sinus rhythm. Efficacy data were obtained from a randomised controlled trial and cost data were collected from health care settings in Brazil. It was considered **not applicable** because efficacy and cost data were estimated in a non-OECD country.
Saborido 2010[795]	A comparison of a 'pill-in-the-pocket' strategy (self-administered pharmacological cardioversion) with in-hospital pharmacological cardioversion and with prophylactic continuous AAD therapy in paroxysmal AF. However, the study permitted AAD therapy to consist of any one of five different drugs (flecainide, propafenone, or class III agents such as sotalol or amiodarone). The study had potentially serious limitations because the individual AAD therapies could not be directly compared, and electrical cardioversion was not a comparator.

K.10.2 Maintenance of sinus rhythm

Reference	Reason for exclusion
Catherwood 1999[179]	A cost utility analysis assesses strategies of both anticoagulation and antiarrhythmic use which are not consistent with current practice and had assumptions contrary to findings in subsequent randomised trials. Therefore it was excluded on the account of having **very serious limitations.**
Eckman 1999[304]	A cost utility analysis assesses strategies of both anticoagulation and antiarrhythmic use which are not consistent with current practice and had assumptions contrary to findings in subsequent randomised trials. Therefore it was excluded on the account of having **very serious limitations.**
Lumer 2002[628]	A comparison of costs of low-dose amiodarone vs. sotalol or propafenone with results presented as average costs per patient in the first year of follow-up in an RCT. A summary of key efficacy results were reported for information purposes only. Overall, it was considered **not applicable** to assess costs because of the date of the study (2002) and the setting was not UK (Canada).
Hagens 2004[408]	A comparison of cardioversion plus AAD therapy with rate control in patients with persistent AF It was considered partially applicable because of the Netherlands setting. It was considered to have **very serious limitations** because the AAD therapy consisted of serial drug treatment (first choice sotalol, thereafter class IC anti-arrhythmics, and lastly amiodarone) and it was not possible to directly compare the individual drug therapies. It therefore was excluded.
Saborido 2010	A comparison of a 'pill-in-the-pocket' strategy (self-administered

Reference	Reason for exclusion
	pharmacological cardioversion) with in-hospital pharmacological cardioversion and with prophylactic continuous AAD therapy in paroxysmal AF. However, the study permitted AAD therapy to consist of any one of five different drugs (flecainide, propafenone, or class III agents such as sotalol or amiodarone). The study had **very serious limitations** because the individual AAD therapies could not be directly compared. It therefore was excluded.
The research group for antiarrhythmic drugs therapy, 2001[855]	This Japanese study evaluated cost effectiveness of antiarrhythmic drugs with a focus on their use for stroke prevention (an assumption which has been found as flawed in subsequent reviews). It was considered to therefore have serious limitations and excluded.

K.11 Left atrial ablation

Reference	Reason for exclusion
Assasi 2012[54]	Canadian study on ablation procedures for rhythm control in patients with atrial fibrillation was partially applicable and judged to have potentially serious limitations. However, developers felt this study was superseded by other available evidence in terms of its applicability and/or methodological quality, and therefore this study was **selectively excluded.** In particular, the study did not report methods of the economic evaluation.
Benussi 2008[87]	Costing embedded into an observational study of 70 consecutive patients undergoing complete left atrial ablation with bipolar radiofrequency. No quality of life data collated. Assumed to be from a Swiss setting and had partial applicability. No details of costing method or source presented. **Excluded** due to lack of comparator and very serious limitations.
Goldberg 2002[384]	Costing from USA provider perspective embedded into a longitudinal study examining ablation (n=33) with no comparator. Quality of life data collated with SF36, but health effects were not expressed in QALYs. Overall assessed to have partial applicability. Overall study design and reliance of this one source for resource use and treatment effect led to this study being **excluded** due to very serious limitations.
Gula 2010[397]	This evaluation explored the impact of routine transoesophageal echocardiography on safety, outcomes, and cost of pulmonary vein ablation. However it was excluded as **not applicable** as the analysis did not assess the cost effectiveness of ablation specifically.
Jensen 1995[487]	Costing from Swiss perspective embedded into a observational longitudinal study of patients (n=50) undergoing radiofrequency ablation of the atrioventricular junction as second line therapy with no comparator. Population included patients with atrial flutter. Subjective assessment of quality of life collated from patients. Overall assessed to have partial applicability. No details of costing method or source presented. **Excluded** due to having very serious limitations in comparison to available literature included in the review.
Khaykin 2007[522]	A comparative costing of ablation versus anti-arrhythmic and rate control strategies using Canadian registry data and supplementing with data from published studies. No quality of life data collated. Overall assessed to have partial applicability. Due to use of registry data to estimate resource use, the comparators are poorly specified and treatment effect is uncertain. **Selectively excluded** due to having very serious limitations in comparison to available literature included in the review.
Knight 1997[529]	This cost comparison of radiofrequency modification and ablation of the atrioventricular junction in patients with chronic atrial fibrillation was excluded as the intervention assessed was judged **not applicable** to the

Reference	Reason for exclusion
	review question.
Ladapo 2012[561]	USA cost minimisation study of catheter ablation with no comparator, using a population taken from employer and public health insurance database (n=770/3194 aged 65 and over). No quality of life data collated. Overall assessed to have partial applicability. Treatment effect and resource use taken from retrospective longitudinal study using 2001 registry data, and did not take into account all relevant considerations (e.g. need for repeat procedures). **Selectively excluded** due to having very serious limitations in comparison to available literature included in the review.
Noro 2011[699]	Model evaluating the cost of radiofrequency catheter ablation from a Japanese payer perspective, and as such no quality of life data was evaluated. Overall assessed to have partial applicability. Many of the sources for the unit costs and estimates of resource consumption were unclear, and unlikely to be from the best source (as they indicated RCT data had been excluded due to lack of applicability to the Japanese population). The probability of adverse events which incurred cost was not detailed. This study was **excluded** due very serious limitations.
Weerasooriya 2003[903]	A retrospective costing comparing radiofrequency catheter ablation to drug therapy in a drug refractory AF population from a French payer perspective (n=20). A 5% discount rate was applied. No quality of life data was collated. Overall assessed to have partial applicability. Deterministic sensitivity analysis to take into account uncertainty was undertaken. It is unclear whether the best sources for resource use were used (one observational study and abstract). Assumed ablation had a success rate of 72% and a mean of 1.5 procedures with 5 days of hospitalisation and therapeutic results are durable. The study did not consider stroke risk, or the adverse event of stroke. This study was **excluded** on the account of having very serious limitations.

K.12 Pace and ablate

There were no excluded studies for this review.

K.13 Acute

Reference	Reason for exclusion
Reisinger, 2004.[772]	A cost effectiveness comparison of flecainide vs. ibutilide for immediate cardioversion of AF set in Austria. It was considered only **partially applicable** for this reason. Results of a randomised controlled trial were presented as conversion rates for each treatment. In addition, the mean cost per successful treatment (sinus rhythm within 90 min was reported for each treatment, but these data only included costs of drugs. It was therefore considered to **have very serious limitations and excluded.**
Kim 2009 [524]	A comparison of sotalol and dofetilide in an inpatient setting in the USA. It was a retrospective cohort study using data from billing/discharge records from a hospital database It was considered only partially applicable because of the USA setting. It included only cost data in the analysis and costs were limited to inpatient resource use only, and judged **not applicable** to assess UK costs.

Appendix L: Cost effectiveness of stroke prevention strategies in patients with AF

L.1 Acknowledgements

The economic analysis presented in this appendix was conducted by the NCGC using the MAPGuide AF model. This model was developed by Julie Eatock, Marta Trapero Bertran and Joanne Lord of Brunel University as part of an MRC and NIHR funded project [Methodology Research Programme grant number G0901504]. Intellectual property rights for the model are owned by Brunel University.

We would like to thank the MAPGuide project team at Brunel University for their kind permission to use the model and research that informed it. In particular we would like to thank Joanne Lord and Julie Eatock for their kind support and assistance in the update.

L.2 Introduction

Strokes in AF are associated with a greater mortality and morbidity, with greater disability, longer hospital stays and lower rates of discharge to their own home. This AF-related stroke carries a very major health and economic burden.

The landscape of stroke prevention in AF has changed recently with the availability of novel oral anticoagulants (NOACs) that overcome the many limitations associated with warfarin. Technology appraisals recommend that these new agents should be considered against the risks and benefits of warfarin when the person with AF presents with given risk factors for ischaemic stroke. The level of risk indicated by the technology appraisals could be viewed as the equivalent level of risk indicated by a $CHADS_2$ score of 1 or a CHA_2DS_2-VASc score of 2. Alternatives to anticoagulation, such as antiplatelets and dual antiplatelets, are also offered as stroke prevention interventions, especially where the person's risk factors for ischaemic stroke would not currently indicate anticoagulation. However, it is questionable whether these alternatives offer clinical and economic benefit in comparison to a "do nothing" approach when patients are at low risk of thromboembolic events, given these alternatives are known to also carry risks of bleeding events.

The assessment of bleeding risk has also gained much attention. Many risk factors for bleeding are also stroke risk factors. Bleeding risk assessments have been introduced to 'flag up' patients potentially at risk, for careful review and follow-up – as well as to address correctable or reversible risk factors for bleeding. [160,569].

When assessing a patient with AF, the clinician has to balance stroke versus bleeding risk, although the net clinical benefit when considering ischaemic stroke versus serious bleeding is usually in favour of anticoagulation. With the NOACs, one Markov decision analysis model has suggested that the threshold for treatment may even be as low as a stroke rate of 0.9% per year [306], however this analysis did not consider the costs involved and as such was not a full economic evaluation of the decision problem.

The GDG therefore prioritised economic evaluation to explore the trade-offs between stroke and bleeding when using current stroke and bleeding risk scores, and to find the optimal strategy to prevent stroke with antithrombotic therapy.

The model informs or is related to a set of recommendations which spanned the following clinical reviews in the guideline:

1. What is the most clinical and cost-effective antithrombotic therapy for stroke prevention in people with AF?

2. What is the clinically and cost effective risk stratification tools for stroke or thromboembolic events in atrial fibrillation?

3. What is the clinically and cost effectiveness of HAS-BLED compared to other tools in assessing bleeding risk in people with AF?

This document details how an existing complete care pathway discrete event simulation model was simplified, updated and adapted for the purposes of informing these review questions.

L.3 Methods

L.3.1 Model overview

An existing patient level discrete event simulation (DES) pathway model was adapted and updated in order to answer which antithrombotic therapy is optimal for patient groups with different underlying risks of stroke and bleeding events. The base case analysis considers quality of life and cost associated with the changed management of antithrombotic therapy using the complete care pathway model to estimate baseline risk factors and survival. No cost, quality of life improvement, or survival improvement results from the management of AF. The below sub-sections detail the rationale for using an existing care pathway model and the simplifications made for the present analysis.

L.3.1.1 Background to the MAPGuide AF model.

A Discrete Event Simulation (DES) intended to reflect the course of atrial fibrillation for a representative UK cohort of patients diagnosed and treated in accordance with the service pathway recommended in NICE Clinical Guideline CG36 had been developed by an academic group at Brunel University as part of the MAPGuide MRC and NIHR funded project. The model was designed to predict the incidence of AF-related risks and associated health outcomes and expenditure, and to estimate the cost-effectiveness of some possible changes to the currently-recommended pathway. A further aim of the project was to assess the potential for a complete care pathway model to inform and be adapted for the next atrial fibrillation guideline.

For this reason this technical account of the updated model for this guideline focuses on areas of update and change required for the questions it addresses. For a detailed reports on components of the modelled care pathway outside the focus of this update and remain unchanged from the original model (i.e. the diagnostic pathway) we refer the reader to the full report[625]

L.3.1.2 Rationale for updating the MAPGuide AF model

The advantages and limitations of the existing complete pathway discrete event simulation, over and above constructing a new cohort model, were discussed with guideline developers prior to the update. Methodological and pragmatic considerations were taken into account.

The methodological advantage of a DES model over a traditional Markov or cohort model is that it allows patient history to be tracked and used to determine transitions, costs and quality of life. Rather than a focus on determining the probability of movement between health states, the model is focused on the time spent in each health state.

Methodological limitations of a DES model were also raised. A DES model requires greater parameterisation and therefore data to inform it. It is also potentially computationally burdensome, with several runs required to simulate a cohort of patients (taking into account patient heterogeneity), and several further runs required to assess uncertainty (i.e. to resample from the simulated cohort that is to say the distribution of possible input values). Having said this, software

such as Simul8 assist programming of such models, and sufficient data existed to inform the model in an AF population, i.e. the THIN database.

For the purposes of modelling a complete pathway, using DESis useful if treatment choices are to be determined by previously failed treatments and a complete pathway model gave potential for a range of decision problems to be evaluated.

However, the use of a complete pathway model raised concern that particular aspects of care could not be assessed in isolation and that unnecessary assumptions would need to be made. There was concern that the effect of modelled care outside the immediate decision problem (i.e. optimal anticoagulation therapy) would confound results. This was of particular concern in light of poor or incomplete clinical effectiveness evidence which would inform the other aspects of care (i.e. optimal rate or rhythm control).

The clinical effectiveness reviews on the management of rate and rhythm control in AF patients indicated that such management had no effect on the risk of stroke or bleeding events in this population. As such developers felt inclusion and examination of rate and rhythm control strategies within the same decision model to assess antithrombotic therapy may confuse and overcomplicate the interpretation of results. Although the original MAPGuide AF model made the assumption that rate and rhythm control did not impact on risk of stroke, the developers were keen to ensure that the management of stroke risk and the management of AF were presented and evaluated as two completely separated issues within the guideline.

A further concern was that the recommended care pathway resulting from the current guideline would differ from that of NICE Clinical Guideline CG36, on which the MAPGuide AF model was structured. Given that the new pathway would not be known until the end of guideline development, it was felt updating the structure of the management of AF symptoms (i.e. rate and rhythm control) in line with the current guidelines recommendations would not be feasible or pragmatic in regards to assisting decision making on this topic. To note, the GDG did not feel the strength and completeness of clinical evidence given for rhythm and rate control was sufficient to enable a new decision model on the management of AF symptoms to be useful in reducing uncertainty regarding cost effectiveness.

However, several advantages of updating the original MAPGuide DES model were recognised. Firstly that despite the lack of updated the model structure regarding AF symptom management, the DES model offered a means where the average life expectancy and quality of life of current AF patients managed by the NICE CG36 guideline could be modelled and estimated. It also allowed the richness of data from datasets such as the THIN database to be used to its full potential. Both these considerations allowed the model to be very applicable to the UK NHS context.

Moreover, the use of the DES model allowed a flexible examination of competing risk (i.e. that of stroke and bleeding risk), which was a fundamental element of the decision problem in deciding optimal antithrombotic therapy. Several risk factors (for both stroke and bleeds) which accrue over the patient's lifetime can be incorporated into the patient's history and model memory with ease, and the dynamic nature of risk within the patient's lifetime incorporated..

For the reasons outlined above, it was appropriate to update the MAPGuide model rather than to construct a new cohort model. The agreed approach to the update was to hold all decisions regarding management of AF constant, following the recommended pathway of this guideline as closely as possible, whilst assessing only the impact of the use of different risk tools for choice of antithrombotic therapy. Comparators would include strategies of no risk stratification (i.e. no risk tool employed) to allow assessment of the stroke reduction agents in a mixed population. As the original model worked on the assumption treatment for AF would not impact on risk of bleeding or stroke, this approach would mean the management of AF would not impact on the differential cost or QALY gain, and therefore the incremental differences observed between strategies would be as a

result of stroke risk management strategies in isolation. Reprogramming was only undertaken where absolutely necessary in order to preserve the robust validation of the original model.

L.3.2 Comparators

L.3.2.1 Choice of antithrombotic therapies compared

The model compared the following three antithrombotic therapies and a do nothing approach.

- Anti-platelets
- Dual anti-platelets
- Anticoagulants

There was insufficient evidence of anticoagulation combined with single or dual antiplatelet therapy against the comparators listed above. In particular, data regarding combination therapy lay outside the network for meta-analysis and a coherent effect size of this strategy relative to the comparators listed could not be estimated. Analysis of cost effectiveness of these combinations of antithrombotic therapy was not possible.

L.3.2.2 Choice of decision rules to offer antithrombotic therapies

Alongside assessment of strategies where blanket stroke prevention therapies (i.e. where risk scoring was not applied), the cost effectiveness model also compared strategies where anticoagulation was offered at a given risk threshold for thromboembolic (measured by the $CHADS_2$ or CHA_2DS_2-VASc score) or bleeding (measured by the HAS-BLED score) events. In particular the analysis aimed to assess which stroke prevention strategy may be suitable for patients at low risk of stroke or at high risk of bleeding (given the adverse event profile of anticoagulation)

If the patient was below the stroke risk threshold or above the bleeding risk threshold specified in the decision rule assessed, the options of giving dual antiplatelet, single antiplatelet or "doing nothing" were compared as an alternative to anticoagulation. The compared strategies looking at thresholds therefore could consist of two interventions (i.e. offer nothing or, single or dual antiplatelet, until a risk threshold has been met, and then offer anticoagulation).

Further this analysis aimed to find the most optimal scoring system to identify patients who are at low risk of stroke (i.e. at or under CHA_2DS_2-VASc score of 2 or $CHADS_2$ score of 1), given that anticoagulation is already indicated for patients with risk factors which would equate to higher thresholds.

In regards to bleeding risk assessment, effectiveness evidence and expert opinion supported the use of the HAS-BLED tool to allow the clinician to identify modifiable risk factors. However, in order to assess whether the HAS-BLED score should be routinely used in full to determine optimal antithrombotic therapy, developers required further evidence of economic benefit (see chapter 10). The analysis therefore also assesses the use of the HAS-BLED tool in relation to no stratification.

The decision rule analysis compares a range of strategies as summarised below, where x = HAS-BLED scores 0-6:

Where stroke risk only was taken into account:

- Anticoagulation should only be given if the CHA_2DS_2-VASc score is at or above 1, regardless of bleeding risk (with a do nothing approach or antiplatelets or dual antiplatelets otherwise).
- Anticoagulation should only be given if the CHA_2DS_2-VASc score is at or above 2, regardless of bleeding risk (with a do nothing approach or antiplatelets or dual antiplatelets otherwise).

- Anticoagulation should only be given if the $CHADS_2$ score is at or above 1, regardless of bleeding risk (with a do nothing approach or antiplatelets or dual antiplatelets otherwise).

Where bleeding risk only was taken into account:

- Anticoagulation should only be given if the HAS-BLED score is under X (with a do nothing approach or antiplatelets or dual antiplatelets otherwise).

Where bleeding and stroke risk were taken into account:

- Anticoagulation should only be given if the $CHADS_2$ score is at or above 1, and if the HAS-BLED score is under X (with a do nothing approach or antiplatelets or dual antiplatelets otherwise).

- Anticoagulation should only be given if the CHA_2DS_2-VASc score is at or above 1, and if the HAS-BLED score is under X (with a do nothing approach or antiplatelets or dual antiplatelets otherwise).

- Anticoagulation should only be given if the CHA_2DS_2-VASc score is at or above 2, and if the HAS-BLED score is under X (with a do nothing approach or antiplatelets or dual antiplatelets otherwise).

L.3.3 Population

The model uses a UK incident general practice primary dataset of UK patients who were diagnosed with AF.

The model does not include tests or interventional procedures for patients with structural heart defects, or for people with AF refractory to medical treatment (e.g. ablation or implantable devices).

To note, decision rules using risk scoring tools such as HAS-BLED, $CHADS_2$, and CHA_2DS_2-VASc to guide appropriate therapy were assessed by applying the rule to the same population, rather than taking a subgroup approach typical of models which use a prevalent data set, where the treatment effect given to different populations (i.e. with different risk factors) are compared. The present approach allows for stochastic evaluation of the impact of reclassification and reassignment of treatment dependent on which risk tool is used.

L.3.4 Time horizon, perspective, discount rates used

The analysis follows the standard assumptions of the reference case. The model took a lifetime horizon from point of diagnosis. Costs and QALYs were discounted at a rate of 3.5%, and sensitivity analysis was undertaken using no discounting function. An incremental analysis was conducted using a healthcare NHS and PSS perspective. Probabilistic sensitivity was performed to assess second order uncertainty.

L.3.5 Deviations from NICE reference case

No deviation from the NICE reference case was necessary..

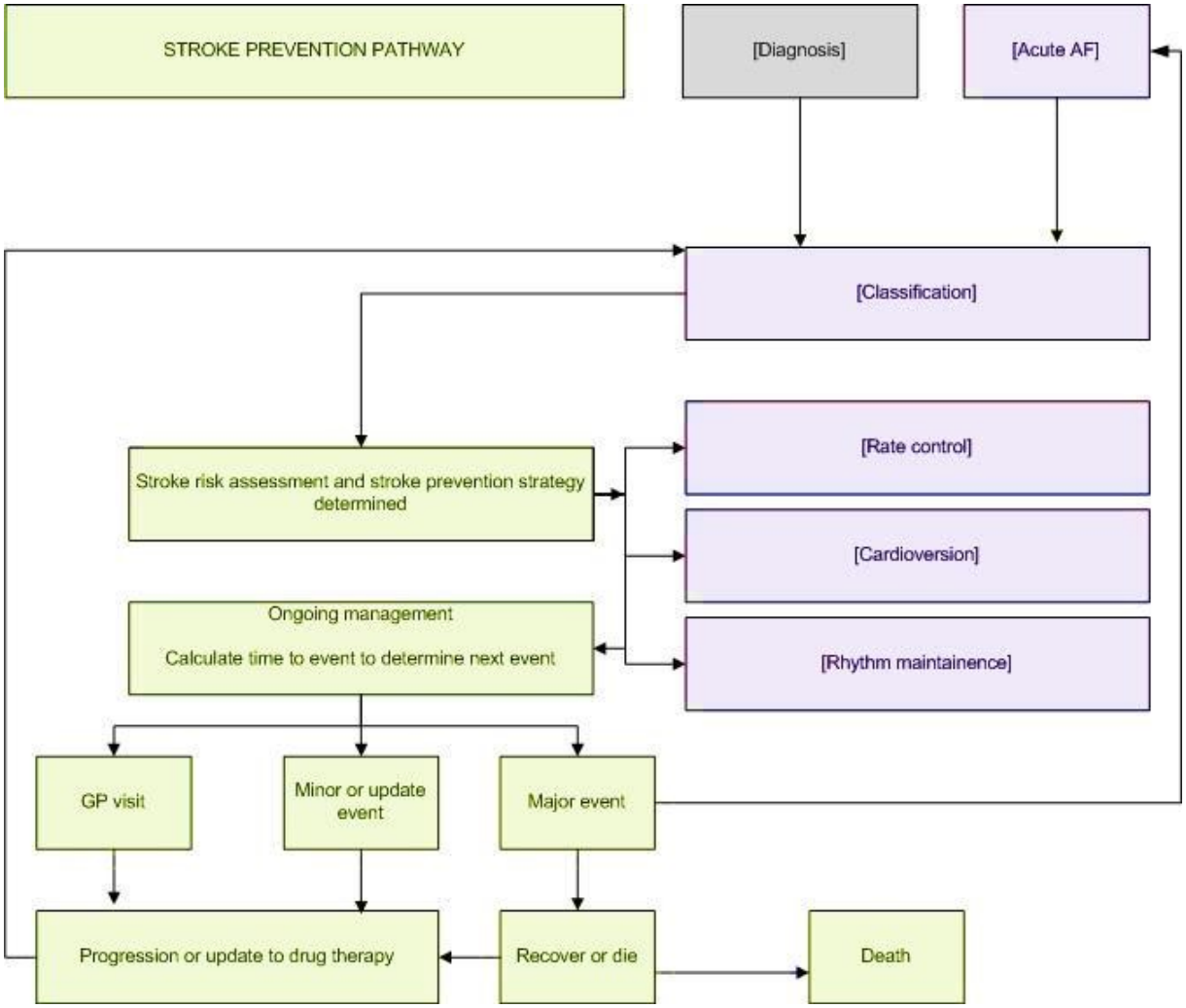
L.3.6 Model structure

The MAPGuide model consists of eight subcomponents of the clinical pathway, each of which are a module containing internal programming that attaches or updates a variety of labels attached to the simulated patient. It is these labels that store the patient's characteristics and history, from which the next time to event is calculated, and direct the patient around the model in a particular pathway. The eight modules of the model where these labels are updated are:

- Diagnosis
- Classification
- Stroke assessment and treatment assignment
- Rate control assignment
- Rhythm control assignment
- Cardioversion
- On-going management
- Acute AF care

Of these components, only the diagnostic and on-going management modules allow the simulated patient to experience time (i.e. life expectancy at a given quality of life and modification of risk). All other modules of the model were structured so that no time was accrued in these areas of the pathway. This is important to note as technically the order in which patients are assessed and classified for different management strategies occurs in the same instance of time within the model. Internal programming of time to event and other calculations unrelated to patient flow between each of the eight components, remain unchanged from the MAPGuide model. Due to the robust validation of the MAPGuide AF model, the structural internal programming was only updated where absolutely necessary to achieve the aims of the new analysis which focuses specifically on the stroke prevention pathway – a simplified map is shown below.

Figure 194: Simplified map of model components



Note: Components shaded in green represent key components of the stroke prevention pathway under evaluation. Components in purple remain active in the model but only influence the stroke prevention pathway by determining number of additional contacts (and therefore stroke risk assessments) that the patient may have.

L.3.6.1 Overview of patient movement through the model

The first model module the patients enter is the diagnostic module. For simplification, all patients are diagnosed with AF immediately and enter straight into the classification module where their "AF status" for control of AF is determined. This module feeds immediately into a stroke risk assessment, and choice of antithrombotic therapy is determined to pre-set decision rule of the strategy compared. The stroke preventative agent, if appropriate, is then assigned to the patient and they immediately go either to rate or rhythm control management according to their AF status. All these decisions are made in the same instantaneous moment that the patient arrives in the model, at time zero.

Once AF control strategies are in place, the patient enters the "on-going management" module of model where time accrues with a cost determined by the stroke prevention strategy. In this module the patient's risk of developing comorbidities and other clinical events is used to calculate the time to the next event. Dependent on the next scheduled event, the patient may exit the model through death (inclusive of death from non-AF related causes), be routed to another model module (for example to have their stroke risk reassessed when passing an age threshold or have an additional comorbidity), or continue in the on-going management module. The events which are considered in the on-going management of the module are associated with:

- AF Control, in particular:
  - Undocumented loss of sinus rhythm (AF recurrence) leading to on-going continued management.
  - Documented AF recurrence leading to medical attention, which may be:
    - An acute occurrence leading to the Acute Care module.
    - Non acute occurrence leading to classification and allocation of new treatments.
  - If the patient returns to sinus rhythm within 7 days without medical intervention, the patient continues with a label of "paroxysmal AF"; however if the AF continues for more than 7 days we label the patient with "persistent" AF. IF cardioversion is required to alleviate symptoms, that is to say all both lines of rate control have failed, and then the patient is relabelled to have "persistent AF - rhythm".
  - The new rate or rhythm control treatment assigned will in part depend on which line of treatment the patient has previously tried, comorbidities, and whether the patient is symptomatic. As soon as the patient is labelled with "persistent AF - rhythm" a cardioversion is scheduled.
  - An increase in resting heart rate above 80 beats per minute, which may be:
    - Acute onset leading to the acute module, prior to classification, stroke risk review and allocation of new rate treatments.
    - Non acute onset leading to classification, stroke risk review and allocation of new rate treatments.
- Major adverse events, in particular:
  - Thromboembolic events (ischaemic strokes, Transient Ischaemic Attacks (TIA) and other major thromboembolic events) leading either to death, or if survived leading to the reclassification and assessment for stroke risk with a review of the stroke prevention strategy (given the risk factors of stroke and bleeding will have changed.
  - Bleeds (haemorrhagic stroke or major bleed). These events may be fatal. If the patient survives, they will be routed to the classification module, where their treatment will be reassessed.
- New risk factors, in particular:
  - An increase in age (updated yearly), which may prompt a scheduled review at certain age thresholds in line with the new recommendations made in this guideline (i.e. at the age of 65). A review would mean that the patient would go back to the reclassification module and have their treatment assessed.
  - Onset of diabetes, coronary heart disease and heart failure, hypertension which would prompt a medical attention, which in turn prompts a medical review. The patient is rerouted to classification and treatment in reviewed.
  - The onset of new risk factors, such as hypertension, diabetes or passing an age threshold increases individuals' risk of major events, reducing the time to their next major event within the on-going management module.
- Drug withdrawal, in particular:
  - Patients might stop taking a drug, either due to an adverse effect or for some other reason. After a drug withdrawal, patients are sent to classification, and will pass again through the pathway to have alternative treatment considered.
- Death, in particular:
  - Mortality unrelated to AF was modelled independently of the other risk factors (other than age and sex).

- Mortality related to AF occurred in the MAPGuide model by applying case-fatality rates to thromboembolic events and bleeds, as well as acute-onset arrhythmias (disabled in this analysis as outside of the stroke prevention pathway).

The patient cycles between the on-going management module and the complete care pathway until death occurs. In the present analysis no cost or effect is attributed by AF control. This means that differences in survival, quality of life and cost are derived only by baseline characteristics, decisions and events which occur in the stroke prevention pathway. Stroke risk is reassessed whenever the patient has contact with clinical services, or called in for review due to obtaining another risk factor for bleeding or stroke (i.e. passing an age threshold or developing diabetes for instance).

L.3.6.2 Programming of patient movement through the model

Patients diagnosed with AF enter the treatment pathway, where they have their risk assessed and are allocated treatments based on their personal characteristics, each of which is represented by a label assigned to the patient on model entry using primary patient level data.

The process by which the patients pass through the model depends on their classification, which is recorded on a label called “AF status”. This is programmed and assigned in the classification module using the patient characteristic labels. The MAPGuide model offers three options in how the patient’s “AF status” is used to determine the flow of patients to rate or rhythm control. In order to follow the new recommended pathway as closely as possible, the model was set to give all patients labelled with persistent or permanent AF rate control first, allowing for patients with paroxysmal AF to undergo a pill in the pocket strategy, and other rhythm control strategies first if appropriate.

The proportion of patients in each classification being assigned a particular drug, and the sequence in which drugs are given, is determined by updating a spread sheet that feeds into the model. These treatments may include anti-thrombotic drugs, drugs to control their heart rate and/or interventions to promote and maintain sinus rhythm. Referral to specialist interventionist management is made possible when all pharmacological options have been exhausted, however in terms of lifetime costs it is still assumed the patient continues on their last drug therapy.

In practice, the structural elements of the model outside the stroke prevention pathway can be controlled and kept constant through data entry. This allows for the internal programming within each module – including calculations of adjusted risk and time to event to remain unchanged and preserves the integrity of the original model.

To ensure a focused analysis on stroke prevention, the relative efficacy of all rate and rhythm control drugs to improve outcomes (inclusive of quality of life and mortality) was set to 1, meaning pragmatically no difference would be observed between those taking the drugs or not. Equally the cost of these drugs were set to zero, to ensure no costs outside of the stroke prevention pathway would influence the incremental differences observed for different stroke prevention strategies. To determine the optimal stroke prevention strategy (inclusive of at which risk score anticoagulation should be offered) downstream thromboembolic and bleeding events were modelled in all analyses.

L.3.6.3 Key updates to the original MAPGuide model

Treatments are grouped into four classes, defined by their major outcome targets; cardioversion (aim to regain sinus rhythm), rhythm control drugs (aim to prevent AF recurrence); rate control (aim to achieve control of heart rate); and antithrombotic (aim to reduce the risk of thromboembolism, while minimising impacts on bleeding). In addition, a withdrawal rate is defined for each drug. The developers wished to simplify the model by removing the impact that all but the anti-thrombotic agents would have on survival, quality of life and cost. In order to do this for the base case analysis we undertook the following action:

- We do not consider the cost, impact and effect of medication or intervention initiated for AF control or for comorbidities. Disease progression is in line with that for a patient untreated for AF. In doing so we make our estimates of cost effectiveness conservative, as it is assumed that with improved management of AF control the patient will have an improved life expectancy whereby the incremental differences resulting from the analysis would be magnified due to having a longer period of time at risk.
- Setting the risk of death due to acute on-set arrhythmia to one. Mortality related to AF occurred in the MAPGuide model by applying case-fatality rates to acute-onset arrhythmias, thromboembolic events and bleeds. By setting the relative risk of mortality to 1 for all interventions (pharmacological and interventional), no difference would be observed in life expectancy on the account of the patient's management for their AF. Mortality unrelated to AF was modelled independently of the other risk factors (other than age and sex) and parameterisation of these factors remained unchanged. Mortality related to thromboembolic events and bleeds were determined by baseline risk and updated
- Using a quality of life multiplier to account for presence of AF, however, removing any differentiation caused by symptomatic AF or whether the patient was in or not in sinus rhythm. Quality of life in the primary analysis was therefore only determined by the impact of the five adverse clinical events associated with the stroke prevention pathway (ischaemic stroke, transient ischaemic attack, other thromboembolic complications, haemorrhagic stroke and major bleeding). Only stroke (whether due to ischemia or bleeding) had a sustained impact on quality of life (with a differential quality of life applied within the acute period of 90 days).
- Setting all costs outside of the stroke prevention pathway to zero, and only incorporating the consultation cost of a primary care or tertiary consultation should the patient contact health services. Primarily this was undertaken using the data sheets feeding into the model; however any costs which were not updated via external spread sheets (i.e. drugs associated with cardioversion inclusive of heparin and a 4 week course of warfarin) were removed within the simul8 model.
- To note, treatment effects of interventions were not set to zero so that healthcare contact, and therefore stroke risk assessment frequency was realistic of that which would occur given the updated guidelines. In the base case, however, patients who have non self-terminating AF only follow the rate control pathway, which only allows for acute AF so contact would be governed by baseline rates of:

a) Proportion of documented and undocumented AF recurrence

b) Onset of new risk factors (i.e. passing an age threshold or onset of new comorbidities)

c) Acute AF (after which stroke risk is reassessed)

- Where possible, we updated the efficacy of the rate and rhythm control pathway in line with evidence found in the clinical review and recommendations in the present guideline. In practice, only one input parameter was updated. This related to the success of pharmacological versus electrical cardioversion for patients with persistent AF. This parameter was made redundant in the current analysis by directing people with persistent AF to rate control first.
- The original MAPGuide model considered rivaroxaban and dabigatran as comparators, however due to the focus on intra class comparison reference to these options were removed. We added to the model the comparator of dual anti-platelets using the cost of aspirin and clopidogrel with dosage as reported by the ACTIVE 2006[13] trial. In order to preserve the original structure and integrity of the model, we rerun the model four times where on each occasion a different comparator drug is given as an alternative to anticoagulation. An internal table within simul8 was modified to reflect when the alternative drug should be given in relation to the patient's bleeding and stroke risk score, and the decision rule strategy under assessment.

- The original MAPGuide model used a series of conditional probabilities that fed into the time to event calculations of bleeding and thromboembolic events. The relative risk of treatment was applied to the risk of having a bleeding or thromboembolic event, rather than being applied to a specific event directly. However, the NCGC update and network meta-analysis gave opportunity to derive hazard ratios which could be applied directly to the likelihood of a specific event. Therefore the datasheets and the internal programming within the model was updated to allow these relative effects to be used directly.
- The remainder of the internal programming changes were to assist the user to cycle through the analyses required for the evaluation of bleeding and stroke risk tools.

The developers reviewed the simplifications and assumptions contained within aspects of the model which primarily fell outside the stroke prevention pathway, and agreed these were reasonable. Further detail on the complete MAPGuide care pathway is detailed elsewhere.[625] Developers were keen to stress that within the model structure all AF patients have stroke and bleeding risk assessed, with appropriate stroke prevention therapy, prior to experiencing time under a new treatment regimen. All patients, regardless of whether they have episodic AF, persistent AF, or permanent AF, and regardless of whether they are symptomatic or not, will have their stroke risk and preventative treatment reviewed prior to undertaking any new AF control strategy.

L.3.7 Uncertainty

Discrete event simulation with the use of patient level data primarily assesses first order uncertainty that is to say that which reflects the natural variability between patients. The output of one patient level simulation will therefore give you the mean and confidence of one sample taken from the population. In the deterministic base case we ran the simulation with 5000 patients.

In order to assess second order uncertainty of the population mean, it is necessary to run several patient simulations to build a sample of means, each first order simulation being termed a trial. Prior to running the trials, a simulation is undertaken in excel to generate a list of 4,000 possible values for each parameter subject to probabilistic sensitivity analysis.

For each trial, the model was programmed to randomly select the same “run” or line from these generated lists of potential input values, to note in the patient level simulation model the label given for this purpose is SOUR (Second Order Uncertainty Run). Where the input of a network meta-analysis was required, each trial read from a selected line of CODA instead to preserve the correlation in the network.

For each trial, the mean cost and QALY is calculated representing the mean of that sample. 500 trials were run, which represents 500 iterations within a probabilistic sensitivity analysis and in effect builds a sample of means. Due to the run time of the model and the number of analyses which were required, the number of patients in each trial was restricted to 1000, as per the original MAP Guide analysis. The average of these means was taken to be the population mean, with the credibility interval calculated by taking the 2.5th and 97.5th percentiles of this sample of means. This credible interval represents the second order uncertainty within our estimate (i.e. that representing uncertainty around our estimated inputs due to sampling error, rather than heterogeneity in our population). Second order uncertainty can be taken into account when interpreting results by considering the probability that a particular strategy will be ranked optimal.

Within the datasheets, a probability distribution is defined for each model input parameter subject to probabilistic sensitivity analysis. When the excel probabilistic simulation was run, a value for each input was randomly selected simultaneously from its respective probability distribution. The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by zero and one, reflecting that a quality of life weighting will not be outside this range. Probability distributions in the analysis were parameterised using error

estimates from data sources. Details of the distributional parameters of variables which were probabilistic are detailed in Table 150.

Table 150: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Any determined by clinical experts' estimation, or where data to parameterise the distribution was lacking in the evidence.	Uniform	Bounded between specified maximum and minimum values. In a probabilistic run, there is an equal chance of any value being selected between these extremes. In the model this was applied to some diagnostic probabilities estimated by clinical experts, or where data to parameterise the distribution was lacking in the evidence.
Instantaneous rates and hazard ratios	Lognormal, with finding exponentiated	The lognormal distribution is parameterised by the log of the mean, and the log of the standard error where, Natural log of the mean = [Ln(mean) – (lnSE)^2]/2 Natural log of the standard error (lnSE) = $\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$
Probability of binomial event	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated as follows: Alpha=(number of events) Beta=(Number of patients in sample)-(number of events)
Probability of multinomial event, i.e. being in a particular subgroup or having a particular thromboembolic event when more than two types of event are possible)	Dirichlet	Fitted to multinomial data. Represents a series of conditional distributions, bounded on 0-1 interval. Derived by the number of patients in the sample and the number of patients in a particular subgroup. A gamma distribution, where $\alpha = number\ in\ subgroup$, $\beta = 1$ is applied to each subgroup to return a probabilistic sample size. Using all the newly generated sample sizes, a probabilistic probability of being a in a particular subgroup is returned. Due to a known bug in excel, where the expected sample size of the subgroup is expected to be >345, an inverse normal distribution is applied, with the mean subgroup sample size and square root of these mean is used to parameterise.
Utility Multiplier and event incidence rates (probability of event per year per population)	Beta	Bounded between 0 and 1. Parameterisation of the beta distribution was then derived from mean of the multiplier and its standard error, using the method of moments. Standard error, Alpha and Beta values were calculated as follows:

Parameter	Type of distribution	Properties of distribution
		$SE = \sqrt{\frac{\tilde{x} \times (1 - \tilde{x})}{N}}$ $\alpha = \tilde{x}^2 \times \left(1 - \left(\tilde{x} / SE^2\right)\right) - \tilde{x}$ $\beta = \alpha \times \left(\frac{1 - \tilde{x}}{\tilde{x}}\right)$ Where SE = Standard Error; $\tilde{x}$ = mean; N = sample size
NHS Reference Costs or Event costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and Beta values were calculated as follows: Alpha = $(mean/SE)^2$ Beta = $SE^2/Mean$
NHS Reference Costs	Lognormal	Where appropriate, the lognormal distribution may provide a better fit than the gamma distribution for costs. The natural log of the mean was calculated as follows: Natural log of the mean = $[Ln(mean) - (lnSE)^2]/2$ Where the natural log of the standard error (lnSE) was calculated by: $\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$

The following variables were left deterministic (i.e. not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- the acquisition cost of pharmacological agents (fixed by the drug tariff)
- the cost and number of a GP visit (assumed to be fixed according to national pay scales and time spent per patient)

L.3.8 Model Inputs

L.3.9 Summary data finding methods

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. We aimed to find the best available data, however due to the scale of the complete care pathway model our approach was pragmatic. Key data sources for the parameters associated with antithrombotic therapy were reviewed in detail and updated where necessary. Our approach included;

- A new network meta-analysis to estimate treatment effect of antithrombotic agents,
- A systematic quality of life search, inclusive of cross checking values in published models.
- A systematic search for costs associated with AF, as part of our overall economic literature review.

- Checking sources and estimates of published models retrieved by our own systematic review for superior data sources regarding treatment effect, as well as checking the references of published health economic reviews on the topic of atrial fibrillation.
- Cross checking the findings of our own meta-analyses for data on relative treatment effect (including control arm quality of life estimation) of non-antithrombotic interventions to the estimates used in the original MAPGuide model.
- Model inputs were validated with clinical members of the GDG.

In many instances, data sources and the original estimates were not updated. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

To note, in this analysis of the stroke prevention pathway, the developers were keen to only evaluate the stroke prevention pathway and as such all parameters impacting on AF control were held constant, with costs set to £0 and relative effect on quality of life and survival set to 1 (no difference).

L.3.10 Initial cohort settings

The Health Improvement Network (THIN) primary care database was used by the MAPGuide AF model[625] developers to define a representative cohort of newly diagnosed patients. Using information on 12,776 patients with newly diagnosed AF, sampling from the list of eligible patients is random 'with replacement'. The below table details the risk factors which were defined in advance of model entry, as variables of the THIN individual-patient dataset and the factors which were assigned as patients move through the simulation model (as determined by risk algorithms, pre-existing comorbidities and treatment effect where applicable).

The THIN data source and method of defining the simulated cohort was discussed with clinical members and update was not required given epidemiology, medication and management has not changed substantially since 2008.

There was concern that an incident cohort was younger than the prevalent cohort of today's population who live with AF. However, use of an incident cohort captures the impact of the decisions made from the beginning of the patient's journey. Given that the recommendations formulated from the interpretation of the models result aim to stratify by risk, and thereby take account of the patient's gender, age and comorbidities, the use of an incident cohort was felt appropriate.

The baseline characteristics of the AF population entering the model appeared representative of the current UK population by clinical experts on the guideline group. The incident cases of AF were on average 73.6 years old and 47% female. Around 5% had a family history of CHD. Their average blood pressure was 78/137 mmHg, their average BMI was 28.5kg/m2 and 12% were current smokers. In terms of medication, around 40% were on antiplatelet or lipid lowering medication, and 65% were on antihypertensive medication. 21% had a history of haemorrhage, such as an ulcer or bleed.

A lookup table was used to tailor the baseline risk of different comorbidities or events according to the individual simulated patient's baseline characteristics. This risk would be updated as the patient aged and progressed through the model acquiring more risk factors.

Risk factors drawn from THIN data

Definitions
Unique identifier for patients
Sex
Age

Definitions
Incident AF cases
Family history of diabetes/hypertension
Systolic blood pressure
Diastolic blood pressure
Body mass index (height/weight squared)
Current smoker
Total serum cholesterol
HDL cholesterol
Antiplatelet drugs (BNF 2.9)
Non-steroidal anti-inflammatory drugs (BNF 10.1.1)
Vascular disease: MI (I21, I252) or PAD (170-73)
CHD: Angina, MI, coronary insufficiency
Thromboembolism: IS (I63-4), TIA (G45) or Other TE (I74,I26)
Bleed: Intracranial (I160-2) or other major bleed (I850, I983, K25-28 (0-2,4-6), K625, K922, D629)
Heart Failure: CHF/LVD (I50)
Left Ventricular Hypertrophy
Hypertension (I10-15) - CHA_2DS_2-VASc definition
Diabetes (E10-14)
Alcoholic disease
Renal disease (N17-19, transplant or dialysis)
Liver disease (K70-77, transplant or resection)

L.3.11 Baseline risks and incidence of new onset comorbidities (risk factors for stoke and bleeding).

L.3.11.1 Baseline risk of new onset Coronary Heart Disease (CHD), hypertension and diabetes

The risks of new-onset Coronary Heart Disease (CHD), hypertension and diabetes were calculated using multivariate risk equations estimated from the Framingham cohort study.[34,724,909] Note that this data was from a general population cohort, not specific to AF. The updated model uses the risk calculator as provided by the MAPGuide model developers.

L.3.11.2 Baseline incidence rates of Chronic Heart Failure

The risk of new onset heart failure was estimated based on age/sex specific rates from a general population cohort.[243] Note that this data was from a general population cohort, not specific to AF. This parameter was not subject to systematic review in the new guideline, and the data source was not updated.

Table 151: Baseline incidence rates of Chronic Heart Failure (Cowie 1999).

CHF score	Point estimate	Distribution	SE	Alpha	Beta
Male					
< 25	0.0000	Beta	0.0000	0.00	0.00
25-34	0.0000	Beta	0.0000	0.00	0.00

CHF score	Point estimate	Distribution	SE	Alpha	Beta
35-44	0.0002	Beta	0.0001	2.9998	18554.3335
45-54	0.0003	Beta	0.0001	3.9997	15670.0003
55-64	0.0017	Beta	0.0004	20.9983	12324.6684
65-74	0.0039	Beta	0.0007	33.9961	8731.6705
75-84	0.0098	Beta	0.0015	40.9902	4134.6765
85+	0.0168	Beta	0.0043	14.9832	879.0168
Female					
< 25	0.0000	Beta	0.0000	0.00	0.00
25-34	0.0000	Beta	0.0000	1.0000	22698.0000
35-44	0.0002	Beta	0.0001	2.9998	16756.0002
45-54	0.0001	Beta	0.0001	0.9999	14709.6667
55-64	0.0007	Beta	0.0002	7.9993	11919.3340
65-74	0.0023	Beta	0.0005	23.9977	10380.0023
75-84	0.0059	Beta	0.0009	41.9941	7047.0059
85+	0.0096	Beta	0.0020	22.9904	2367.6763

L.3.12 Risks of bleeding and thromboembolism

The risk of thromboembolic and bleeding events were defined by published risk algorithms for patients with AF: CHA_2DS_2-VASc and HAS-BLED respectively. As the patient accrued risk factors (i.e. experiencing an ischaemic event or developing a new risk factor) a new risk score using these algorithms is calculated and the risk of event updated in line with those observed in the SAF cohort study, and further detail is given below. The baseline and updated individual risk of a specific thromboembolic or bleeding event is influenced by three sets of calculated probabilities in the model:

- The risk of having certain risk factors and the probability of having a certain risk score. This is determined by the epidemiological profile of the cohort, i.e. that of the THIN dataset, and the application of risk algorithms for comorbidities such as CHD.
- The risk of any bleeding or thromboembolic event given a certain risk score. These risks were defined using published risk algorithms for patients with AF: CHA_2DS_2-VASc and HAS-BLED respectively. As the patient accrued risk factors (i.e. experiencing a ischaemic event or developing a new risk factor) a new risk score using these algorithms is calculated and the risk of event updated in line with those observed in the SAF cohort study (see below and Table 152) [352]
- The risk of a specific type of event, i.e. major bleed, given that a bleeding or thromboembolic event has occurred. This is determined by the Incident thromboembolic or bleeding events during follow up of the SAF study (see Table 153). [352]

The risk of death caused by an adverse event was calculated by using case fatality estimates given an ischaemic or haemorrhagic stroke, or a major bleed, had occurred (see L.3.12)

L.3.12.1 Data sources for baseline incidence rates and risks of bleeding and stroke

The need to update the data source to estimate the baseline risk of bleeding and thromboembolism was undertaken in consideration of the available studies retrieved by systematic review for the bleeding and stroke prediction tool questions in the current guideline (chapters 8 and 10).

The MAPGuide AF model uses data from the Swedish AF (SAF) cohort study to estimate incidence rates for thromboembolic and haemorrhagic events. [352]From the studies identified by the guideline's

systematic prognostic reviews, this data source was considered optimal to estimate baseline risks for the following reasons:

- The study gave event incidence rates according to each risk stratification. These rates were derived from the same cohort allowing coherent estimates of the related risks of bleeding and thrombo-embolic events.
- The study was one of the largest cohort studies retrieved in the systematic review, containing 182,678 individuals with a diagnosis of AF (ICD-10 code I489:A-F) who were treated as an inpatient or outpatient at Swedish hospitals between July 2005 and December 2008. Average follow-up was 1.5 years.
- Rates used in the model were calculated using patients who were not on oral anticoagulation. If figures included patients who were taking aspirin, this was adjusted to provide estimates for an untreated cohort by using a 22% reduction in thromboembolic risk (all types of thromboembolic events).[424]
- Information was given to estimate incidence on the type of thromboembolic and bleeding event which occurred, closely matching the key outcome events of interest in the review question on stroke prevention (please see Table 153)
- In the absence of a similar UK study, it was felt that a Swedish population was appropriate.

For this reason it was felt that the baseline risks for thromboembolism or bleeding in the MAPGuide model did not require updating. The following limitations were, however, noted:

- That patients with 'silent AF' and patients managed only in primary care and open clinics were excluded by the sampling method.
- Due to small numbers, event rates for HAS-BLED scores of 4 or more and CHA_2DS_2-VASc scores of 7 were pooled.

Table 152: Rates of thromboembolism and bleeding from the Swedish AF cohort study. Calculated from Friberg, Rosenqvist & Lip EHJ 2012 [352]

Parameter description	Point estimate	Probability distribution and parameterisation
Rate of Major Bleeding by HAS-BLED score		
0	0.0050	Beta (SE = 0.0017, α = 8.76, β = 1744.07)
1	0.0210	Beta (SE = 0.0017, α = 144.28, β = 6726.11)
2	0.0360	Beta (SE = 0.0017, α = 439.86, β = 11778.35)
3	0.0550	Beta (SE = 0.0024, α = 501.95, β = 8624.48)
4+	0.1091	Beta (SE = 0.0056, α =335.42, β = 2739.81)
CHA_2DS_2-VASc score	Mean (TE event rate per year) **	
0	0.0030	Beta (SE = 0.0007, α =16.03, β = 5325.97)
1	0.0100	Beta (SE = 0.0012, α =67.69, β = 6701.31)
2	0.0330	Beta (SE = 0.0017, α =370.89, β = 10868.11)
3	0.0530	Beta (SE = 0.0056, α =937.46, β = 16750.54)
4	0.0780	Beta (SE = 0.0019, α =1489.02, β = 17600.98)
5	0.1170	Beta (SE = 0.0027, α =1694.98, β =12792.02)
6	0.1590	Beta (SE = 0.0037, α =1522.58, β = 8053.42)
≥7	0.1836	Beta (SE = 0.0049, α =1554.84, β = 5136.16)

** Estimated from distribution of HAS-BLED scores in the whole cohort (170,291) and number on no prophylaxis (33,486), No oral anticoagulation or aspirin)*

***Estimates stroke/TIA/peripheral emboli events for patients not prescribed warfarin during follow-up, and adjusted for aspirin use (assumed 22% increase in TE risk with aspirin, Hart et al 2007)*

Table 153: Incident thromboembolic or bleeding events during follow up (260,000 patient years at risk, all treatment groups) Source: Friberg, Rosenqvist & Lip, Circulation 2012 [352]

Event	Number of events	Baseline probability of a given type of thromboembolic or bleeding event should one occur.	Probability distribution and parameterisation
Ischaemic stroke	14653	69.99%	Dirichlet, parameterised by the number of events within each subgroup and the subtotal of patients having a thromboembolic event
Transient Ischaemic Attack	5114	25.09%	
Other thromboembolic complication	1001	4.91%	
Sub Total	20768		
Haemorrhagic stroke	1600	27.54%	Dirichlet, parameterised by the number of events within each subgroup and the subtotal of patients having a bleeding event
Major bleed	4210	72.46%	
Sub Total	10607		

(a) Note, this table is updated in the "Diseases spread sheet" of the model

L.3.13 Baseline risk of death and case fatality rates (NCGC updated)

The systematic review on antithrombotic therapy did not determine case fatality rates given a clinical event. Various data sources were retrieved and discussed with the clinical members of the group. To note, only death from ischaemic stroke, haemorrhagic stroke and major bleed, alongside all-cause mortality, was considered in the model.

L.3.13.1 Ischaemic stroke

Evidence from Hylek et al. 2003[480] suggests that case fatality of ischaemic stroke was effected by the type of stroke preventive treatment, for example case fatality post ischaemic stroke in patients with well controlled warfarin was greatly reduced, even post adjustment for confounding factors, in comparison to that for patients who had poor control of anticoagulation, treated with antiplatelet or with nothing. The below table details the adjusted probability of fatality by treatment type.

Table 154: Data informing 30 day case fatality rate of ischaemic stroke by treatment, including no antithrombotic therapy. Source: Hylek 2003[480], a retrospective USA cohort study based on patients from 1997.

Treatment	N (in sample)	n (events)	Probability	SE	% on treatment	HR (adjusted)	RR (adjusted)	Adjusted probability	SE	n(events - adjusted)
Nothing	248	24	0.10	0.019	42%	4.90	4.16	0.35	0.051	87.10
Aspirin	160	15	0.09	0.023	27%	2.50	2.34	0.20	0.071	31.69
Warfarin INR	117	16	0.14	0.032	20%	3.40	3.07	0.26	0.080	30.34

Treatment	N (in sample)	n (events)	Probability	SE	% on treatment	HR (adjusted)	RR (adjusted)	Adjusted probability	SE	n(events - adjusted)
less than 2										
Warfarin INR 2 or greater	71	6	0.08	0.033	12%	1.00	1.00	0.08	0.114	6.00
Warfarin pooled	188	22	0.12	0.023	32%	-	-	0.23	0.069	36.34
Pooled (all treatment types)	596	61	0.10	0.012			Adjusted pooled probability	0.26		

In order to use these adjusted case fatality rates for ischaemic stroke, an estimated time in therapeutic range was required. Gallagher (2011) [365] provides analysis of a UK general practice dataset and estimates average time spent in therapeutic range is 0.63% (n=18113, SE = 0.0016, Alpha =54983, Beta = 32153). The model used this estimate to pool the adjusted risk of case fatality for anticoagulation in the model to apply a weighted average of 15%. The case fatality used for both antiplatelets and dual antiplatelet was 20% and a do nothing approach had a 35% case fatality post ischaemic stroke. These disaggregated estimates would favour anticoagulation in relation to the alternatives.

L.3.13.2 Bleeding events

Gomes et al (2011) [386] report on a large Canadian cohort study and gives 7 day mortality rates. Due to the size of the study this was selected as the best available source, although limitations in applicability were acknowledged. Details of the estimates used are given in the below table (noting some estimates were recalculated using information provided in the table rather than in text). Whilst the case fatality for haemorrhagic stroke compares with a recent but smaller UK analysis which found a 30 day case fatality rate of 47% (Luengo-Fernandez et al[627], 2012 n= 17), it is lower than the 56% case fatality reported in the SPORTIF III & IV trials (Douketis et al[297], 2006 n=18). This is most likely to be explained by the unknown time to death in the trials and the 7 day period of follow up in the cohort study.

In regards to case fatality of major bleeding, the below cohort study suggests almost double the risk than that reported in the SPORTIF trial (which reported a case fatality rate of 8%, n=234) [297]. This is most likely to explained by an older population in the cohort study, which although may be more reflective of a typical AF population may pose a limitation, against anticoagulation, if applied to groups who are younger and less at risk of bleeding.

We used the rate taken over a 7 day period as a proxy for the 30 day acute period, potentially underestimating the case fatality within this time for both bleeding events. This is under the assumption that a death is more likely to occur nearer the time of event.

Table 155: Seven day case fatality rates for bleeding events, source Gomes et al 2013[386].

	7 day mortality %	Number of deaths	Number of AF patient experiencing a bleed	% type of bleed	Case fatality (mean and SE)	
ICH	41.71%	229	549	5%	41.71%	0.0210
Gastro bleed	14.78%	1003	6785	59%		
Other bleeds	12.58%	527	4190	36%		
All non ICH bleeds	13.94%	1530.00	10975.00	95%	13.94%	0.0033
All (NCGC calculated)	15.26%	1759	11524	100%		
All (as reported by paper)	18%	1963	10840			

L.3.13.3 All-cause mortality

Mortality rates from non-AF related causes were based on national life table data [702] dated from 2008 to 2010 in line with use of the THIN database. The mortality rates were adjusted for AF by removing all deaths which may be caused directly by AF, or indirectly through related complications (i.e. stroke) or treatment (bleeds). This data sources were not updated.

L.3.14 Costs and resource use.

This analysis on the stroke prevention pathway only considered the costs which were associated with antithrombotic treatment, these included consultation costs for stroke risk assessment and review of therapy, cost of medications (and monitoring for anticoagulation), and costs associated to the adverse event profile of these drugs.

All costs were updated to reflect 2012 UK pounds. NHS reference costs [276] were used to find cost estimates for diagnostic, review and follow up consultation, anticoagulation services, and clinical events requiring hospitalisation. If the event we were costing was better defined by a previous year's HRG code, we inflated this cost to 2012 using the HCHS index. [248] Primary care consultation was estimated from the PSSRU. [248] Due to the publication of a detailed costing of stroke in the AF population [627], we used this study instead of NHS reference costs as it was more applicable to our population.

We parameterised the NHS reference costs from the interquartile range and the number of episodes to undertake the probabilistic sensitivity analysis. Where the interquartile range was not reported, we used a 10% standard error as default. A gamma distribution was applied except for pharmacological acquisition costs which were assumed to be fixed by dose and the drug tariff. These were left deterministic.

The unit cost of pharmaceutical stroke prevention treatments are presented in Table 156. Daily costs were applied for the duration of time the patient was on a particular treatment.

One approach to costing class comparisons is to weight the intervention costs according to estimated use, i.e. through using prescription data. Prescription data, however, is not condition specific and may be misrepresentative of the true weighted cost for intervention use by people with AF. This may be particularly true when considering the anticoagulation class use in people with AF but of a low risk of stroke, where warfarin is seen as the first line anticoagulant and use of new agents are indicated in existing NICE guidance only for people with certain risk factors in AF.

Further, the evidence collated to estimate effect generally specified a particular drug within the class. Aspirin was the only specified single antiplatelet strategy specified within the literature. Likewise a combination of clopidogrel and aspirin was the only dual antiplatelet strategy specified. Therefore the intervention costs of these strategies were based on these particular drugs.

The network meta-analysis undertaken to estimate effect size pooled evidence regarding warfarin and the new agents (such as apixaban) for class comparisons. However, direct evidence regarding a 'do nothing strategy' versus anticoagulation predated the new agents and mainly specified warfarin as the comparator. On balance, and given the focus of the analysis on the appropriate stroke prevention management strategy for people with AF at low risk of stroke (i.e. at or under the risk indicated by the risk factors where new agents are considered in related NICE guidance), the cost of warfarin as a proxy for this class was used to assist decision making. In recognition that warfarin (inclusive of monitoring) had the lowest daily intervention cost, two further analyses were undertaken to ensure conclusions would not change. These used the weighted cost based on primary care prescription data and the most expensive anticoagulant cost (see section L.3.17.3).

The developers felt it was important to highlight that additional costs may be incurred when taking warfarin if the patient was housebound. No specific data on this was found to incorporate into the model, and further we have not added additional costs for housebound patients requiring review. Through use of the reference costs, we assume these additional costs have been taken into account under the average anticoagulation service cost. The annual cost was estimated using NHS reference costs (code 324). [276]

We only considered the pathway costs of consultation, as part of stroke risk assessment. All contact with tertiary care was assumed to have the cost of a cardiologist follow up (see Table 157). These were applied as a one off cost each time the patient had contact with the healthcare services.

Clinical events which incurred a one off cost at the time of the event were transient ischemic attacks, other thromboembolic events, and major bleeding due to their assumed transient nature. These were estimated using NHS reference costs (see Table 158). The costing of haemorrhagic and ischaemic stroke, which have long term cost implications, is detailed in the below section.

Table 156: Unit cost of pharmaceutical stroke prevention

Drug	Dose	Pack size	Net price pack (£)	Price per tablet (£)	Daily dose	Price (£) per		Source: Drug tariff – August 2013 (except where specified)[692]
						day	year	
Anti-platelets			**0.83**	**0.03**		**0.03**	**11**	**Average of below**
Aspirin Dispersible tablets (mg) (Non-proprietary)	75	28	0.84	0.03	75	0.03	11	Part VIIIA - Basic Prices of Drugs Product List
Aspirin Tablets (mg) (Non-proprietary)	75	28	0.82	0.03	75	0.03	11	
Dual anti-platelets			**2.66**	**0.095**		**0.095**	**34.675**	**Clopidogrel and average cost of aspirin**
Clopidogrel	75	28	1.83	0.07	75	0.07	24	Part VIIIA - Basic Prices of Drugs
Warfarin Tablets (mg) (Non-proprietary)			**1.08**	**0.04**		**0.23**	**85**	**Average of below**
	0.5	28	1.48	0.05	6	0.63	232	BNF August 2013[489]

Drug	Dose	Pack size	Net price pack (£)	Price per tablet (£)	Daily dose	Price (£) per day	Price (£) per year	Source: Drug tariff – August 2013 (except where specified)[692]
	1	28	0.9	0.03	6	0.19	70	Part VIIIA products W
	3	28	0.94	0.03	6	0.07	25	
	5	28	0.99	0.04	6	0.04	15	
Warfarin Maintenance cost (on-going)						**0.70**	**255**	Anticoagulation services (NHS reference cost: code 324). 10% standard error applied in PSA, with gamma distribution To note cost used in rivaroxaban technology appraisal = £242 pa.[310]

Table 157: Cost of consultation for stroke risk assessment

	Code	Number of episodes	Cost per episode			Parameterisation of Gamma distribution			Source
			Mean	Min	Max	SE	Alpha	Beta	
Consultations									
GP appointment (a)			43.00			4.30	100.00	0.43	PSSRU [248]
Cardiologist follow up (b)	320		75.68	70.08	87.29	3.70	418.61	0.18	NHS ref. cost [276]

(a) Cost per surgery visit - 11.7 minutes (including direct care staff costs and including qualification costs; excluding travel costs)

(b) NHS Trusts Consultant Led: Follow up Attendance Non-Admitted Face to Face (TCLFUSFF) code 320.

Table 158: NHS reference costs of competing events associated with thromboembolic agents

	Code	Number of episodes	Cost per episode			Parameterisation of Gamma distribution			Source
			Mean	LQR	UQR	SE	Alpha	Beta	
Transient Ischaemic Attack		20,910	462	319	517	42.55	118.03	3.92	Average of below
	AA29A	19,102	467	321	523				NHS Ref Costs (a) [276]
	AA29B	1,808	413	294	445				
Thromboembolic complications (Using proxy		39,904	1,638			164	100	16	Average of below
	QZ17A	2,174	3,487						NHS Ref Costs
	QZ17B	24,623	1,862						

	Code	Number of	Cost per episode			Parameterisation of Gamma distribution			Source
of systemic embolism)	QZ17C	13,107	912						(b) [276]
Major bleeding (Using proxy of gastrointestinal bleeding)		83,831	1,065			107	100	11	Average of below
	FZ38D (c)	16,458	2,282						NHS Ref Costs (f) [276]
	FZ38E (d)	19,814	1,512						
	FZ38F (e)	47,559	458						

(a) Non elective short stay
(b) Taken from NHS Ref Costs Total HRGs, across all settings. A standard error of 10% assumed as max and min not reported
(c) Gastrointestinal Bleed with length of stay 2 days or more with Major CC
(d) Gastrointestinal Bleed with length of stay 2 days or more without Major CC
(e) Gastrointestinal Bleed with length of stay 1 day or less
(f) Taken from NHS Ref Costs Total HRGs, across all settings. A standard error of 10% assumed as quartile range not reported.

L.3.14.1 Cost of stroke

The costs are estimated from a well-constructed cost analysis of both haemorrhagic and ischaemic stroke in the UK AF population. [627] This was identified as the most applicable and high quality source for costs from the systematic economic search and the calculations are as used in the original MAPGuide model. A breakdown of how the costs were estimated is given in the following tables, whereby a cost for the acute care period of 90 days is estimated and averaged given the total number of people surviving the period as the denominator. The costs are also weighted by the probability of different severities of stroke. Long term care costs are incorporated into the on-going costs which are applied throughout the lifetime of a stroke survivor. The model uses a fixed cost per day for the first stroke, and then adjusts this for successive strokes using a table of stroke cost multipliers. It assumes constant risk that each stroke will be moderate or totally disabling, but level of disability is defined by most severe stroke experienced.

After inflation, the cost of the acute stage (90 days) of ischaemic stroke was estimated at £12,055 (SE = 1,236), and the acute stage (90 days) of haemorrhagic stroke was estimated at £11,876 (SE = 3,125), with both forms of stroke having an on-going daily cost of £23.40 (SE = 3.74)

Table 159: Summary of costs associated with stroke, Luengo-Fernandez et al, 2012[627]

Healthcare costs over acute period (90 days)		N	Mean	SD	SE
Ischaemic stroke		162	**10,844**	15,733	1,236
Haemorrhagic stroke		17	**10,683**	12,885	3,125
Unknown stroke type		12	4,206	5,650	1,631
Total		191	10,413		
Additional health care costs after acute period (per year)					
		N	Mean	95% CI	
No disability		66	382	-781	1,546
Moderate disability		58	825	-2,133	3,783
Severe disability		12	3,019	-8,841	14,880
Total		136	804	-832	2,440

Long term nursing and residential costs care costs (per year)					
		N	Mean	SD	SE
No disability		66	942	3,765	463
Moderate disability		58	10,646	19,068	2,504
Severe disability		12	21,335	22,463	6,485
Total		136	6,880	12,600	1,080
Estimated cost of long-term care by number of stroke (weighted by disability)					
	Level of disability				
	None	Moderate	Total	All strokes	SE
Total cost of care	£1,324	£11,471	£24,354	£ 7,684	3.74
Number of strokes	66	58	12	136	
% of 90 day survivors	49%	43%	9%	100%	
Increasing cost of each additional stroke				**Cost (pa)**	**Stroke cost multiplier**
First stroke	49%	43%	9%	**£ 7,683**	**1.00**
Second stroke	24%	60%	17%	£ 11,254	0.46
Third stroke	11%	64%	24%	£ 13,429	0.28
Fourth stroke	6%	64%	31%	£ 14,888	0.19
Fifth stroke	3%	60%	37%	£ 15,963	0.14

L.3.15 Utilities

A quality of life filter (see appendix search terms) was added to the health economic systematic searches undertaken for the systematic review for the guideline, and all entries were sifted for relevance. Utilities used in other economic models as well as quality of life estimates identified within the systematic reviews undertaken for the guideline were reviewed for applicability against the NICE reference case. No sources were found to be superior to those used in the original MAPGuide model, and as such data sources and the calculations were not updated.

To note that an age adjustment was applied to quality of life. This differs from the approach traditionally applied in a prevalent cohort model where patients enter the model at the same age and with a given utility, and no further adjustment of utility is made according to the patient's age. In a patient simulation model an incidence cohort is typically used, with patient's entering the model at different ages, in order to simulate the cohort. Therefore, utility was adjusted for age throughout the lifetimes of the individual patients

L.3.15.1 Baseline utilities

Baseline utility values were estimated using the EQ5D and from members of the UK public with no history of heart problems by 5-year age band were taken from the analysis of Health Survey for England data reported by Ara and Brazier. [46] This source had the advantage of adjusting by health condition. These estimates were applied to the patient according to their age as they travelled

through the model, to which the appropriate utility multiplier was applied to determine the quality of life of the patient given their clinical status and treatment option. In the analysis of the stroke prevention pathway, no change in quality of life was associated with treatment effect of AF control interventions; only quality of life associated with thromboembolic or bleeding events were considered.

Table 160. General population utilities by age (no other heart problems). (Ara and Brazier 2011, (Appendix. Table A4) [46] Utilities estimated using the EQ5D and time trade off method

Age group	Mean utility	95% CI		Distribution
<30	0.9389	0.935	0.942	Beta (SE = 0.0071, α = 1054.8, β = 68.64)
30 to ≤35	0.9148	0.907	0.922	Beta (SE = 0.0153, α = 303.4, β = 28.26)
35 to ≤40	0.9075	0.901	0.913	Beta (SE = 0.0122, α = 507.2, β = 51.69)
40 to ≤45	0.8855	0.876	0.894	Beta (SE = 0.0184, α = 265.2, β = 34.30)
45 to ≤50	0.8664	0.854	0.877	Beta (SE = 0.0235, α = 181.2, β = 27.94)
50 to ≤55	0.8376	0.828	0.847	Beta (SE = 0.0194, α = 302.3, β = 58.61)
55 to ≤60	0.8269	0.815	0.837	Beta (SE = 0.0224, α = 234.0, β = 48.99)
60 to ≤65	0.8189	0.805	0.832	Beta (SE = 0.0276, α = 159.2, β = 35.20)
65 to ≤70	0.8132	0.799	0.827	Beta (SE = 0.0286, α = 150.5, β = 34.57)
70 to ≤75	0.7892	0.766	0.802	Beta (SE = 0.0367, α = 96.5, β = 25.78)
75 to ≤80	0.7602	0.745	0.774	Beta (SE = 0.0296, α = 157.5, β = 49.68)
80 to ≤85	0.7070	0.684	0.729	Beta (SE = 0.0459, α = 68.8, β=28.49)
>85	0.6692	0.642	0.695	Beta (SE = 0.0541, α = 50.0, β = 24.71)

Utilities were adjusted for the patient's AF status using an international cohort study of patients with AF, the Realise AF study [831]. For simplicity, as it was not expected that the stroke prevention pathway would impact on AF status, we assume all patients in the model would have a quality of life similar to an AF patient with perfect AF control. The utility multiplier calculated was applied to the utility which would be expected for a healthy patient of the same age, an example is given below using a baseline utility for 65 to 70 year olds (as detailed in Table 160).

Table 161. Utility multipliers for AF health states, estimated from Realise AF data [831] Utilities estimated using the EQ5D, single index utility score.

AF status	Mean utility	Baseline	Disutility	Multiplier	Distribution
AF in sinus rhythm vs. no AF	0.75	0.8132*	0.0632	0.922	Beta (SE = 0.0053, α = 2374.8, β =

AF status	Mean utility	Baseline	Disutility	Multiplier	Distribution
					200.12)

L.3.15.2 Differential quality of life due to antithrombotic agent employed

The model assumes that transient ischaemic attacks and other thromboembolic events (systemic embolism) and bleeds are transient, which is consistent with the approach taken in other economic appraisals in this clinical topic area. (p81 ERG report [310])

No evidence for the quality of life on different antithrombotic agents was retrieved in the systematic review undertaken for the guideline. Therefore no differential utility was associated with taking different antithrombotic agents. Differences in quality of life resulting between the antithrombotic strategies were driven by the number of adverse events and the quality of life associated with them.

For each bleeding and thromboembolic event, utilities were estimated using a US panel of patients with a range of chronic conditions [841]. The limitation that these estimates are not directly applicable to the UK population was noted, however this data source was not updated as estimates were derived from the same population and offered consistency

Table 162: Utility associated with an adverse event, as measured by the EQ5D, time trade off method. Source: MEPS data - Sullivan et al (2005, 2005) [841]

Event	Mean utility	Baseline	Disutility	Multiplier	Distribution
Ischaemic stroke (permanent)	0.6715	0.8100	0.1385	0.829	Beta (SE = 0.0019, α = 32063.7, β = 6613.29)
Transient ischaemic attack (acute period only)	0.7068	0.8100	0.10322	0.873	Beta (SE = 0.0017, α = 33748.3, β = 4928.69)
Systemic embolism as proxy for thromboembolic complications (acute period only)	0.6901	0.8100	0.1199	0.852	Beta (SE = 0.0018, α = 32951.8, β = 203.48)
Haemorrhagic stroke (permanent)	0.6715	0.8100	0.1385	0.829	Beta (SE = 0.0019, α = 32063.7, β = 6613.29)
Major bleeding (acute period only)	0.6286	0.8100	0.1814	0.776	Beta (SE = 0.0021, α = 30015.3, β = 8661.74)

L.3.16 Treatment effect: Conclusions of the network meta-analysis for antithrombotic therapy.

To find the treatment effect of stroke preventive therapies we undertook a network meta-analysis using the studies retrieved by a systematic review for the antithrombotic chapter. Full details can be found in appendix M, including a summary of conclusions and the limitations of this analysis. The hazard ratios given below were used in the deterministic analysis, with the probabilistic analysis using direct outputs (CODA) from the winbugs model.

Table 163: Summary of Hazard ratios per outcome in comparison to control (do nothing strategy) As adverse events, HR below 1 indicates that the strategy is effective in avoiding the event.

Outcome	Strategy	Hazard ratio	Lower confidence interval	Upper confidence interval
All-cause mortality	AP	0.847	0.709	1.012
	DAP	0.825	0.661	1.037
	AC	0.769	0.641	0.926
Ischaemic stroke	AP	0.775	0.550	1.089
	DAP	0.585	0.377	0.940
	AC	0.311	0.217	0.445
Haemorrhagic stroke	AP	1.876	0.617	6.521
	DAP	2.104	0.533	9.593
	AC	3.438	1.122	12.5
Bleeding	AP	1.55	0.652	3.931
	DAP	2.883	0.728	12.566
	AC	2.721	1.214	6.623
Thromboembolic complications	AP	0.696	0.289	1.543
	DAP	0.834	0.271	2.714
	AC	0.305	0.122	0.733

L.3.17 Sensitivity Analysis on case fatality rates and relative effect of haemorrhagic stroke

The GDG felt that the base case analysis would give a conservative representation of anticoagulation, and for this reason asked for the following sensitivity analyses to be performed.

L.3.17.1 Sensitivity analysis on relative effect of anticoagulation on rates of bleeding and haemorrhagic stroke

Many on the data sources informing the NCGC NMA were considered to be of low applicability when considering the potential adverse effect of anticoagulation. It was felt that since the date of the trials, quality of anticoagulation control had improved and as a result the NMA may overestimate the rate of bleeding and haemorrhagic stroke. Removing the older trials from the NMA was not possible as there would not be sufficient data to inform the network. Therefore, the analyses was rerun using the adverse event rates of antiplatelets, which developers felt were more likely to be reflective of rates found with good anticoagulation control today.

L.3.17.2 Sensitivity analysis on case fatality of haemorrhagic stroke and major bleeding.

All data sources concurred that haemorrhagic stroke carried the highest 30 day case fatality rate (with point estimates ranging from 38% to 56%), followed by ischaemic stroke (13% to 15%) and major bleeding carried the lowest but most varied estimates (ranging from 2% to 12%). Given the high case fatality rates of haemorrhagic stroke, and uncertainty surrounding the relative impact of

antithrombotic therapy on this parameter, a sensitivity analysis on this aspect was warranted. We therefore tested case fatality parameters by applying the lowest estimates used a submission for a rivaroxaban technology appraisal. This was estimated using the manufacturer's own analysis using the findings of the ROCKET AF study. [778]

Table 164: Case fatality rates used in the 2011 Rivaroxaban technology appraisal submission, p161.[81]

Event	mean	LCI	UCI	SE	Beta
Stroke	13%	9%	16%	0.0161	371.76
ICH, inclusive of HS (p152)	39%	29%	49%	0.0497	58.11
Bleed	2%	1%	2%	0.0020	3793.44

L.3.17.3 Sensitivity analysis on cost of anticoagulation.

To test robustness of findings using an alternative cost for anticoagulation, two deterministic sensitivity analyses were conducted. The model was rerun using firstly an intervention cost which was weighted according to primary care use of different anticoagulant drugs. Secondly the model was rerun using the most expensive anticoagulant available at the time of writing (Table 165: Weighted cost of anticoagulation, based on primary care prescription data (October 2013{NHS Prescription Services, 2013 PCA2013 /id})

Drug	Items	%	Unit cost per day (including monitoring of warfarin)	Cost per day of anticoagulation (weighted average)
Warfarin	90990	96%	£ 0.93	£ 0.90
Rivaroxaban	1521	2%	£ 2.43	£ 0.04
Dabigatran	1700	2%	£ 2.20	£ 0.04
Apixaban	452	0%	£ 1.83	£ 0.01
Total	94663			£ 0.98

Table 166)

Table 165: Weighted cost of anticoagulation, based on primary care prescription data (October 2013{NHS Prescription Services, 2013 PCA2013 /id})

Drug	Items	%	Unit cost per day (including monitoring of warfarin)	Cost per day of anticoagulation (weighted average)
Warfarin	90990	96%	£ 0.93	£ 0.90
Rivaroxaban	1521	2%	£ 2.43	£ 0.04
Dabigatran	1700	2%	£ 2.20	£ 0.04
Apixaban	452	0%	£ 1.83	£ 0.01
Total	94663			£ 0.98

Table 166: Unit cost of pharmaceutical stroke prevention (new agents)

Drug	Dose	Pack	Net	Price	Daily	Price (£) per	Source: Drug

Apixaban (mg)			**49.79**	**1.10**		**1.83**	**601**	**Average of below**
		size	**price pack (£)**	**per tablet (£)**	**dose**	**day**	**year**	**tariff – August 2013 [692] unless otherwise indicated.**
Rivaroxaban (mg)			**51.2**	**1.80**		**2.43**	**888**	**Average of below**
	10	30	36	1.20	20	2.40	876	Part VIIIA products R
	15	28	58.8	2.10	20	2.80	1,022	
	20	28	58.8	2.10	20	2.10	767	
Dabigatran (mg)	**150**	**60**	**65.9**	**1.10**	**300**	**2.20**	**802**	Part VIIIA products D
	5	56	61.5	1.10	5	1.10	401	BNF, August 2013
	2.5	20	21.96	1.10	5	2.20	601	
	2.5	60	65.9	1.10	5	2.20	802	

L.3.18 Computations

L.3.18.1 Time dependency

The simulation model was constructed in simul8 with data read from excel .csv files. Time dependency was built into the model through update of a patient's age, which in turn acted as a respective risk factor for a number of events, including mortality. Baseline utility was also time dependent and was conditional on the number of years post entry to the model. Patients start in the model prior to diagnosis, and are subject to various events and build up "patient history" as they go through the model. Events are determined by firstly calculating the time to each event (taking treatment effect into account when appropriate). Given the estimated time of competing events, the event which comes first in the patient's expected history is chosen (i.e. the event which has the minimum difference between the expected time of the event and the time at which the events are calculated). Once the event occurs, the patient's risk and therefore time until the subsequent event may change accordingly. The final event is that of death whereby the patient leaves the model

L.3.18.2 Mapping functions

No quality of life mapping function was used in the model.

L.3.18.3 Preserving correlation

Labels for baseline risk factors were attached to a simulated patient according to that observed in the baseline patient level dataset, preserving possible correlation between baseline risk factors. To preserve correlation that may exist between relative risks calculated by the network meta-analysis for antithrombotic treatment effect, the simulation model was programmed to read from the same CODA line for each second order uncertainty run, as it did for any other input which was subject to probabilistic analysis.

L.3.18.4 Rates and probabilities

Data which was used to estimate time to event was manipulated in excel and expressed in instantaneous rates before import into the main simulation model, which was constructed in simul8. Where probabilities or incidence rates were reported in the literature, these were transformed to

instantaneous rates using the below formula before inputting into the simul8 model. The simul8 model's internal programming calculated the time to event firstly in years and then transformed the time period to days.

$Probability\ or\ cumulative\ incidence\ (P) = 1 - e^{-rt}$	Where r = selected rate t= length of time (months)
$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where P=probability of event over time t t=time over which probability occurs
$Time\ to\ event(t) in\ years = \frac{-\ln(1-P)}{r}$	Where P=probability of event over time t t=time over which probability occurs r = instantaneous rate
$Time\ to\ event(t) in\ days = \frac{-\ln(1-P)}{r * 365}$	

L.3.18.5 Calculating time to next event, determining the order of events and updating risks

Unlike a typical Markov model where time cycles of set duration are used, discrete event simulation uses estimated risk to calculate the time until the next event occurs. As risks are updated in accordance to the patient's risk factors or modified through treatment effect, the time to the next event is also updated. The model compares the calculated time each event is expected to occur, and the patient will experience whichever event will occur first. Once the event occurs, the expected time of the next competing events is calculated based on updated risks. The patient therefore moves individually at different time increments, rather than moving as a cohort in predefined time intervals.

The adjusted risk is modelled using an exponential survival function, which assumes the hazard remains constant over the discrete time period modelled. However, over the period of the lifetime of the patient the hazard does not remain constant; rather it is modelled dynamically as risks are updated after each discrete time period.

The time of the event is also determined by a random number which is assigned to the patient on model entry, representing a propensity for a particular type of event due to unknown factors. Further random numbers are assigned to ensure that events which are not independent and relationships between certain types of events are modelled appropriately. For example, to ensure that the predicted time to a thromboembolic event does not increase following a bleed. To avoid this, the random numbers used to determine the time to the next events (e.g. U_bleed, U_diabetes) are only re-sampled when that specific type of event has occurred.

L.3.18.6 Relative risks and hazard ratios

In some instances it may be appropriate to transform the hazard ratio into a relative risk and vice versa. The hazard ratio may be calculated from the relative risk and the probability of an event in the control group provided that the probability and relative risk used refer to the same time point. The control group probability was that calculated to be the baseline risk for an individual patient.

The internal visual logic code of the model was checked to ensure treatment effect (expressed by hazard ratios) from the updated NMA would be correctly applied in the model. The adjusted risk calculation in the model transforms the baseline probabilities expressed as incidence rates per year

into an instantaneous rate prior to modification by treatment effect. As such a hazard ratio is the correct measure of relative treatment effect to apply.

$\mathrm{RR} = \frac{1 - \exp(\mathrm{HR} * \ln(1 - \mathrm{CGP}))}{CGP}$	Where: RR = relative risk CGP = control group probability HR = hazard ratio
$\mathrm{HR} = \frac{\ln(-RR * CGP + 1)}{ln(1 - CGP)}$	

L.3.18.7 Calculating costs and QALYs

The patient travels through the model in discrete time period. The QALY and cost associated with each time period is determined by the labels that the patient has in accordance to the events they have experienced. For example, once a patient has an ischaemic or haemorrhagic stroke which has lasting implications, each discrete time period thereafter will be associated with lower quality of life and a cost. Dependent on the type of event, a short term multiplier may be applied, followed by the long term multiplier in the case of utilities. In the case of costs, a one off cost may be applied for a given procedure or event, and dependent on the event, an on-going daily cost may be added for subsequent time periods. The patient accrues costs and QALYs which are tallied and collated to give a total cost and QALY gain for the whole population.

Costs and QALYs are updated on the patient's individual tally each time the patient passes through a section of the pathway where costs are applied, or at a minimum of every 90 days. The costs and QALYs calculated for each discrete time period are discounted prior to being added to the tally. That is to say the model employs a continuous time approach to the time of the model entry for each patient.

L.3.18.8 Discounting

Both costs and QALYs accrued in the model were discounted to reflect time preference. The discounting function was applied each time costs and QALYs were updated in the simulated lifetime of the patient. For example, if a year had passed between one event occurring and the next, the cost and QALY accrued for that one time period would be calculated and the discount function applied would be appropriate to the time which had elapsed since the patient had entered the model and when the update had occurred. Further if a patient experienced a one off cost at a particular time in the model, due to an event or clinical intervention, this cost was discounted using the formula given.

The total discounted QALYs were the sum of the discounted QALYs of each discrete time period. The total discounted costs were the sum of discounted costs accrued over each discrete time period, as well as the sum of discounted one off costs associated with events or interventions.

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: r = discount rate per annum n = time (years), for a daily rate this is 1/365
$\mathrm{X} = \frac{DailyIncrement * (1-r)^{-n}}{r}$	Where: r = daily discount rate n = time elapsed in model (days) X = discounted cost or QALY per day within discrete time period

L.3.19 Model validation

The updated model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The MAPGuide AF model was subject to robust validation, and in particular consisted of:

- Double checking of data entry, synthesis and interface with the model by different authors
- Double coding of the more complicated formulae in different software
- Clinical and systematic validation of patient diaries (including case checking of 500 patients)
- Verification of coding was commissioned to an expert external modeller, inclusive of:
  - Checking that the SIMUL8 logic correctly reflected the AF pathway;
  - Checking the coding of costs, QALYs and discounting calculations; and
  - Checking the model logic via the patient diaries.

Further, comprehensive review of excel and simul8 code and methods was undertaken during the update.

The updated model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs and systematic checking of the calculations that determined the updated parameter values.

L.3.20 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs/QALYs(X) = total costs/QALYs for option X	• Cost-effective if: ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of two other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Benefit(X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$ *Where: Costs/QALYs(X) = total costs/QALYs for option X; λ = threshold*	• Cost-effective if: highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

L.3.21 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several strategies which we are comparing (i.e. offering anticoagulation for given risk factor combinations), we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

However, we also take into account the uncertainty of our parameter inputs, and therefore consider the probability that a strategy will rank optimal. For positive outcomes (i.e. net benefit) results are presented according to which strategies ranked highest; conversely for negative outcomes (i.e. stroke) results are presented according to which strategies ranked lowest. If two or more strategies have the same probability of ranking optimal, then there is a high possibility either option could be cost effective.

L.4 Results

L.4.1.1 Base case: probabilistic results

Probabilistic base case analysis shows greatest net benefit is most likely (given the uncertainty in our parameter inputs) if no drug is given until CHA_2DS_2-VASc = 2, and only to give anticoagulation at lowest risk of bleeding by HAS-BLED score. The results show that the greatest QALY gained and the lowest cost, as well as highest net monetary benefit was achieved in strategies where anticoagulation is restricted to patients with lower risks of bleeding. This was true when outcomes were discounted, not discounted and when the threshold increased to £30,000.

The probability that other stroke thresholds could be optimal, given you would only give anticoagulation at the lowest risk of bleeding at these low stroke risk thresholds, are as follows:

- CHA_2DS_2-VASc = 1 = 12% probability
- $CHADS_2$ = 1 = 12% probability
- CHA_2DS_2-VASc = 2 = 16% probability

Due to the number of strategies compared even a percentage increase in the likelihood of optimality is important, so from these findings CHA_2DS_2-VASc 2 seems to be the most likely to be optimal

The below tables (Table 167, Table 168 and Table 169) show the probabilistic results for discounted costs and QALYs, and resulting net benefit for the strategies examined (i.e. using a stroke risk threshold to switch to anticoagulation at or below that which is currently recommended by the NICE technology appraisals). The probabilistic results show that there may be uncertainty regarding which

stroke risk scoring system is optimal to initiate the decision. The probabilistic analysis also shows that it is highly unlikely that antiplatelets or dual antiplatelets will be preferable to a do nothing approach prior to initiating warfarin. It also shows that not considering bleeding risk when stroke risk is low, and offering anticoagulation to patients with a HAS-BLED score of 1 or greater is extremely unlikely to be cost effective.

Table 170 gives a breakdown of the outcomes recorded from the model for these blanket strategies. The number of clinical events per 1000 patients is given in the figures following. It is notable that the pharmacological strategies have wide confidence intervals in respect to the expected average number of bleeds per patient, which also impacts on the expected QALY gain. In comparison to a do nothing strategy, the potential number of bleeds indicated by the upper confidence interval is great.

Table 167: Probabilistic results by comparator and decision rule: Discounted QALY per patient

Strategy, where by anticoagulation is given at or above the stroke risk specified, otherwise alternative listed below is offered			Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….								Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….						
		Do not give AC	0	1	2	3	4	5	N/A	Do not give AC	0	1	2	3	4	5	N/A
Do nothing	NA	5.244	5.240	5.207	5.152	5.084	5.034	5.027	5.149	5%	6%	1%	0%	0%	2%	1%	1%
	CHA_2DS_2-VASc 1		5.244	5.213	5.156	5.090	5.039	5.033	5.140		4%	1%	0%	1%	1%	3%	1%
	$CHADS_2$ 1		5.244	5.207	5.168	5.099	5.053	5.027	5.149		5%	1%	0%	0%	2%	1%	1%
	CHA_2DS_2-VASc 2		5.245	5.231	5.185	5.124	5.073	5.066	5.162		6%	3%	1%	2%	3%	4%	2%
AP	N/A	5.033	5.033	5.024	5.025	5.031	5.014	5.013	5.149	0%	1%	1%	0%	1%	1%	1%	1%
	CHA_2DS_2-VASc 1		5.031	5.027	5.029	5.029	5.018	5.017	5.045		0%	0%	0%	1%	1%	2%	0%
	$CHADS_2$ 1		5.030	5.028	5.029	5.029	5.023	5.022	5.049		0%	0%	1%	1%	2%	2%	1%
	CHA_2DS_2-VASc 2		5.033	5.035	5.043	5.042	5.034	5.030	5.056		1%	0%	1%	1%	2%	2%	2%
DAP	N/A	4.801	4.803	4.822	4.893	4.972	5.007	5.012	5.149	1%	1%	1%	0%	1%	1%	3%	1%
	CHA_2DS_2-VASc 1		4.802	4.820	4.891	4.970	5.006	5.009	4.964		1%	0%	0%	0%	2%	3%	0%
	$CHADS_2$ 1		4.801	4.960	4.885	4.960	4.993	5.003	4.957		0%	0%	0%	0%	1%	1%	0%
	CHA_2DS_2-VASc 2		4.803	4.815	4.881	4.959	4.995	4.998	4.954		0%	1%	1%	0%	1%	2%	1%

Abbreviations: IS = ischaemic bleed, TIA = transient ischaemic attack, TE = Thromboembolic event, HS = Haemorrhagic stroke, Bleed = Major Bleed, LCI = Lower confidence interval, UCI = upper confidence interval, SE = Standard Error, N/A = not applicable (i.e. do not take risk score into account when deciding to anticoagulate)

Table 168: Probabilistic results by comparator and decision rule: Discounted cost (£) per patient

Strategy, where by anticoagulation is given at or above the stroke risk specified, otherwise alternative listed below is offered			Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….								Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….						
		Do not give AC	0	1	2	3	4	5	N/A	Do not give AC	0	1	2	3	4	5	N/A
Do nothing	N/A	19319	19429	20480	23543	26400	27631	27893	25591	7%	8%	0%	0%	0%	0%	0%	7%
	CHA_2DS_2-VASc 1		19393	20362	23425	26340	27569	27710	25778		10%	1%	0%	0%	0%	0%	0%
	$CHADS_2$ 1		19324	20480	23130	26015	27239	27893	25591		11%	0%	0%	0%	0%	0%	0%
	CHA_2DS_2-VASc 2		19320	20096	22968	25858	27066	27260	25445		9%	2%	0%	0%	0%	0%	0%
AP	N/A	20521	20698	21383	23781	26305	27376	27592	25591	5%	2%	1%	0%	0%	0%	0%	5%
	CHA_2DS_2-VASc 1		20598	21317	23654	26195	27334	27551	25726		5%	1%	0%	0%	0%	0%	0%
	$CHADS_2$ 1		20513	21157	25854	25854	27066	27282	25567		4%	1%	0%	0%	0%	0%	0%
	CHA_2DS_2-VASc 2		20577	21074	23349	25768	26977	27178	25421		5%	2%	0%	0%	0%	0%	0%
DAP	N/A	20573	20639	21355	23539	26160	27716	28024	25591	5%	6%	1%	0%	0%	0%	0%	5%
	CHA_2DS_2-VASc 1		20660	21253	23460	26146	27640	27909	25593		3%	1%	0%	0%	0%	0%	0%
	$CHADS_2$ 1		20580	25913	23251	25913	27437	27810	25463		4%	0%	0%	0%	0%	0%	0%
	CHA_2DS_2-VASc 2		20617	21029	23220	25776	27343	27630	25347		4%	1%	0%	0%	0%	0%	0%

Abbreviations: IS = ischaemic bleed, TIA = transient ischaemic attack, TE = Thromboembolic event, HS = Haemorrhagic stroke, Bleed = Major Bleed, LCI = Lower confidence interval, UCI = upper confidence interval, SE = Standard Error, N/A = not applicable (i.e. do not take risk score into account when deciding to anticoagulate)

Table 169: Probabilistic results by comparator and decision rule: Discounted net monetary benefit (£20,000) per patient

Strategy, where by anticoagulation is given at or above the stroke risk specified, otherwise alternative listed below is offered			Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….								Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….						
		Do not give AC	0	1	2	3	4	5	N/A	Do not give AC	0	1	2	3	4	5	N/A
Do nothing	N/A	85561	85371	83657	79503	75289	73046	72651	77386	9%	10%	1%	0%	0%	0%	0%	0%
	CHA_2DS_2-VASc 1		85488	83891	79703	75462	73204	72942	77015		12%	1%	0%	0%	0%	0%	0%
	$CHADS_2$ 1		85556	83657	80231	75965	73815	72651	77386		12%	1%	0%	0%	1%	0%	0%
	CHA_2DS_2-VASc 2		85584	84532	80724	76618	74394	74065	77803		16%	2%	1%	0%	0%	0%	0%
AP	N/A	80133	79961	79093	76724	74308	72913	72674	77386	2%	3%	1%	0%	0%	0%	0%	0%
	CHA_2DS_2-VASc 1		80031	79217	76929	74378	73029	72795	75172		3%	0%	0%	0%	0%	0%	0%
	$CHADS_2$ 1		80092	79404	74732	74732	73387	73159	75410		4%	1%	0%	0%	0%	0%	0%
	CHA_2DS_2-VASc 2		80090	79617	77515	75070	73705	73413	75692		3%	2%	0%	0%	0%	0%	0%
DAP	N/A	75448	75425	75082	74328	73272	72426	72207	77386	3%	3%	0%	0%	0%	0%	0%	0%
	CHA_2DS_2-VASc 1		75386	75141	74355	73245	72475	72264	73683		2%	0%	0%	0%	0%	0%	0%
	$CHADS_2$ 1		75449	73280	74440	73280	72425	72244	73674		3%	0%	0%	0%	0%	0%	0%
	CHA_2DS_2-VASc 2		75438	75264	74410	73409	72564	72325	73731		2%	1%	0%	0%	0%	0%	0%

Abbreviations: IS = ischaemic bleed, TIA = transient ischaemic attack, TE = Thromboembolic event, HS = Haemorrhagic stroke, Bleed = Major Bleed, LCI = Lower confidence interval, UCI = upper confidence interval, SE = Standard Error, N/A = not applicable (i.e. do not take risk score into account when deciding to anticoagulate)

Table 170: Breakdown of the outcomes recorded from the model for blanket strategies without use of a risk scoring tool.

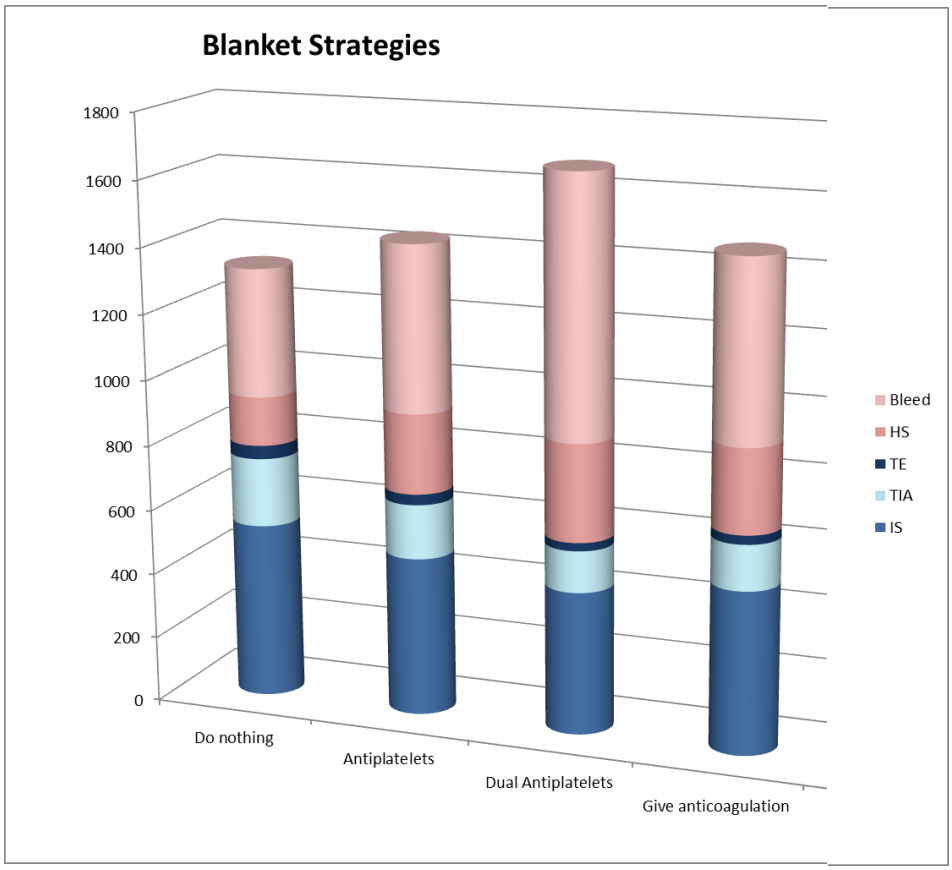
	Do nothing				Antiplatelets				Dual Antiplatelets				Give anticoagulation			
	mean	LCI	UCI	SE	mean	LCI	UCI	SE	mean	LCI	UCI	SE	mean	LCI	UCI	SE
Cost effectiveness outcomes																
Cost (discounted)	£19,319	£15,339	£24,334	£2,355	£20,521	£15,649	£26,170	£2,673	£20,573	£15,670	£26,695	£2,928	£25,591	£20,035	£31,879	£3,012
QALY (discounted)	5.244	5.042	5.476	0.111	5.033	4.244	5.464	0.305	4.801	3.451	5.467	0.538	5.149	4.709	5.563	0.214
NB (discounted)	£85,561	£80,097	£90,779	£2,786	£80,133	£63,936	£91,367	£6,982	£75,448	£46,439	£90,676	£11,475	£77,386	£66,733	£87,128	£5,075
Cost	£28,722	£22,440	£36,435	£3,713	£29,902	£22,918	£38,284	£3,927	£29,493	£22,232	£38,229	£4,246	£37,133	£28,797	£46,457	£4,495
QALY	6.78	6.45	7.13	0.17	6.47	5.27	7.15	0.47	6.12	4.09	7.15	0.81	6.66	6.02	7.30	0.32
Clinical Benefit Outcomes																
QALY	6.780	6.448	7.132	0.172	6.466	5.265	7.150	0.470	6.118	4.095	7.155	0.813	6.658	6.015	7.298	0.322
QALY (discounted)	5.244	5.042	5.476	0.111	5.033	4.244	5.464	0.305	4.801	3.451	5.467	0.538	5.149	4.709	5.563	0.214
Life years	10.192	9.664	10.809	0.285	9.745	7.934	10.738	0.704	9.219	6.169	10.824	1.234	10.156	9.156	11.220	0.503
TE events	0.788	0.696	0.885	0.049	0.686	0.526	0.836	0.078	0.590	0.357	0.788	0.111	0.665	0.568	0.754	0.047
Bleeding events	0.539	0.475	0.603	0.035	0.750	0.293	1.802	0.371	1.086	0.233	2.643	0.665	0.804	0.483	1.139	0.171
Relative Risk against a do nothing strategy																
QALY	1.000	1.000	1.000		0.954	0.817	1.003		0.902	0.635	1.003		0.982	0.933	1.023	
QALY (discounted)	1.000	1.000	1.000		0.960	0.842	0.998		0.916	0.684	0.998		0.982	0.934	1.016	
Life years	1.000	1.000	1.000		0.956	0.821	0.993		0.905	0.638	1.001		0.997	0.947	1.038	
TE events	1.000	1.000	1.000		0.870	0.756	0.945		0.748	0.513	0.890		0.843	0.815	0.852	
Bleeding events	1.000	1.000	1.000		1.390	0.618	2.988		2.015	0.491	4.383		1.490	1.017	1.888	
Cost Outcomes																
Cost	£28,722	£22,44	£36,435	£3,71	£29,90	£22,91	£38,284	£3,927	£29,49	£22,23	£38,229	£4,246	£37,13	£28,79	£46,457	£4,49

		0		3	2	8			3	2			3	7		5
Cost (discounted)	£19,319	£15,339	£24,334	£2,355	£20,521	£15,649	£26,170	£2,673	£20,573	£15,670	£26,695	£2,928	£25,591	£20,035	£31,879	£3,012
Medication cost (£)	£0	£0	£0	£0	£104	£85	£115	£8	£316	£210	£372	£43	£2,116	£1,279	£2,990	£435
Other costs (undiscounted)	£106,882	£98,635	£115,065	£4,243	£99,422	£76,531	£115,628	£10,054	£92,868	£53,298	£115,254	£16,241	£96,027	£81,527	£109,819	£7,128
Other costs (undiscounted)	£106,882	£98,635	£115,065	£4,243	£99,422	£76,531	£115,628	£10,054	£92,868	£53,298	£115,254	£16,241	£96,027	£81,527	£109,819	£7,128
Relative Risk against a do nothing strategy																
Cost	1.000	1.000	1.000		1.041	1.021	1.051		1.027	0.991	1.049		1.293	1.283	1.275	
Cost (discounted)	1.000	1.000	1.000		1.062	1.020	1.075		1.065	1.022	1.097		1.325	1.306	1.310	
Medication cost (£)																
Other costs (undiscounted)	1.000	1.000	1.000		0.930	0.776	1.005		0.869	0.540	1.002		0.898	0.827	0.954	
Other costs (undiscounted)	1.000	1.000	1.000		0.930	0.776	1.005		0.869	0.540	1.002		0.898	0.827	0.954	
Clinical Event Outcomes																
IS	537	462	604	37	486	384	583	53	438	270	564	76	498	418	577	40
TIA	210	176	243	17	167	117	226	29	127	57	200	34	139	109	176	17
TE	41	27	56	7	33	19	50	8	25	11	43	8	27	17	39	6
HS	149	120	178	15	243	103	462	91	297	99	645	141	256	165	342	46
Bleed	390	343	442	28	506	143	1416	306	789	103	2031	553	547	276	833	146
Relative Risk against a do nothing strategy																
IS	1.000	1.000	1.000		0.906	0.831	0.965		0.815	0.584	0.933		0.927	0.905	0.955	
TIA	1.000	1.000	1.000		0.796	0.663	0.928		0.605	0.325	0.823		0.664	0.618	0.724	
TE	1.000	1.000	1.000		0.790	0.704	0.884		0.604	0.407	0.768		0.665	0.630	0.696	

HS	1.000	1.000	1.000		1.632	0.862	2.593		1.991	0.829	3.624		1.719	1.374	1.919	
Bleed	1.000	1.000	1.000		1.298	0.416	3.206		2.024	0.301	4.599		1.403	0.805	1.887	

Abbreviations: IS = ischaemic bleed, TIA = transient ischaemic attack, TE = Thromboembolic event, HS = Haemorrhagic stroke, Bleed = Major Bleed, LCI = Lower confidence interval, UCI = upper confidence interval, SE = Standard Error

Figure 195: Number of each clinical event (measured per 1000 patients per event) for strategies where risk scoring was not considered.



Abbreviations: IS = ischaemic bleed, TIA = transient ischaemic attack, TE = Thromboembolic event, HS = Haemorrhagic stroke, Bleed = Major Bleed

The above figure shows how the number of thromboembolic events (in blue) is reduced with both dual antiplatelets and anticoagulation in comparison to a do nothing strategy or when single antiplatelets are offered. However, the overall number of clinical events is increased if dual antiplatelets or anticoagulation is offered due to the heightened chance of adverse bleeding events.

L.4.2 Breakdown of results for the strategy with the highest likelihood of highest net benefit.

In comparison to the above blanket strategies, the following tables give results for a strategy of giving anticoagulation at the lowest risk of bleeding and at a CHA_2DS_2-VASc score of `2 or above following a precursor of "do nothing", antiplatelets or dual antiplatelets. Note how restricting the use of anticoagulation to the lowest risk groups of bleeding reduces the uncertainty that adverse bleeding events and high cost will occur. This can be seen by comparing the confidence intervals of the strategies which include risk scoring to the blanket strategies previously reported.

Table 171: Probabilistic results by outcome: strategy of giving anticoagulation at the lowest risk of bleeding and at a CHA_2DS_2-VASc score of `2 following a precursor of "do nothing", antiplatelets or dual antiplatelets

	Do nothing				Antiplatelets				Dual Antiplatelets				Give anticoagulation			
	mean	LCI	UCI	SE	mean	LCI	UCI	SE	mean	LCI	UCI	SE	mean	LCI	UCI	SE
Cost effectiveness outcomes																
Cost (discounted)	£19,319	£15,339	£24,334	£2,355	£20,521	£15,649	£26,170	£2,673	£20,573	£15,670	£26,695	£2,928	£25,591	£20,035	£31,879	£3,012
QALY (discounted)	5.244	5.042	5.476	0.111	5.033	4.244	5.464	0.305	4.801	3.451	5.467	0.538	5.149	4.709	5.563	0.214
NB (discounted)	£85,561	£80,097	£90,779	£2,786	£80,133	£63,936	£91,367	£6,982	£75,448	£46,439	£90,676	£11,475	£77,386	£66,733	£87,128	£5,075
Cost	£28,722	£22,440	£36,435	£3,713	£29,902	£22,918	£38,284	£3,927	£29,493	£22,232	£38,229	£4,246	£37,133	£28,797	£46,457	£4,495
QALY	6.78	6.45	7.13	0.17	6.47	5.27	7.15	0.47	6.12	4.09	7.15	0.81	6.66	6.02	7.30	0.32
Clinical Benefit Outcomes																
QALY	6.780	6.448	7.132	0.172	6.466	5.265	7.150	0.470	6.118	4.095	7.155	0.813	6.658	6.015	7.298	0.322
QALY (discounted)	5.244	5.042	5.476	0.111	5.033	4.244	5.464	0.305	4.801	3.451	5.467	0.538	5.149	4.709	5.563	0.214
Life years	10.192	9.664	10.809	0.285	9.745	7.934	10.738	0.704	9.219	6.169	10.824	1.234	10.156	9.156	11.220	0.503
TE events	0.788	0.696	0.885	0.049	0.686	0.526	0.836	0.078	0.590	0.357	0.788	0.111	0.665	0.568	0.754	0.047
Bleeding events	0.539	0.475	0.603	0.035	0.750	0.293	1.802	0.371	1.086	0.233	2.643	0.665	0.804	0.483	1.139	0.171
Relative Risk against a do nothing strategy																
QALY	1.000	1.000	1.000		0.954	0.817	1.003		0.902	0.635	1.003		0.982	0.933	1.023	
QALY (discounted)	1.000	1.000	1.000		0.960	0.842	0.998		0.916	0.684	0.998		0.982	0.934	1.016	
Life years	1.000	1.000	1.000		0.956	0.821	0.993		0.905	0.638	1.001		0.997	0.947	1.038	
TE events	1.000	1.000	1.000		0.870	0.756	0.945		0.748	0.513	0.890		0.843	0.815	0.852	
Bleeding events	1.000	1.000	1.000		1.390	0.618	2.988		2.015	0.491	4.383		1.490	1.017	1.888	
Cost Outcomes																
Cost	£28,722	£22,440	£36,435	£3,713	£29,902	£22,918	£38,284	£3,927	£29,493	£22,232	£38,229	£4,246	£37,133	£28,797	£46,457	£4,495
Cost (discounted)	£19,319	£15,339	£24,334	£2,355	£20,521	£15,649	£26,170	£2,673	£20,573	£15,670	£26,695	£2,928	£25,591	£20,035	£31,879	£3,012
Medication cost (£)	£0	£0	£0	£0	£104	£85	£115	£8	£316	£210	£372	£43	£2,116	£1,279	£2,990	£435

Other costs (undiscounted)	£106,882	£98,635	£115,065	£4,243	£99,422	£76,531	£115,628	£10,054	£92,868	£53,298	£115,254	£16,241	£96,027	£81,527	£109,819	£7,128
Other costs (undiscounted)	£106,882	£98,635	£115,065	£4,243	£99,422	£76,531	£115,628	£10,054	£92,868	£53,298	£115,254	£16,241	£96,027	£81,527	£109,819	£7,128
Relative Risk against a do nothing strategy																
Cost	1.000	1.000	1.000		1.041	1.021	1.051		1.027	0.991	1.049		1.293	1.283	1.275	
Cost (discounted)	1.000	1.000	1.000		1.062	1.020	1.075		1.065	1.022	1.097		1.325	1.306	1.310	
Medication cost (£)																
Other costs (undiscounted)	1.000	1.000	1.000		0.930	0.776	1.005		0.869	0.540	1.002		0.898	0.827	0.954	
Other costs (undiscounted)	1.000	1.000	1.000		0.930	0.776	1.005		0.869	0.540	1.002		0.898	0.827	0.954	
Clinical Event Outcomes																
IS	537	462	604	37	486	384	583	53	438	270	564	76	498	418	577	40
TIA	210	176	243	17	167	117	226	29	127	57	200	34	139	109	176	17
TE	41	27	56	7	33	19	50	8	25	11	43	8	27	17	39	6
HS	149	120	178	15	243	103	462	91	297	99	645	141	256	165	342	46
Bleed	390	343	442	28	506	143	1416	306	789	103	2031	553	547	276	833	146
Relative Risk against a do nothing strategy																
IS	1.000	1.000	1.000		0.906	0.831	0.965		0.815	0.584	0.933		0.927	0.905	0.955	
TIA	1.000	1.000	1.000		0.796	0.663	0.928		0.605	0.325	0.823		0.664	0.618	0.724	
TE	1.000	1.000	1.000		0.790	0.704	0.884		0.604	0.407	0.768		0.665	0.630	0.696	
HS	1.000	1.000	1.000		1.632	0.862	2.593		1.991	0.829	3.624		1.719	1.374	1.919	
Bleed	1.000	1.000	1.000		1.298	0.416	3.206		2.024	0.301	4.599		1.403	0.805	1.887	

Abbreviations: IS = ischaemic bleed, TIA = transient ischaemic attack, TE = Thromboembolic event, HS = Haemorrhagic stroke, Bleed = Major Bleed, LCI = Lower confidence interval, UCI = upper confidence interval, SE = Standard Error

L.4.3 Deterministic analyses

The results of the deterministic analyses mirrored those of the probabilistic and found that a do nothing approach was optimal to offering a single antiplatelet or dual antiplatelets when anticoagulation was not indicated due to a low risk of stroke or high risk of bleed. However, there was variation in the conclusions drawn to the optimal decision rule dependent on the adverse event rate of anticoagulation and the case fatality rate associated with those adverse events.

In the base case, overall a do nothing approach was found marginally optimal in comparison to other strategies. A reduction in case fatality of bleeding events did not change this finding. However, if the adverse event rate of anticoagulation is reduced, giving anticoagulation to patients with a CHA_2DS_2-VASc score = 2 could be found cost effective if patients are also at the lowest bleeding risk score. Changing the cost of anticoagulant to the most expensive therapy or using a weighted average did not change the ranking of the optimal threshold to that found in the base case.

Table 172: Expected QALY (discounted) per patient for deterministic analyses.

Strategy (NA= do not take risk into account)			Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….						
		Do not give AC	0	1	2	3	4	5	NA
Base case									
Give anticoagulation if at, or above, the stroke risk score of…	NA	5.323	5.291	5.291	5.114	4.969	4.847	4.819	5.066
	$CHADS_2$ = 1	5.323	5.307	5.258	5.161	4.990	4.840	4.850	5.066
	CHA_2DS_2-VASc = 1	5.323	5.310	5.227	5.114	4.984	4.874	4.835	5.076
	CHA_2DS_2-VASc = 2	5.323	5.296	5.304	5.172	5.019	4.911	4.917	5.109
Sensitivity analysis whereby anticoagulation assumes the same bleeding adverse event rate found for antiplatelets									
Give anticoagulation if at, or above, the stroke risk score of…	NA	5.323	5.315	5.292	5.308	5.303	5.335	5.283	5.318
	$CHADS_2$ = 1	5.323	5.291	5.324	5.302	5.309	5.305	5.308	5.305
	CHA_2DS_2-VASc = 1	5.323	5.325	5.318	5.317	5.331	5.306	5.314	5.312
	CHA_2DS_2-VASc = 2	5.323	5.325	5.316	5.319	5.340	5.329	5.315	5.328
Sensitivity analysis whereby case fatality rates mirror those used by rivaroxaban submission.									
Give anticoagulation if at, or above, the stroke risk score of…	NA	5.428	5.447	5.415	5.359	5.267	5.225	5.182	5.188
	$CHADS_2$ = 1	5.428	5.421	5.440	5.383	5.277	5.179	5.198	5.337
	CHA_2DS_2-VASc = 1	5.428	5.419	5.428	5.361	5.262	5.183	5.182	5.348
	CHA_2DS_2-VASc = 2	5.428	5.442	5.452	5.416	5.321	5.211	5.224	5.358

QALY gain for sensitivity analyses whereby cost of anticoagulation is altered remains the same as the base case.

Table 173: Expected cost (discounted) (£) per patient for deterministic analyses.

Strategy (NA= do not take risk into account)			Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….						
		Do not give AC	0	1	2	3	4	5	NA
Base case									
Give anticoagulation if at, or above, the stroke risk score of…	NA	18457	18440	20200	22129	25747	26207	26033	23536
	$CHADS_2$ = 1	18457	18342	18902	21415	24011	25086	25503	23536
	CHA_2DS_2-VASc = 1	18457	18290	19187	22189	25365	26135	25922	24273
	CHA_2DS_2-VASc = 2	18457	18116	19727	21797	24646	25244	25441	24125
Sensitivity analysis whereby anticoagulation assumes the same bleeding adverse event rate found for antiplatelets									
Give anticoagulation if at, or above, the stroke risk score of…	NA	18457	18578	19177	21358	24011	25724	25777	25419
	$CHADS_2$ = 1	18457	18067	18973	20975	23370	24980	25257	23424
	CHA_2DS_2-VASc = 1	18457	18457	19054	21339	24002	25729	25639	24037
	CHA_2DS_2-VASc = 2	18457	18175	18563	21253	23214	24754	25286	23388
Sensitivity analysis whereby case fatality rates mirror those used by rivaroxaban submission.									
Give anticoagulation if at, or above, the stroke risk score of…	NA	28876	29398	31765	36206	40869	45872	44300	45207
	$CHADS_2$ = 1	28876	29180	31233	34619	41095	43422	44074	38415
	CHA_2DS_2-VASc = 1	28876	28699	31251	35811	41267	44326	44726	39476
	CHA_2DS_2-VASc = 2	28876	29551	30578	35283	40925	43725	45463	38123
Sensitivity analysis whereby weighted anticoagulation cost is used									
Give anticoagulation if at, or above, the stroke risk	NA	18457	18446	20223	22194	25854	26334	26163	26785
	$CHADS_2$ = 1		18343	18916	21468	24106	25200	25621	23612
	CHA_2DS_2-VASc = 1		18293	19207	22249	25468	26258	26048	24355

Strategy (NA= do not take risk			Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….						
score of…	CHA_2DS_2-VASc = 2		18117	19739	21846	24737	25355	25555	24199
Sensitivity analysis whereby cost of most expensive anticoagulant is used.									
Give anticoagulation if at, or above, the stroke risk score of…	NA	18457	18602	20897	24027	28875	29938	29838	30496
	$CHADS_2$ = 1		18355	19309	22987	26796	28446	28973	23536
	CHA_2DS_2-VASc = 1		18367	19768	23968	28381	29757	29613	24273
	CHA_2DS_2-VASc = 2		18132	20071	23249	27320	28506	28808	24125

Table 174: Expected net monetary benefit (discounted) (£20,000) per patient for deterministic analyses.

Strategy (NA= do not take risk into account)			Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….						
		Do not give AC	0	1	2	3	4	5	NA
Base case									
Give anticoagulation if at, or above, the stroke risk score of…	NA	88001	87389	85620	80155	73629	70739	70337	77775
	$CHADS_2$ = 1		87801	86258	81811	75791	71710	71497	77775
	CHA_2DS_2-VASc = 1		87904	85347	80092	74306	71351	70781	77246
	CHA_2DS_2-VASc = 2		87802	86350	81646	75737	72985	72907	78062
Sensitivity analysis whereby anticoagulation assumes the same bleeding adverse event rate found for antiplatelets									
Give anticoagulation if at, or above,	NA	88001	87717	86657	84797	82045	80967	79877	80941
	$CHADS_2$ = 1		87750	87516	85070	82802	81124	80898	82685
	CHA_2DS_2-VASc = 1		88051	87302	85000	82628	80392	80639	82202

Strategy (NA= do not take risk			**Give anticoagulation if at, or under, bleeding risk specified by HAS-BLED score of….**						
the stroke risk score of…	CHA_2DS_2-VASc = 2		88318	87766	85128	83591	81836	81020	83170
Sensitivity analysis whereby case fatality rates mirror those used by rivaroxaban submission.									
Give anticoagulation if at, or above, the stroke risk score of…	NA	89358	89370	87137	82771	77510	73455	73500	72967
	$CHADS_2$ = 1		89063	88114	84474	77694	74032	73905	80484
	CHA_2DS_2-VASc = 1		89322	87817	83253	77195	73580	72975	80032
	CHA_2DS_2-VASc = 2		89277	88795	84688	78974	74549	73864	80976
Sensitivity analysis whereby weighted anticoagulation cost is used									
Give anticoagulation if at, or above, the stroke risk score of…	NA	88001	87383	85597	80090	73522	70612	70208	70089
	$CHADS_2$ = 1		87801	86244	81757	75696	71596	71379	77699
	CHA_2DS_2-VASc = 1		87901	85327	80031	74204	71227	70655	77164
	CHA_2DS_2-VASc = 2		87802	86339	81596	75646	72874	72792	77988
Sensitivity analysis whereby cost of most expensive anticoagulant is used.									
Give anticoagulation if at, or above, the stroke risk score of…	NA	88001	87226	84923	78257	70501	67008	66533	66378
	$CHADS_2$ = 1		87788	85850	80238	73006	68350	68028	77775
	CHA_2DS_2-VASc = 1		87827	84766	78312	71291	67729	67090	77246
	CHA_2DS_2-VASc = 2		87787	86006	80193	73063	69722	69540	78062

The below figures illustrate the basecase results are for various outcomes when anticoagulation is offered (as opposed to "do nothing") at or below the HAS-BLED risk threshold and above the stroke risk thresholds of interest. The figures show how the risk of bleeding impacts on the discounted QALYs, costs and net benefit which are achievable if anticoagulation is offered at all but the lowest stroke risk scores. The figures suggest that as more people with higher bleeding risks are given anticoagulation, the lower cost effectiveness of the stoke prevention becomes.

Figure 196: Discounted QALY per patient by bleeding and stroke risk threshold

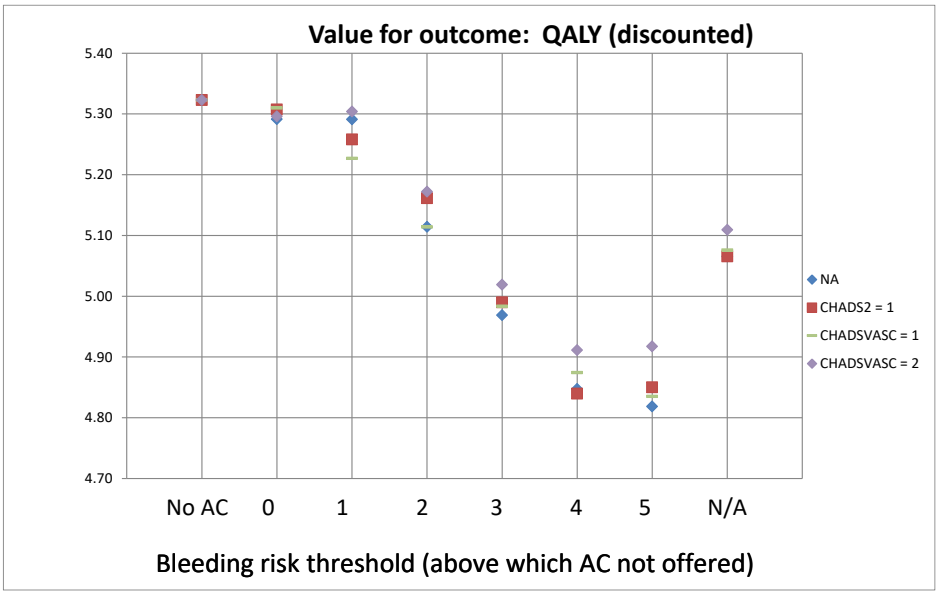


Figure 197: Discounted cost (£) per patient by bleeding and stroke risk threshold

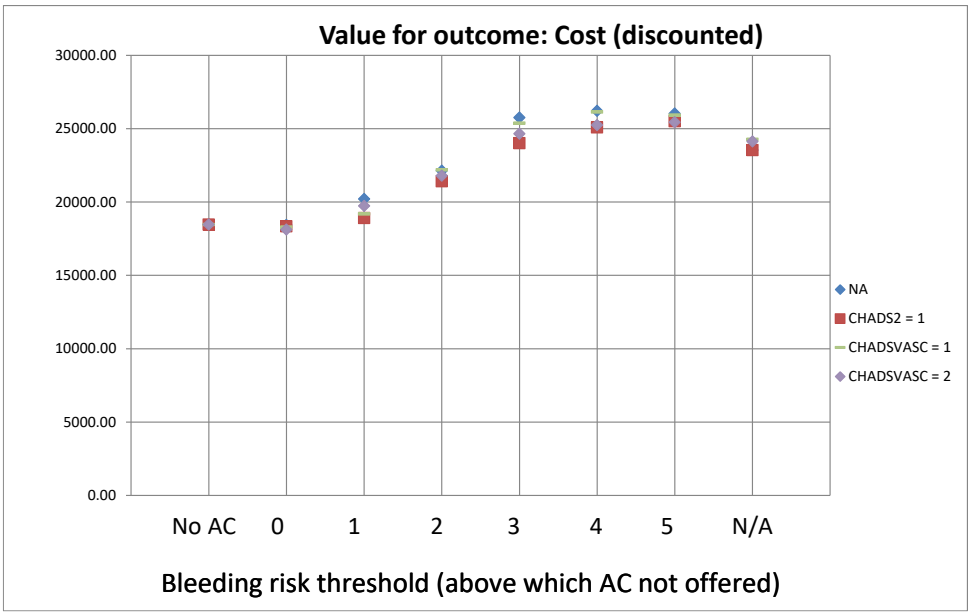
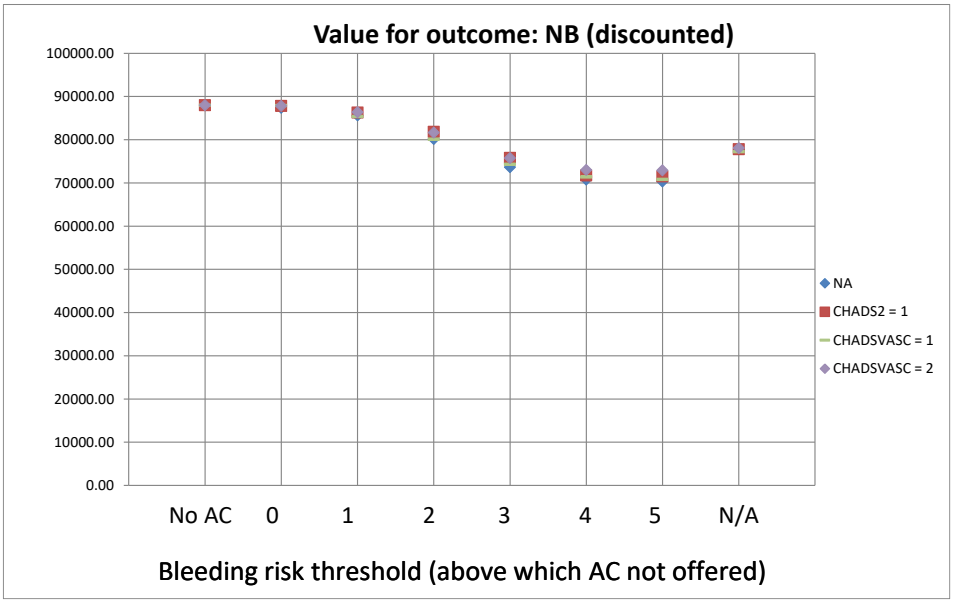


Figure 198: Discounted net monetary benefit (£20,000) per patient by bleeding and stroke risk threshold



Abbreviations: AC = anticoagulation. NA = not applicable, denoting that risk score was not used to determine treatment (i.e. when neither bleeding nor stroke risk score was taken into account, only anticoagulation is offered as a blanket strategy.

The below figures depict the number of clinical events (per 1000 patients) which result from each of the strategies shown above (i.e. to give anticoagulation at or below a bleeding risk threshold if also at or above a given stroke risk threshold of interest). The results show that thromboembolic events decrease the higher the number of patients eligible for anticoagulation (i.e. a decision rule to offer patients anticoagulation at a higher bleeding risk threshold). Results also show an increase in the number of bleeding events as more patient at high risk of bleeding are eligible for anticoagulation. To note, the degree of reduction in the number of ischaemic strokes is less than the degree of increase in haemorrhagic stroke (per additional bleeding risk group anticoagulation). This could be expected given the low absolute risk of ischaemic stroke in the population starting anticoagulation.

Figure 199: Number of ischaemic strokes per 1000 patient by bleeding and stroke risk threshold

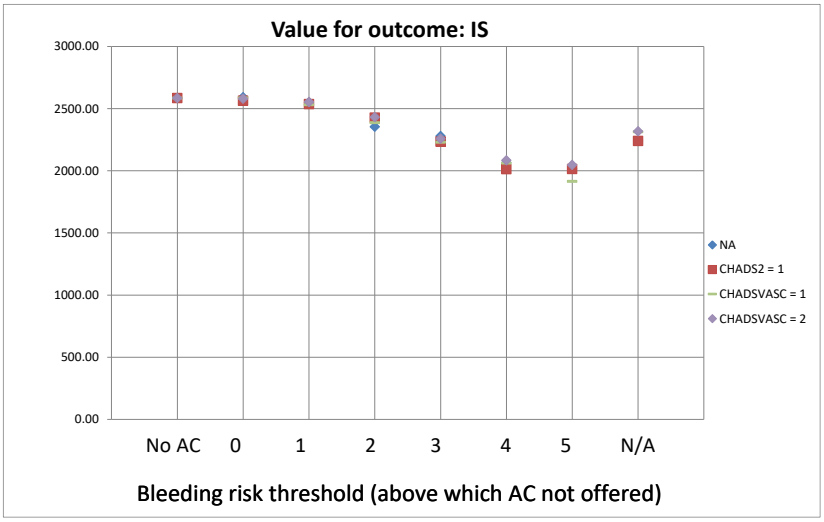


Figure 200: Number of transient ischaemic attacks per 1000 patient by bleeding and stroke risk threshold

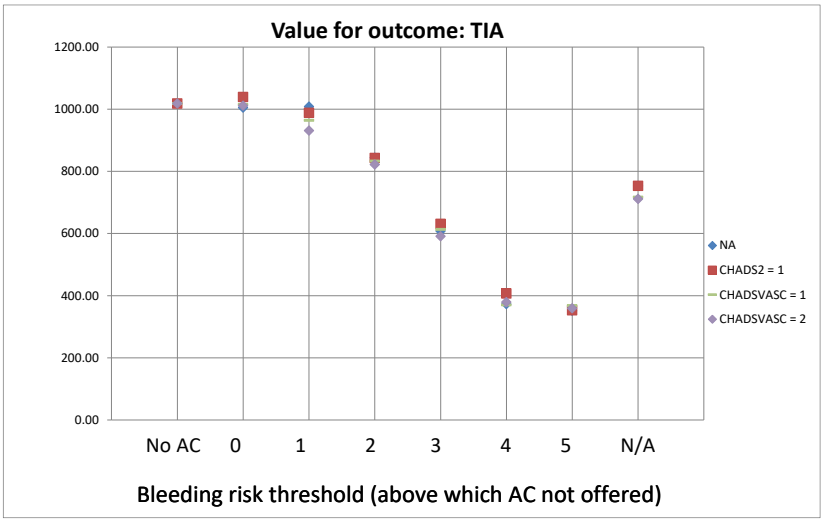


Figure 201: Number of thromboembolic complications per 1000 patient by bleeding and stroke risk threshold

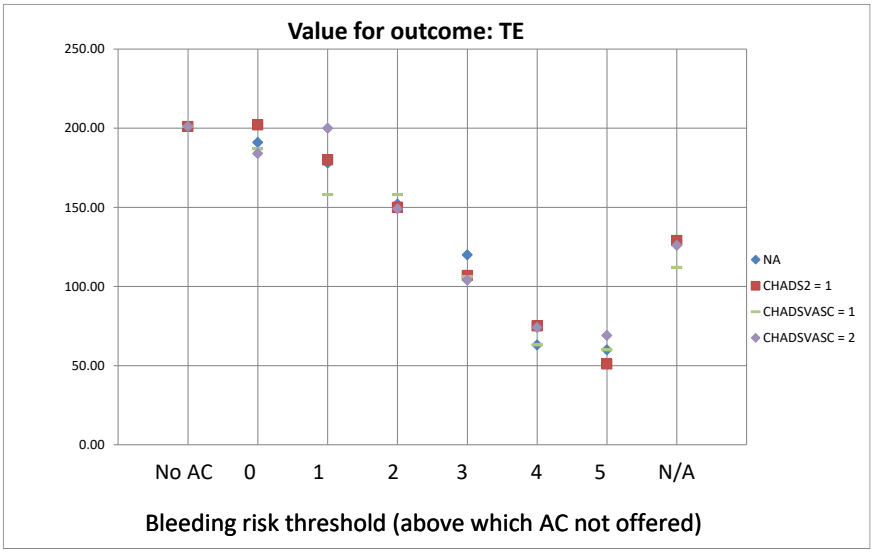


Figure 202: Number of haemorrhagic strokes per 1000 patient by bleeding and stroke risk threshold

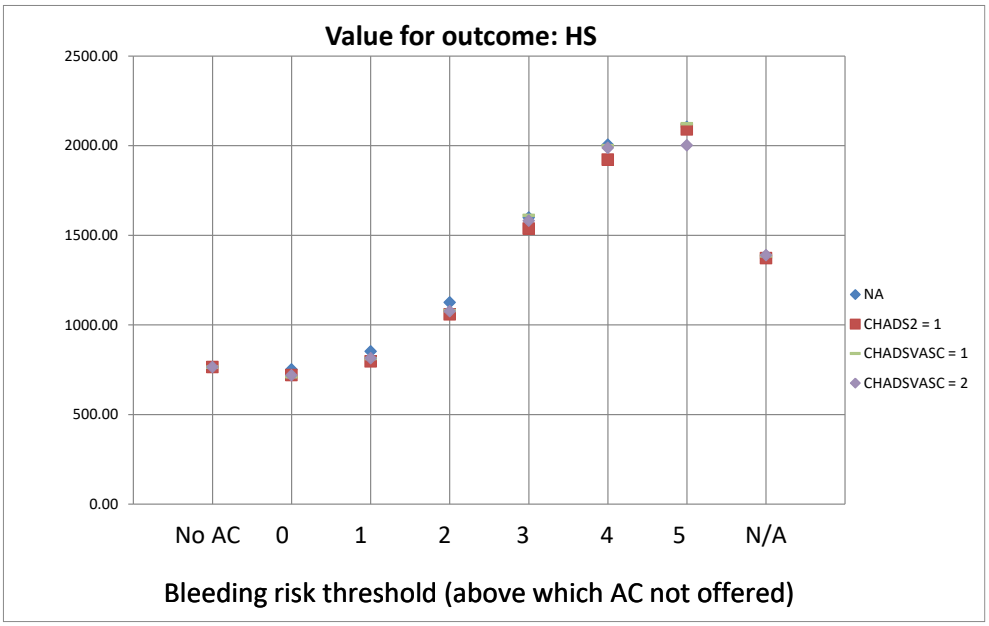
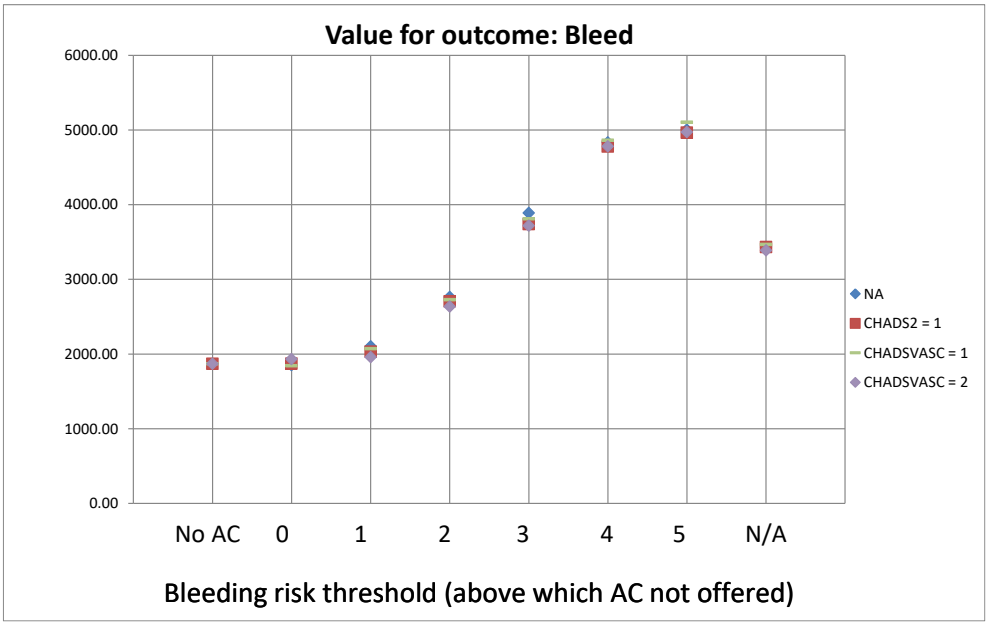


Figure 203: Number of major bleeds per 1000 patient by bleeding and stroke risk threshold



Abbreviations: AC = anticoagulation. NA = not applicable, denoting that risk score was not used to determine treatment (i.e. when neither bleeding nor stroke risk score was taken into account, only anticoagulation is offered as a blanket strategy.

L.5 Discussion

L.5.1 Limitations and interpretation

We present an analysis of the competing risks associated with stroke preventive therapies in a population of UK people with AF using a dynamic discrete event simulation model with kind permission from the Brunel University model developers.

The analysis, reflective of the clinical evidence, provides a clear conclusion that a do nothing approach is preferred over an offer of single or dual antiplatelet when anticoagulation is not indicated. The analysis also shows that the absolute differences in expected QALY gain or cost is small when comparing stroke risk scoring systems to determine treatment at a low stroke risk threshold. A more striking indication is the importance that baseline bleeding risk may have on optimal treatment, as the risk of adverse events increases as more patients with a higher bleeding risk score have anticoagulation.

Thromboembolic and bleeding risk shares many of the same risk factors, for example age and hypertension feature in both bleeding and stroke risk scoring systems. The model captures this relationship as both scores are calculated for each patient given their individual history and risk factors.

Where the decision rule specifies a patient must be under a given bleeding risk threshold, the patient will not have anticoagulation unless they are under this threshold irrespective of their stroke risk. The differences in outcomes that result from the decision rule specifying a higher bleeding risk threshold are due to patients reaching a higher bleeding and stroke risk profile, and being permitted by the decision rule to have anticoagulation at these higher risks.

Conversely the incremental difference found from strategies comparing increasing stroke risk thresholds where the specified bleeding risk threshold is low taper to zero. That is to say the cost effectiveness of a decision rule where 'anticoagulation is given above a $CHADS_2$ score of 3 but below a HAS-BLED score of 1' will be the same as that where 'anticoagulation is given above a $CHADS_2$ score of 7 but below a HAS-BLED score of 1' because the decision to anticoagulate is determined by the (low) bleeding risk score. Some strategies compared do not allow the decision to be constrained by bleeding risk (for example those presented where bleeding risk was not applicable), however none of these strategies were found more cost effective than strategies where bleeding risk was taken into account.

To our knowledge the MAP Guide model is the only model that addresses competing risks of bleeding and thromboembolic events to determine the cost effectiveness of common risk scoring tools for clinical decision making for people with AF in the UK. The model is firmly rooted within UK epidemiology through use of a UK patient level dataset to determine baseline risks to which treatment effect is applied. It uses UK national list prices and conforms to the NICE reference case with utility estimates derived through use of the EQ5D, with baseline utilities valued by the UK population. It therefore is directly applicable.

However, a model is only as good as the data which informs it. Despite a systematic review and network meta-analysis to inform treatment effect, and ratification by clinical experts that the data is what we believe to be the best available, there are a number of limitations to note. In particular, estimates regarding the relative adverse effect of anticoagulation may be limited.

Firstly, the trials which informed treatment effect predate current standards of anticoagulation control, and indeed methods of measuring time in therapeutic range and consensus regarding the optimum control has since changed.

Secondly, there was heterogeneity in the populations informing the treatment effect. Not all studies differentiated between primary and secondary prevention, meaning that data was pooled and differential effect dependent on how many clinical events the patient had was not modelled. If data becomes available this should be easily incorporated due to the model's ability to take into account a patient's history. Differential risk dependent on a patient's previous clinical history therefore was only incorporated through updating the patient's baseline risk.

Further heterogeneity arose due to the intra-class comparisons whereby specific drugs are categorised and compared as a class of drugs. Numerous studies have evaluated warfarin against a

newer agent (for example dabigatran, rivaroxaban, apixaban) to demonstrate a differential in cost effectiveness of these drugs. This would suggest that an analysis which compared anticoagulants individually would further understanding of the most optimal strategy to take within the anticoagulant class. The potential heterogeneity in effect, as well as differential intervention cost, within this class would be further explored. This approach would also remove the need for a proxy or weighted cost, with both approaches having their respective limitations.

As our analysis supports the notion that a do nothing approach is preferable with the lowest stroke risk groups, careful consideration would be needed in how to compare the new agents against a do nothing approach within this risk group (our review did not find any direct evidence comparing a new agent to a do nothing approach).

Thirdly, many of our data sources came from different time points or geographical/cultural locations. Different classification and changes in operational definition of clinical events may impact on the accuracy of estimates informing the model. Indeed estimates arising from national registries (such as the Swedish dataset of the SAF study [352] may not be necessarily aligned with the usual ISTH-criteria that is standardised in RCTs. Further, studies report data where the cause of stroke (haemorrhage or ischaemia) remains unknown, or will differ in their classification of given events such as intracranial haemorrhage (categorising it under haemorrhagic stroke or as a major bleed). Where studies do not clearly report or disaggregate events within classifications, there is a potential to under or overestimate both thromboembolic and bleeding events.

Finally, whilst the data sources informing the model are to our knowledge the best available, case fatality data came from cohort studies which were from non UK contexts. Whilst it was attempted to adjust the case fatality estimates for ischaemic stroke by treatment type and quality of control, data was not available to do so for other clinical events. Clinical members of the group strongly suspect, for example, that severity of haemorrhagic stroke would be associated with the level of anticoagulation control.

A model is simply a framework to synthesize data to enable coherent conclusions and inevitably some assumptions are required in the absence of “perfect” data. However a strength of modelling is that alternative data sources and scenarios can be explored.

The base case used the cost of warfarin as a proxy for the class of anticoagulants for reasons outlined in the methods section. Pooling the effectiveness in the network meta-analysis means that we assume equal effectiveness of the class. Together, these aspects of the model may lead us to the incorrect conclusions regarding the optimality of the new agents in comparison to warfarin, and indeed the appropriate threshold of using new anticoagulants (given they are more expensive than warfarin). Patients who can’t take warfarin, the cost-effective threshold for taking one of the NOACs may well be different than from your pooled analysis using warfarin prices. To test the potential impact, we reran the analysis using the cost of most expensive new agent at the time of writing. The findings did not change the conclusions of the analysis. As such it would seem conclusions regarding the appropriate threshold to commence anticoagulation is more sensitive to the trade-off between bleeding and thromboembolic events than the potential increase in the intervention costs of the anticoagulant therapies. Without evaluation of the individual drugs at each risk threshold in comparison to a do nothing approach, however, there is still uncertainty regarding the optimal strategy. In the sensitivity analysis where the event of bleeding for anticoagulation assumes the same probability of occurrence as that observed for antiplatelets was requested due to the concern that the trial data informing whilst on the likelihood of bleeding events was outdated, and with modern control and monitoring the risk of bleeding events whilst on anticoagulation is much lower.

Indeed changing the likelihood of bleeding when taking anticoagulation did change the pattern of results regarding QALYs and life years. In our base case analysis, in general, the clinical benefit reduced with greater numbers of patients taking anticoagulation at the lower stroke risk scores. With greater clinical benefit being realised at the margin of where the stroke risk equalised the bleeding

risk. In the sensitivity analysis, greater clinical benefit emerged with greater use of anticoagulation, for example offering anticoagulation at higher bleeding risk thresholds despite low stroke risk.

As expected, the consideration of bleeding risk has less importance in predicting the optimal strategies if we have reduced the bleeding risk of anticoagulation. However, if using a low stroke risk threshold to consider anticoagulation, due to low absolute stroke risk, bleeding risk is still influential. Once costs are considered, even the change in the findings for QALYs and life years was not sufficient in magnitude to change the end conclusions regarding net benefit. The optimal strategy, given consideration of cost effectiveness remained the same, with greatest net benefit achieved by giving anticoagulation only to the lowest bleeding risk groups.

Stroke is a devastating event, and patients are prepared to accept a number of major bleeds, just to prevent one stroke. [32,281,356] Reflective of these views and the differences in quality of life experienced by patients post clinical events, the model assumes both haemorrhagic and ischemic stroke cause a lower quality of life which is applied throughout the patient's lifetime, whereas a major bleed is seen as a transient event and a lower quality of life is only applied for the acute period of the major bleed. Therefore in the model, several major bleeds would need to occur before the reduction in the QALY was equalised to the reduction found due to a stroke. However, both haemorrhagic and ischaemic stroke carry severe consequences. This, coupled with the potential for high rates of major bleeding suggests that the tipping point in favour of anticoagulation may only be low in regards to stroke risk when the patient has a low risk of bleeding.

As stroke preventive therapies develop, and the threshold to treat on account of stroke risk, the severity of side effects should not be ignored. Whilst limitations in the data sources informing the model means there is insufficient certainty to determine the precise combination of stroke and bleeding risk score within a decision rule, it none the less gives supportive evidence that a person's risk of bleeding should be considered and reduced as far as possible to optimise the effectiveness and cost effectiveness of the strategy.

L.5.2 Generalisability to other populations/settings

This evaluation suggests that the most cost effective decision rule to apply in a population is in part dependent on the population's propensity to bleeding events, as well as the relative risk of the treatment to aggravate such events. Further, the cost effectiveness of common treatments for thromboembolic and bleeding events will also impact on cost effectiveness of given preventative strategies. This analysis is highly applicable to the UK context, and may be applicable to other contexts which share a similar standard for quality of anticoagulation control, epidemiology, and downstream care arrangements for people who have thromboembolic or bleeding events. Caution should be taken if applying the rule to other populations. In particular, the severity and cost of stroke for people with AF may be higher than in other populations.

L.5.3 Conclusion

This analysis suggests that anticoagulation can be considered after a do nothing approach at CHA_2DS_2-VASc = 2. Once the patient achieves a HAS-BLED score of 1 or more, the risks of bleeding should be taken into account.

L.5.4 Implications for future research

This analysis demonstrates that evaluation of optimal decision rules to initiate, or indeed stop, anticoagulation is dependent on having accurate knowledge of its adverse events, and in particular accurate estimates of bleeding events and case fatality thereafter. Further, there are currently few studies which validate commonly used bleeding and stroke risk scoring systems, meaning the

uncertainty in the scoring system's predictive power cannot be easily evaluated or incorporated into economic models.

Studies frequently report a cohort's stroke risk profile, but infrequently provide description or estimation of the cohort's bleeding risk profile . To assist future evaluations, studies should give consideration to the cohort's risk profile, not only in relation to their stroke risk, but also to their bleeding risk. Further, as risk is dynamic and will change across the patient's lifetime, it may be appropriate to monitor this throughout the study duration and not only give detail of the starting characteristics of the population. For example, an individual who enters the study at low risk may not have the same risk profile when an adverse event occurs. Without documenting the patients risk profile at the time of the event, it is not clear whether the individual's baseline risk could be accountable for such occurrence. Clear reporting and categorisation of adverse events in studies regarding anticoagulation could also reduce error in estimation of the likelihood of adverse events.

Appendix M: Network Meta-analysis (NMA) of Antithrombotic therapy

M.1 Introduction and rationale to NMA

The results of conventional meta-analyses of direct evidence alone make it difficult to determine which intervention is the most effective treatment. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not fully inform the choice between all the possible treatments, and having a series of discrete pair wise comparisons can be disjointed and difficult to interpret
- There are overlapping comparisons that could potentially give inconsistent estimates of effect.

This is particularly problematic for probabilistic analysis. To overcome these problems, a Bayesian network meta-analysis (NMA) [157]was conducted in WinBUGS.

Conventional meta-analysis assumes that, for a fixed-effect analysis, the relative effect of one treatment compared to another is the same across an entire set of trials. In a random-effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same relative effect across all trials of intervention A compared to intervention B as it does across trials of intervention A versus intervention C, and so on. Thus, in a random-effects network meta-analysis, the assumption is that intervention A has the same effect distribution across all trials of A versus B, A versus C and so on.

The aim of the NMA was to calculate treatment-specific probabilities of clinical outcomes following each of the different treatments. These outcomes were those selected by the GDG to be important to decision making and are as follows:

- All-cause mortality
- Ischaemic stroke
- Haemorrhagic stroke
- Bleeding
- Thromboembolic complications

M.2 Methods of Statistical analysis

When modelling the clinical outcomes of interest, it is important to consider the different follow up times of the various trials, as longer follow up is likely to result in more reported events. To account for this, an underlying Poisson process with a constant event rate was assumed for each trial arm, and a complementary log-log (cloglog) link function used to model the event rate. The following logic was used to calculate hazards and hazard ratios:

Let BH and HR denote the baseline hazard (from the surgery arms) and treatment-specific hazard ratio for clinical recurrence; let θ represent the cloglog of the probability of recurrence,p, and let $time$ represent the duration of follow up. Then:

$$\theta = Ln\,(time) + Ln\,(HR) + Ln\,(BH)$$

And:

$$p = 1 - \exp\left[-\exp\theta\right]$$

Anticoagulation therapy was chosen as the baseline comparator as it featured in the most trials.

The baseline hazard was estimated on the clog-log scale through a meta-analysis of the anticoagulation arms of the included trials. The resulting predictive distribution was inputted to the NMA for adjustment by the treatment specific hazard ratios to calculate the probability of the clinical events for each treatment. The codes for both the baseline and relative effects models were adapted from that provided on the NICE decision support unit website, and run in WinBUGS 14.

The baseline and relative effects models were run for 50,000 iterations with burn in periods of 50,000. Vague uninformative priors were combined with the data-driven likelihood functions to produce posterior probability estimates. Convergence was assessed by examining the history and kernel density plots.

M.3 Inputs and Results of NMA by outcome

The number of studies identified by systematic review for each comparison in the network is given in diagrammatic form for each outcome, with the detailed inputs tabulated directly afterwards. The numbers of events and numbers in each arm are those extracted as part of the pairwise meta-analysis given in the systematic review, with the exception of Peterson (1989)[732].

Peterson (1989)[732] is a three arm trial which includes all of our comparators. Three arm trials are internally consistent, and as such there is no potential for inconsistency within our network, only for between-trial heterogeneity. This is discussed further by Dias and colleagues in technical support document 4 [284], in which the authors explain that 'loops of evidence that are potentially inconsistent can only arise from structures in which there are three distinct trials or sets of trials'.

The meta-analyses of pairwise comparisons that incorporated the findings from Peterson (1989)[732] used further information and analysis given by the Cochrane review [20], meaning the sample in each arm differed according to the subgroup analysis. In order to use the strength of a three arm trial for a mixed population in regards to prior risk factors (i.e. similar to that in the model) in the NMA, we used reported numbers in the original paper.

Further details of all of the studies used in the NMA can be found in the associated chapter and appendices (see Chapter 9). To note, studies identified by the systematic review but had zero events in both arms were excluded for the purposes of the NMA.

We give detailed results for the NMA by outcome, with a summary results and conclusions at the end of this appendix. The mean estimates obtained for each outcome were used to parameterise treatment effects in the decision model (see appendix L); point estimates were calculated by the exponentiation the mean log of the hazard ratio which ensured coherent effect estimates, with probabilistic sensitivity values sampled from the WinBUGs CODA output.

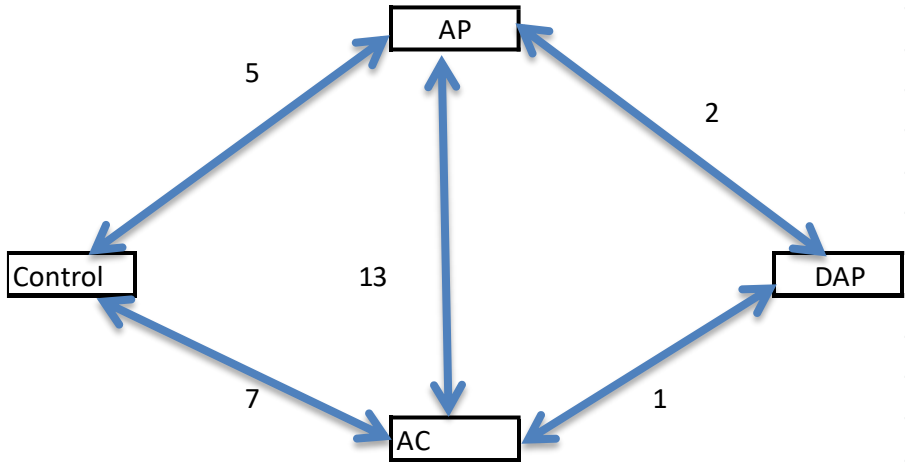
M.3.1 NMA for All-Cause Mortality

M.3.1.1 Networks and Data

There were 26 studies identified for this outcome, one of which was a three arm trial[732]. Two further studies compared three of the comparators, but due to the grouping in the randomisation process,

we could only treat these studies as containing separate two way comparisons.[838,882] The included studies are detailed in the below figure and table.

Figure 204: Network of trials compared in the network meta-analysis for all-cause mortality.



Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

Table 175: Study details and inputs into the NMA for the outcome of all-cause mortality.

Study	Comparison (intervention. vs comparator)	Time of follow up (years)	R1	R2	R3	N1	N2	N3
Singer 1990 (BAATAF) – primary prevention subgroup[816]	AC (1) vs. control(2)	2.20	11	26	NA	212	208	NA
Connolly 1991 (CAFA study)[226]	AC (1) vs control (2)	1.27	10	8	NA	187	191	NA
SAPFI 1991[838]	AC (1) vs control(2)	1.30	6	8	NA	193	194	NA
Ezekowitz 1992 (SPINAF) - primary prevention[318]	AC (1) vs control(2)	3.00	22	29	NA	281	290	NA
Van Latum 1993 (EAFT)- secondary prevention[882]	AC (1) vs control(2)	2.30	41	44	NA	225	214	NA
Ezekowitz 1992 (SPINAF) - secondary prevention[318]	AC (1) vs control(2)	3.00	5	4	NA	21	25	NA
Petersen 1989[732]	AC (1) vs control (2) vs AP (3)	1.20	20	28	23	335	336	336
Gullov 1998 (AFASAK II)[402]	AC (1) vs AP (3)	1.00	17	14	NA	170	169	NA

Vemmos 2006 (Athens)[887]	AC (1) vs AP (3)	0.30	1	1	NA	17	16	NA
Chen 2012[189]	AC (1) vs AP (3)	2.00	5	6	NA	239	201	NA
Chen 2013[194]	AC (1) vs AP (3)	4.25	10	10	NA	650	361	NA
Diener 2012 (AVERROES) [288]	AC (1) vs AP (3)	1.10	89	113	NA	2417	2415	NA
Mant 2007[638]	AC (1) vs AP (3)	2.70	107	108	NA	488	485	NA
Perez Gomez 2004 (NASPEAF[731])	AC (1) vs AP (3)	2.76	20	15	NA	237	242	NA
Hellemons 1999 (PATIF)[430]	AC (1) vs AP (3)	2.70	12	17	NA	131	141	NA
Rash 2007[767]	AC (1) vs AP (3)	1.00	1	2	NA	36	39	NA
Halperin 1994 (Spaf IIa)[414]	AC (1) vs AP (3)	3.10	36	41	NA	358	357	NA
Halperin 1994 (Spaf IIb)[414]	AC (1) vs AP (3)	3.10	26	24	NA	197	188	NA
Diener 2012 – subgroup - AVERROES[288]	AC (1) vs AP (3)	1.10	22	27	NA	390	374	NA
Active 2006 [13]	AC (1) vs DAP (4)	1.28	158	159	NA	3371	3335	NA
Posada 1999 (LASAF)[757]	control (2) vs AP (3)	1.50	9	10	NA	91	194	NA
Sato 2006 [800]	control (2) vs AP (3)	2.10	9	10	NA	445	426	NA
SAPFI 1991[838]	control (2) vs AP (3)	1.30	50	39	NA	568	552	NA
Van Latum 1993 (EAFT)- secondary prevention[882]	control (2) vs AP (3)	2.30	102	99	NA	378	404	NA
Hart 2008[423]	AP (3) vs DAP (4)	2.30	25	29	NA	285	298	NA
Active 2009 (mixed pop 13% stroke)[12]	AP (3) vs DAP (4)	3.60	841	825	NA	3782	3772	NA

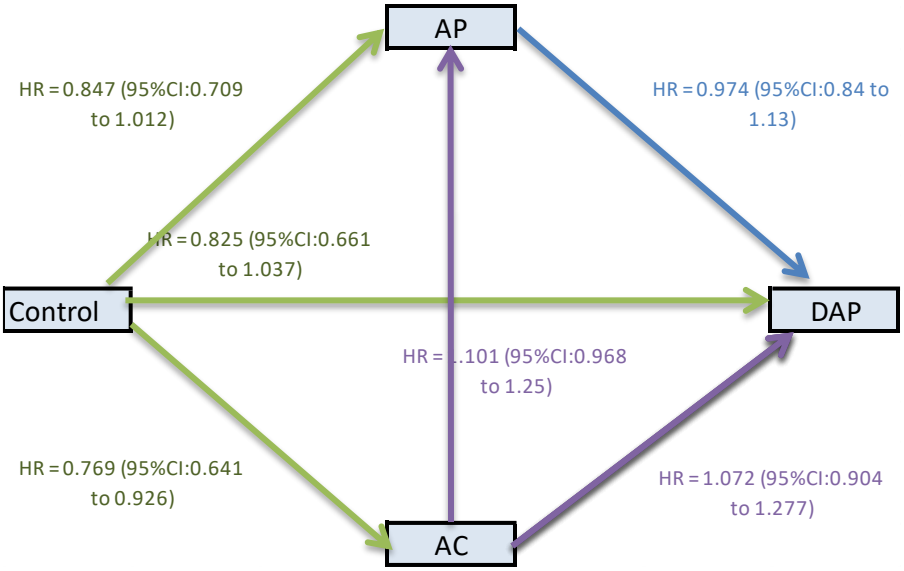
Note: time= follow up in years, R = number of events in 1) intervention or 2 or 3) comparator arms, n = number of patients in 1) intervention or 2 or 3) comparator arms.

AC = anticoagulation, AP = antiplatelet, DAP = Dual antiplatelet therapy

M.3.1.2 Results of the network meta-analysis for all-cause mortality.

The below figure depicts the mean hazard ratios calculated for each comparator in the network meta-analysis.

Figure 205: Mean hazard ratios for the outcome of all-cause mortality.

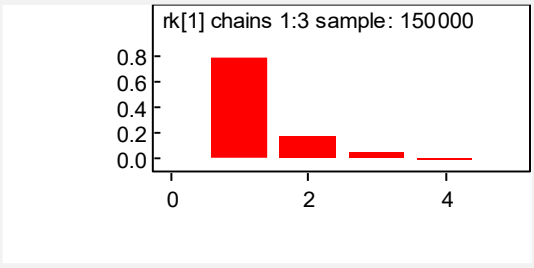


Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

The figures below show the probability that each treatment will be ranked first, second, third, and fourth, with first being lowest risk of death and fourth being highest risk of death. There is a high probability that anticoagulation, and to a lesser extent that a dual antiplatelet strategy, would be ranked optimal when considering this outcome. A control strategy would be the least optimal strategy to follow for this outcome, with both antiplatelet and dual antiplatelet sharing a similar probability that they would be the least optimal pharmacological strategy.

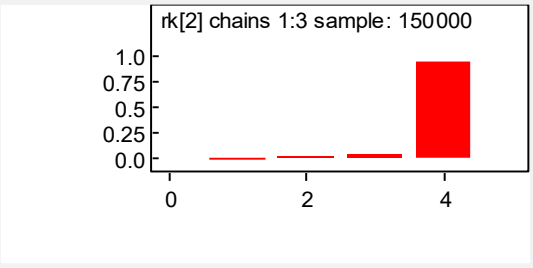
Table 176: Probability of being ranked 1st,2nd,3rd or 4th in comparison to other antithrombotic strategies in regard to the prevention of death from any cause

A: Anticoagulation (AC)



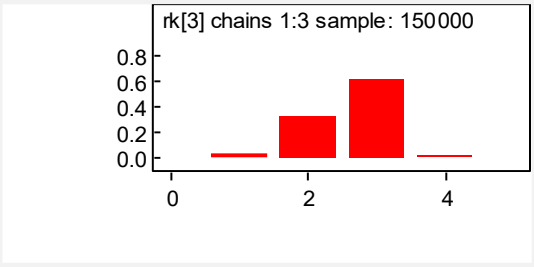
Probability of optimality = 78%

B: Control (C)



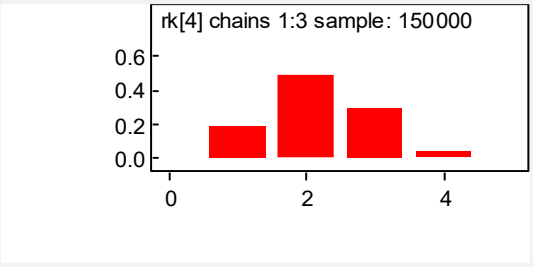
Probability of optimality = 0.1%

C: Antiplatelet (AP)



Probability of optimality = 3%

D: Dual antiplatelet (DAP)



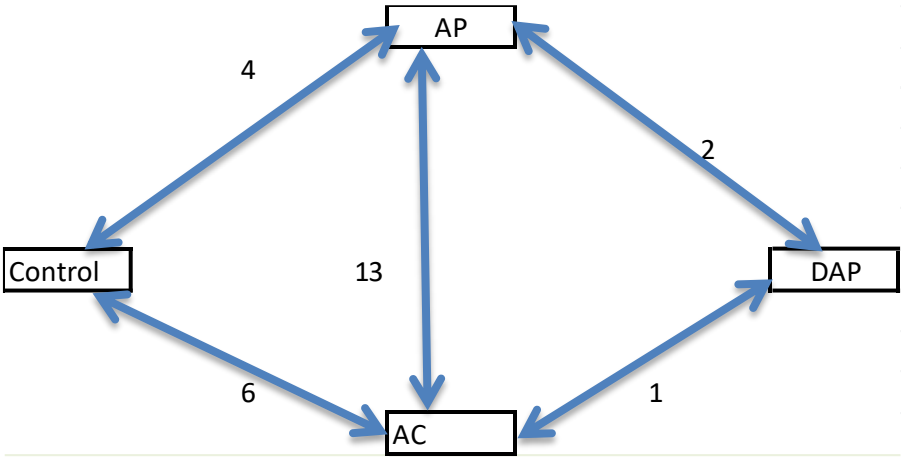
Probability of optimality = 19%

M.3.2 NMA for Ischaemic Stroke

M.3.2.1 Networks and Data

There were 24 studies included for this outcome, one of which was a three arm trial [732]. Also, one paper compared three of the comparators, but due to the grouping in the randomisation process, we could only treat these comparisons seperately.[838,838,882] The included studies are detailed in the below figure and table. One study was excluded from the NMA due to no events in neither arm. [767]

Figure 206: Network of trials compared in the network meta-analysis for ischaemic stroke



Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

Table 177: Study details and inputs into the NMA for the outcome of ischaemic stroke

Study	Comparison (intervention. vs comparator)	Time of follow up (years)	R1	R2	R3	N1	N2	N3
Singer 1990 (BAATAF)[816]	AC (1) vs control(2)	2.20	2	11	NA	205	201	NA
Connolly 1991 (CAFA study)[226]	AC (1) vs control (2)	1.27	5	9	NA	181	184	NA
SPAFI 1991[838]	AC (1) vs control(2)	1.30	5	13	NA	193	194	NA
Ezekowitz 1992 (SPINAF) - primary prevention[318]	AC (1) vs control(2)	3.00	4	19	NA	260	265	NA
Ezekowitz 1992 (SPINAF) - secondary prevention[318]	AC (1) vs control(2)	3.00	2	4	NA	21	25	NA
Petersen 1989[732]	AC (1) vs control (2) vs AP (3)	1.20	4	17	19	335	336	336
Gullov 1998 (AFASAK II)[402]	AC (1) vs AP (3)	1.00	9	8	NA	170	169	NA
Vemmos 2006 (Athens)	AC (1) vs AP (3)	0.30	0	2	NA	16	15	NA
Chen 2012[190]	AC (1) vs AP (3)	2.00	1	8	NA	239	239	NA

Chen 2013[194]	AC (1) vs AP (3)	4.25	9	17	NA	650	361	NA
Diener 2012 - AVERROES[288]	AC (1) vs AP (3)	1.10	34	70	NA	2417	2415	NA
Mant 2007[638]	AC (1) vs AP (3)	2.70	10	32	NA	488	485	NA
Perez Gomez 2004 (NASPEAF)[731]	AC (1) vs AP (3)	2.76	2	9	NA	237	242	NA
Hellemons 1999 - PATIF	AC (1) vs AP (3)	2.70	3	4	NA	131	141	NA
Halperin 1994 (Spaf IIa)[414]	AC (1) vs AP (3)	3.10	13	19	NA	358	357	NA
Halperin 1994 (Spaf IIb)[414]	AC (1) vs AP (3)	3.10	13	18	NA	197	188	NA
Diener 2012 – subgroup - AVERROES[288]	AC (1) vs AP (3)	1.10	9	27	NA	390	374	NA
Van Latum 1993 (EAFT)- secondary prevention[882]	AC (1) vs AP (3)	2.30	20	51	NA	225	230	NA
Active 2006 [13]	AC (1) vs DAP (4)	1.28	42	90	NA	3371	3335	NA
Posada 1999 (LASAF)[757]	control (2) vs AP (3)	1.50	3	4	NA	91	194	NA
Sato 2006 [800]	control (2) vs AP (3)	2.10	16	13	NA	445	426	NA
SAPFI 1991[838]	control (2) vs AP (3)	1.30	32	20	NA	527	519	NA
Hart 2008[423]	AP (3) vs DAP (4)	2.30	14	14	NA	285	298	NA
Active 2009 (mixed pop 13% stroke)[12]	AP (3) vs DAP (4)	3.60	343	235	NA	3782	3772	NA

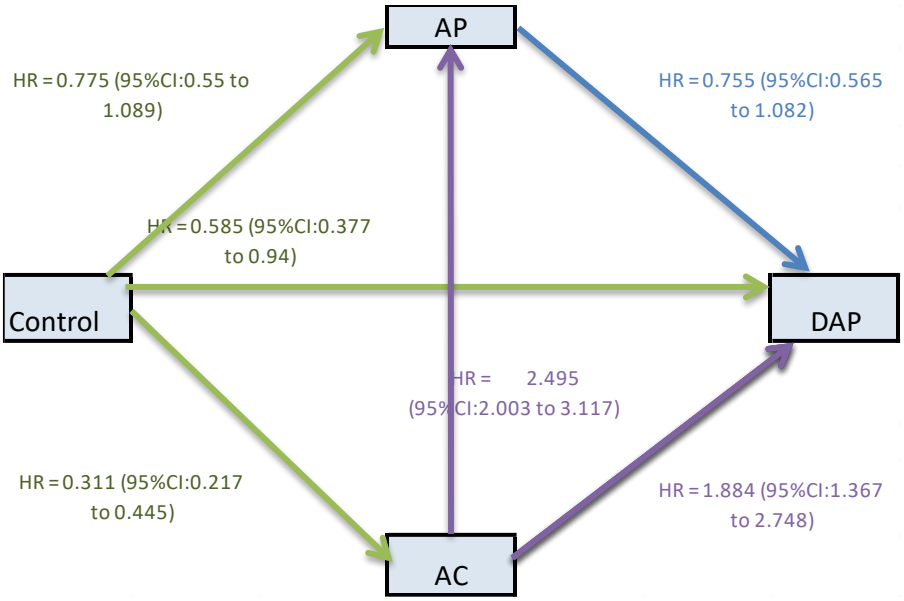
Note: time= follow up in years, R = number of events in 1) intervention or 2 or 3) comparator arms, n = number of patients in 1) intervention or 2 or 3) comparator arms.

AC = anticoagulation, AP = antiplatelet, DAP = Dual antiplatelet therapy

M.3.2.2 Results of the network meta-analysis for Ischaemic stroke.

The below figure depicts the mean hazard ratios calculated for each comparator in the network meta-analysis.

Figure 207: Mean hazard ratios for the outcome of ischaemic stroke

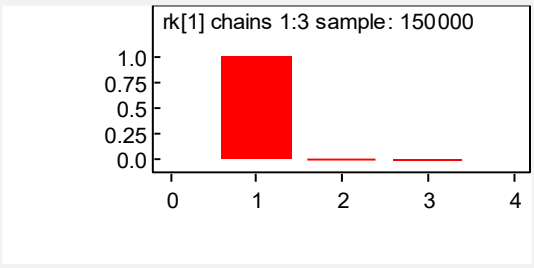


Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

The figures below show the probability that each treatment will be ranked first, second, third, and fourth, with first being lowest risk of ischaemic stroke and fourth being highest risk of ischaemic stroke. It is nearly certain that anticoagulation is the optimal strategy with a very minute chance that dual antiplatelet could be optimal. If anticoagulation is not possible, then on the whole dual antiplatelet ranked second best, followed by antiplatelet, with a high probability that control is the least optimal strategy, ranking fourth.

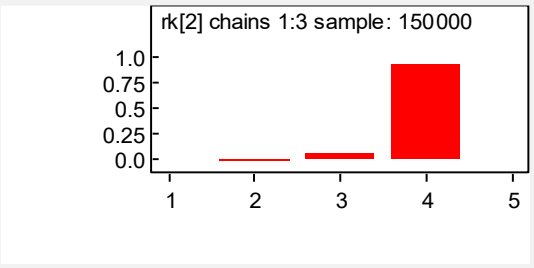
Table 178: Probability of being ranked 1st,2nd,3rd or 4th in comparison to other antithrombotic strategies in regard to the prevention of ischaemic stroke

A: Anticoagulation (AC)



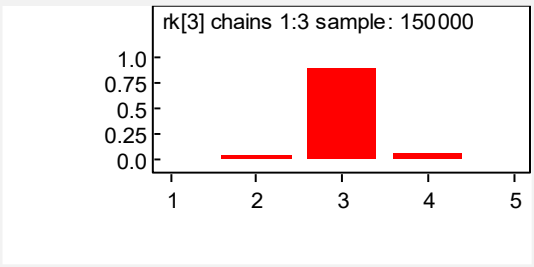
Probability of optimality = 100%

B: Control (C)



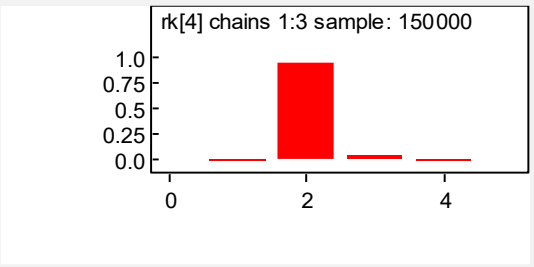
Probability of optimality = 0%

C: Antiplatelet (AP)



Probability of optimality = 0%

D: Dual antiplatelet (DAP)



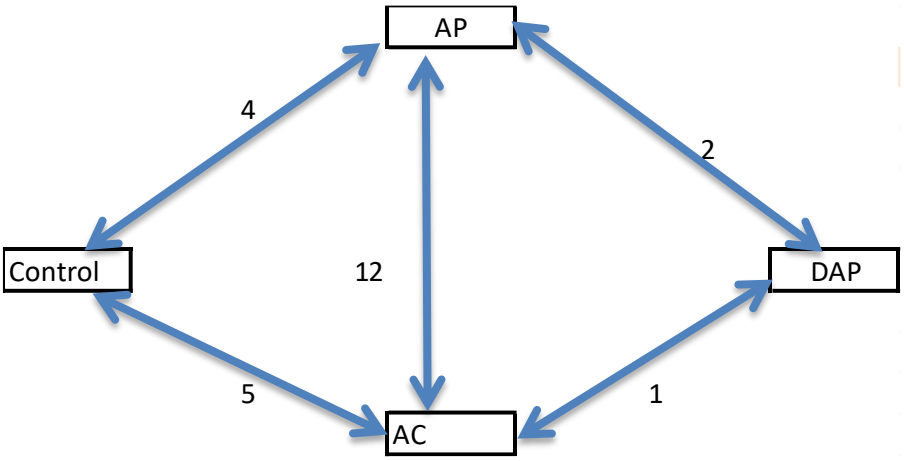
Probability of optimality = 0.1%

M.3.3 NMA for haemorrhagic stroke

M.3.3.1 Networks and Data

There were 22 studies included for this outcome, one of which was a three arm trial.[732] The included studies are detailed in the below figure and table. Three studies were excluded from the NMA due to non-events in both arms.[318,430,766]

Figure 208: Network of trials compared in the network meta-analysis for haemorrhagic stroke



Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

Table 179: Study details and inputs into the NMA for the outcome of haemorrhagic stroke

Study	Comparison (intervention. vs comparator)	Time of follow up (years)	R1	R2	R3	N1	N2	N3
Singer 1990 (BAATAF)[816]	AC (1) vs control(2)	2.20	1	0	NA	205	201	NA
Connolly 1991 (CAFA study)[226]	AC (1) vs control (2)	1.27	1	0	NA	181	184	NA
SAPFI 1991[838]	AC (1) vs control(2)	1.30	2	2	NA	193	194	NA
Ezekowitz 1992 (SPINAF) - primary prevention[318]	AC (1) vs control(2)	3.00	1	0	NA	260	265	NA
Petersen 1989[732]	AC (1) vs control (2) vs AP (3)	1.20	1	0	0	335	336	336
Gullov 1998 (AFASAK II)[402]	AC (1) vs AP (3)	1.00	1	1	NA	170	169	NA
Vemmos 2006 (Athens)[887]	AC (1) vs AP (3)	0.30	1	0	NA	16	15	NA
Chen 2012[189]	AC (1) vs AP (3)	2.00	1	0	NA	239	201	NA
Chen 2013[194]	AC (1) vs AP (3)	4.25	16	3	NA	650	361	NA
Diener 2012 - AVERROES[288]	AC (1) vs AP (3)	1.10	5	5	NA	2417	2415	NA
Mant 2007[640]	AC (1) vs AP (3)	2.70	6	5	NA	488	485	NA
Perez Gomez 2004 (NASPEAF)[731]	AC (1) vs AP (3)	2.76	4	2	NA	237	242	NA

Halperin 1994 (Spaf Iia)[414]	AC (1) vs AP (3)	3.10	6	2	NA	358	357	NA
Halperin 1994 (Spaf Iib)[414]	AC (1) vs AP (3)	3.10	6	3	NA	197	188	NA
Diener 2012 AVERROES (subgroup)[288]	AC (1) vs AP (3)	1.10	1	4	NA	390	374	NA
Van Latum 1993 (EAFT)-secondary prevention[882]	AC (1) vs AP (3)	2.30	0	1	NA	225	230	NA
Active 2006 [13]	AC (1) vs DAP (4)	1.28	15	5	NA	3371	3335	NA
Posada 1999 (LASAF)[757]	control (2) vs AP (3)	1.50	0	1	NA	91	194	NA
Sato 2006 [800]	control (2) vs AP (3)	2.10	2	4	NA	445	426	NA
SAPFI 1991[838]	control (2) vs AP (3)	1.30	2	2	NA	527	519	NA
Hart 2008[423]	AP (3) vs DAP (4)	2.30	0	1	NA	285	298	NA
Active 2009[12]	AP (3) vs DAP (4)	3.60	22	30	NA	3782	3772	NA

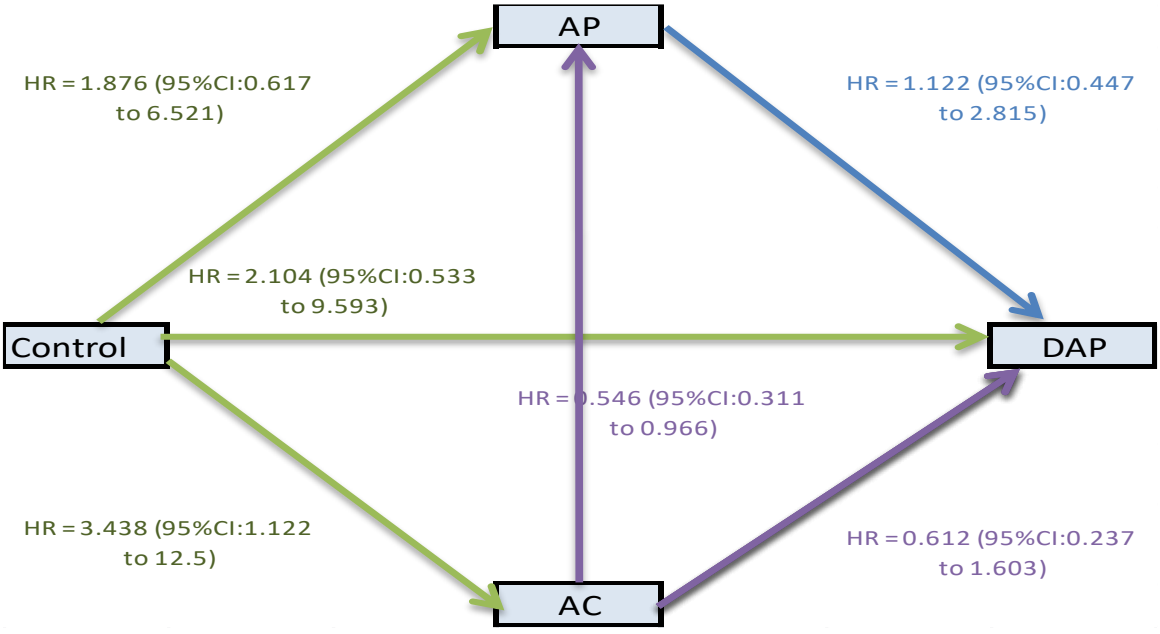
Note: time= follow up in years, R = number of events in 1) intervention or 2 or 3) comparator arms, n = number of patients in 1) intervention or 2 or 3) comparator arms.

AC = anticoagulation, AP = antiplatelet, DAP = Dual antiplatelet therapy

M.3.3.2 Results of the network meta-analysis for haemorrhagic stroke

The below figure depicts the mean hazard ratios calculated for each comparator in the network meta-analysis.

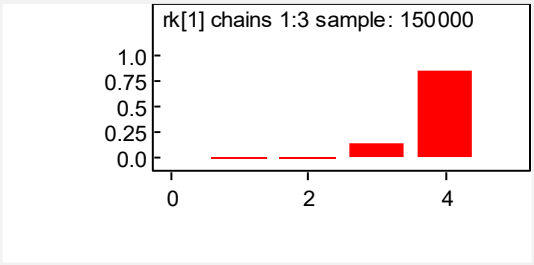
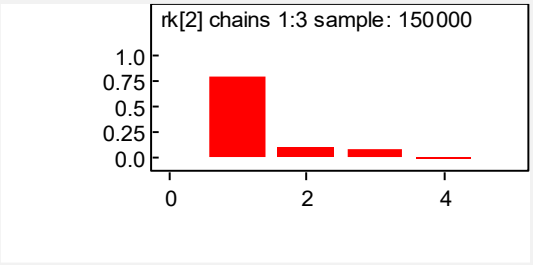
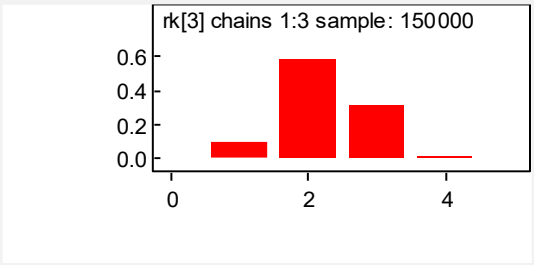
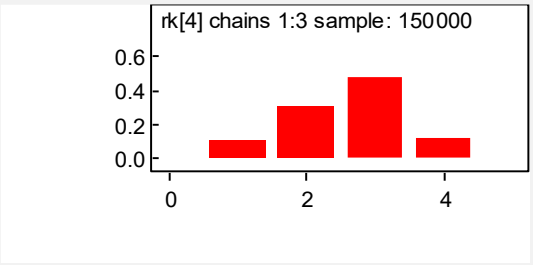
Figure 209: Mean hazard ratios for the outcome of haemorrhagic stroke



Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

The figures below show the probability that each treatment will be ranked first, second, third, and fourth, with first being lowest risk of haemorrhagic stroke and fourth being highest risk of haemorrhagic stroke. It is highly likely that control will rank optimal and anticoagulation least optimal. Antiplatelets are more likely to rate higher than dual platelets in regards to avoiding haemorrhagic stroke.

Table 180: Probability of being ranked 1st,2nd,3rd or 4th in comparison to other antithrombotic strategies in regard to avoiding of haemorrhagic stroke

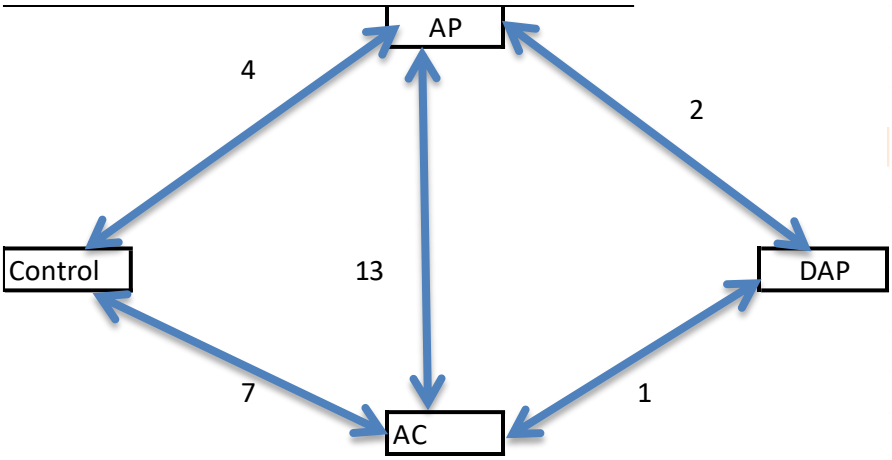
A: Anticoagulation (AC)	**B: Control (C)**
	
Probability of optimality = 0.1%	Probability of optimality = 80%
C: Antiplatelet (AP)	**D: Dual antiplatelet (DAP)**
	
Probability of optimality = 9%	Probability of optimality = 10%

M.3.4 NMA for Major Bleeding (inclusive of intracranial bleeding as per review protocol)

M.3.4.1 Networks and Data

There were 24 studies identified for this outcome, one of which was a three arm trial[732]. Two further studies compared three of the comparators, but due to the grouping in the randomisation process, we could only treat these studies as containing separate two way comparisons.[838,882] The included studies are detailed in the below figure and table. Two study comparisons were excluded from the NMA due to non-events in both arms [318,887]

Figure 210: Network of trials compared in the network meta-analysis for major bleeding.



Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

Table 181: Study details and inputs into the NMA for the outcome of major bleeding

Study	Comparison (intervention. vs comparator)	Time of follow up (years)	R1	R2	R3	N1	N2	N3
Singer 1990 (BAATAF)[816]	AC (1) vs control(2)	2.20	5	8	NA	205	201	NA
Connolly 1991 (CAFA study)[226]	AC (1) vs control (2)	1.27	4	2	NA	181	184	NA
SAPFI 1991[838]	AC (1) vs control(2)	1.30	2	2	NA	193	194	NA
Ezekowitz 1992 (SPINAF) - primary prevention[318]	AC (1) vs control(2)	3.00	6	4	NA	260	265	NA
Van Latum 1993 (EAFT)- secondary prevention[882]	AC (1) vs control(2)	0.02	13	3	NA	225	214	NA
Petersen 1989[732]	AC (1) vs control (2) vs AP (3)	1.20	21	0	2	335	336	336
Gullov 1998 (AFASAK II)[402]	AC (1) vs AP (3)	1.00	2	4	NA	170	169	NA
Chen 2012[189]	AC (1) vs AP (3)	2.00	6	1	NA	239	201	NA
Chen 2013[194]	AC (1) vs AP (3)	4.25	9	5	NA	650	361	NA
Diener 2012 (AVERROES)[288]	AC (1) vs AP (3)	1.10	30	28	NA	2417	2415	NA
Mant 2007[638]	AC (1) vs AP (3)	2.70	19	20	NA	488	485	NA
Perez Gomez 2004 (NASPEAF)[731]	AC (1) vs AP (3)	2.76	6	0	NA	232	235	NA
Hellemons 1999 - PATIF[430]	AC (1) vs AP (3)	2.70	1	0	NA	131	141	NA
Rash 2007[767]	AC (1) vs AP (3)	1.00	0	3	NA	36	39	NA
Halperin 1994 (Spaf Iia)[414]	AC (1) vs AP (3)	3.10	12	8	NA	358	357	NA
Halperin 1994 (Spaf Iib)[414]	AC (1) vs AP (3)	3.10	9	3	NA	197	188	NA

Study	Comparison (intervention. vs comparator)	Time of follow up (years)	R1	R2	R3	N1	N2	N3
Diener 2012 AVERROES (subgroup)[288]	AC (1) vs AP (3)	1.1	14	11	NA	390	374	NA
Van Latum 1993 (EAFT)-secondary prevention[882]	AC (1) vs AP (3)	2.30	13	2	NA	225	230	NA
Active 2006 [13]	AC (1) vs DAP (4)	1.28	93	101	NA	3371	3335	NA
Sato 2006 [800]	control (2) vs AP (3)	2.10	0	3	NA	445	426	NA
SAPFI 1991[838]	control (2) vs AP (3)	1.30	8	8	NA	527	519	NA
Van Latum 1993 (EAFT)-secondary prevention[882]	control (2) vs AP (3)	2.30	4	6	NA	378	404	NA
Hart 2008[423]	AP (3) vs DAP (4)	2.30	4	9	NA	285	298	NA
Active 2009[12]	AP (3) vs DAP (4)	3.60	162	251	NA	3782	3772	NA

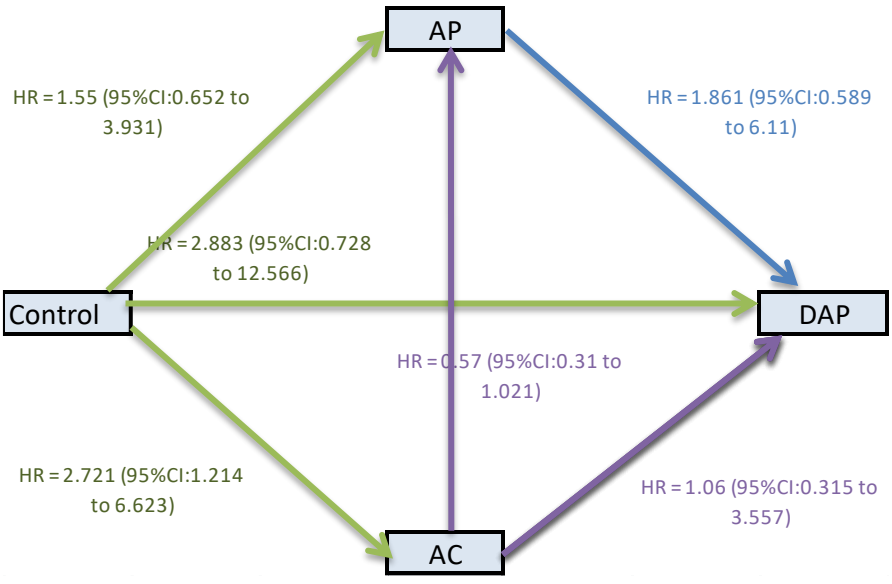
Note: *time= follow up in years, R = number of events in 1) intervention or 2 or 3) comparator arms, n = number of patients in 1) intervention or 2 or 3) comparator arms.*

AC = anticoagulation, AP = antiplatelet, DAP = Dual antiplatelet therapy

M.3.4.2 Results of the network meta-analysis for major bleeding.

The below figure depicts the mean hazard ratios calculated for each comparator in the network meta-analysis.

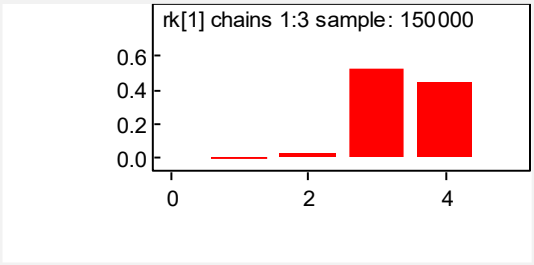
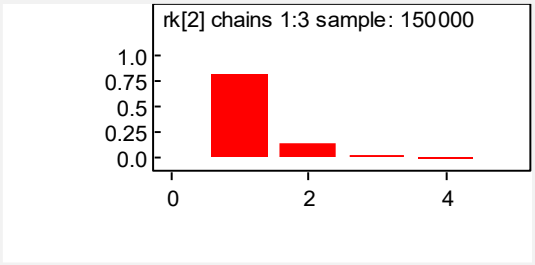
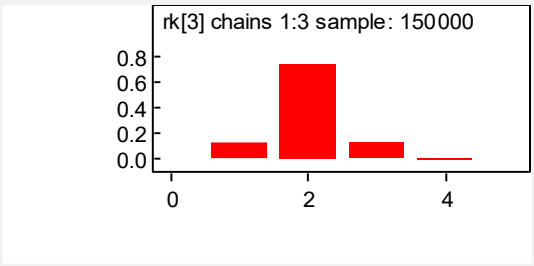
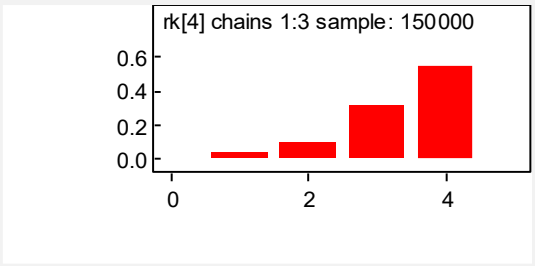
Table 182: Mean hazard ratios for the outcome of major bleeding.



Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

The figures below show the probability that each treatment will be ranked first, second, third, and fourth, with first being lowest risk of bleeding and fourth being highest risk of bleeding. There is a high probability that the control strategy, and a lesser probability that a antiplatelet strategy, would be ranked optimal when considering this outcome. There is a high probability that the dual antiplatelet would rank worst, with warfarin ranked third.

Table 183: Probability of being ranked 1st,2nd,3rd or 4th in comparison to other antithrombotic strategies in regard to the adverse event of bleeding.

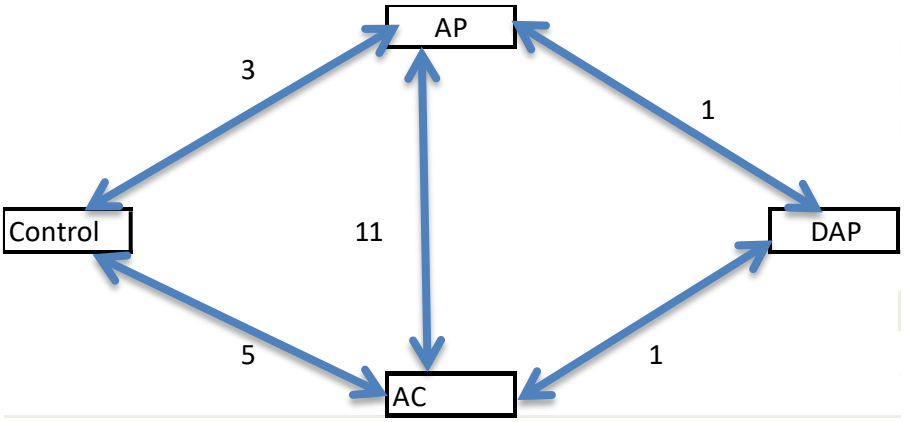
A: Anticoagulation (AC)	**B: Control (C)**
	
Probability of optimality =0.1%	Probability of optimality = 82%
C: Antiplatelet (AP)	**D: Dual antiplatelet (DAP)**
	
Probability of optimality = 14%	Probability of optimality = 4%

M.3.5 NMA for thromboembolic complications

M.3.5.1 Networks and Data

There were 19 studies included for this outcome, one of which was a three arm trial[732]. Two further studies compared three of the comparators, but due to the grouping in the randomisation process, we could only treat these studies as containing separate two way comparisons.[838,882] The included studies are detailed in the below figure and table. Three studies were excluded from the NMA due to non-events in both trial arms.[757,816,887]

Figure 211: Network of trials compared in the network meta-analysis for thromboembolic complications



Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

Table 184: Study details and inputs into the NMA for the outcome of thromboembolic complications

Study	Comparison (intervention. vs comparator)	Time of follow up (years)	R1	R2	R3	N1	N2	N3
Connolly 1991 (CAFA study)[226]	AC (1) vs control (2)	1.27	1	2	NA	181	184	NA
SAPFI 1991[838]	AC (1) vs control(2)	1.30	0	2	NA	193	194	NA
Ezejkowitz 1992 (SPINAF) - primary prevention	AC (1) vs control(2)	3.00	2	1	NA	260	265	NA
Van Latum 1993 (EAFT)- secondary prevention[882]	AC (1) vs control(2)	2.30	1	4	NA	225	214	NA
Petersen 1989[732]	AC (1) vs control (2) vs AP (3)	1.20	0	3	2	335	336	336
Gullov 1998 (AFASAK II)[402]	AC (1) vs AP (3)	1.00	2	1	NA	170	169	NA
Chen 2012[189]	AC (1) vs AP (3)	1.00	1	0	NA	239	201	NA
Chen 2013 [194]	AC (1) vs AP (3)	2.00	4	6	NA	650	361	NA
Diener 2012 (AVERROES)[288]	AC (1) vs AP (3)	1.10	2	5	NA	2417	2415	NA
Mant 2007[638]	AC (1) vs AP (3)	2.70	1	3	NA	488	485	NA
Perez Gomez 2004 (NASPEAF)[731]	AC (1) vs AP (3)	2.76	1	1	NA	237	242	NA
Hellemons 1999 (PATIF)[430]	AC (1) vs AP (3)	2.70	1	1	NA	131	141	NA
Halperin 1994 (Spaf Iia)[414]	AC (1) vs AP (3)	3.10	1	2	NA	358	357	NA
Halperin 1994 (Spaf Iib)[414]	AC (1) vs AP (3)	3.10	1	0	NA	197	188	NA
Diener 2012 AVERROES	AC (1) vs AP (3)	1.10	0	3	NA	390	374	NA

Study	Comparison (intervention. vs comparator)	Time of follow up (years)	R1	R2	R3	N1	N2	N3
(subgroup)[288]								
Active 2006 [13]	AC (1) vs DAP (4)	1.28	4	18	NA	3371	3335	NA
SAPFI 1991[838]	control (2) vs AP (3)	1.30	4	3	NA	527	519	NA
Van Latum 1993 (EAFT)-secondary prevention[882]	control (2) vs AP (3)	2.30	9	6	NA	378	404	NA
Active 2009[12]	AP (3) vs DAP (4)	3.60	56	54	NA	3782	3772	NA

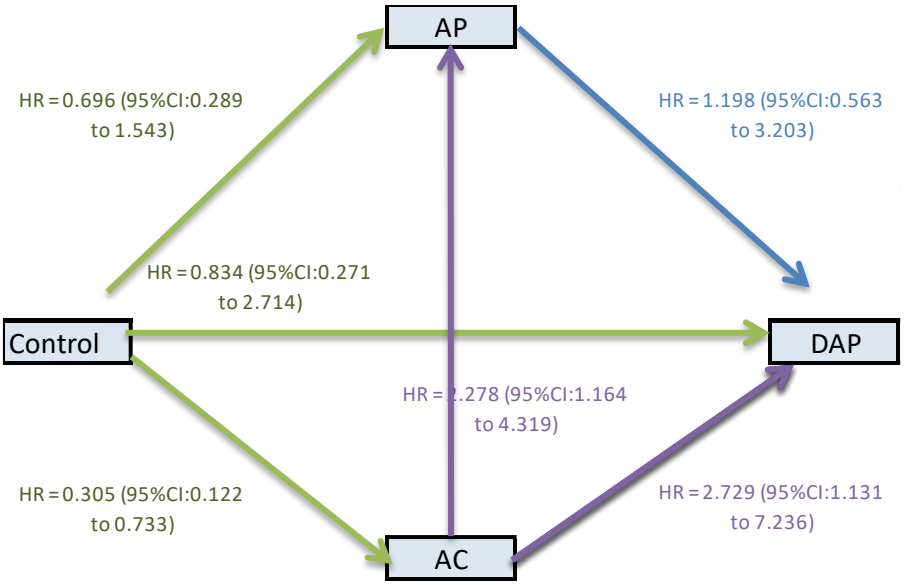
Note: time= follow up in years, R = number of events in 1) intervention or 2 or 3) comparator arms, n = number of patients in 1) intervention or 2 or 3) comparator arms.

AC = anticoagulation, AP = antiplatelet, DAP = Dual antiplatelet therapy

M.3.5.2 Results of the network meta-analysis for thromboembolic complications

The below figure depicts the mean hazard ratios calculated for each comparator in the network meta-analysis.

Figure 212: Mean hazard ratios for the outcome of thromboembolic complications

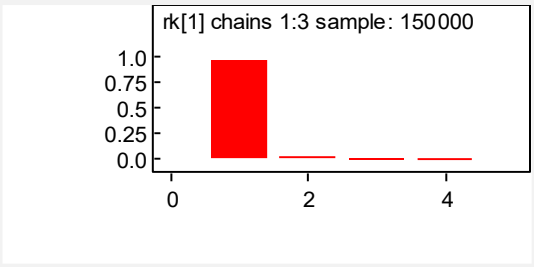


Note: Where AC = Anticoagulation (NMA label = 1), Control (NMA label = 2), AP = Antiplatelet (NMA label = 3, DAP = Dual antiplatelet (NMA label = 4).

The figures below show the probability that each treatment will be ranked first, second, third, and fourth, with first having the lowest risk of thromboembolic complications and fourth being highest risk of thromboembolic complications. There is an extremely high probability that anticoagulation is the optimal strategy. Both control and dual antiplatelet have a high chance of being the least optimal. In regards to prevention of thromboembolic complications, it is likely that an antiplatelet strategy is optimal if anticoagulation is not possible.

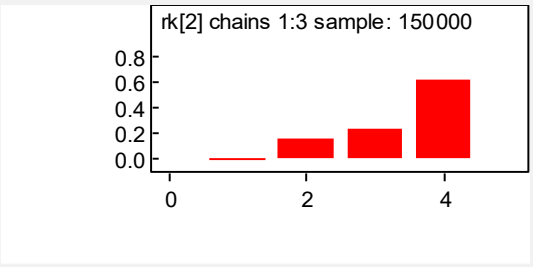
Table 185: Probability of being ranked 1st,2nd,3rd or 4th in comparison to other antithrombotic strategies in regard to the prevention of thromboembolic complications

A: Anticoagulation (AC)



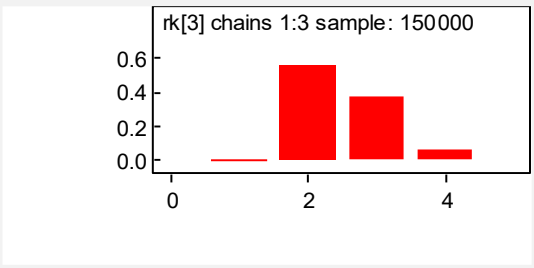
Probability of optimality = 95%

B: Control (C)



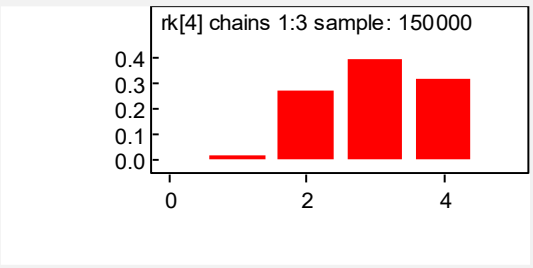
Probability of optimality =1%

C: Antiplatelet (AP)



Probability of optimality = 2%

D: Dual antiplatelet (DAP)



Probability of optimality = 2%

M.4 Limitations

The assumptions of the network meta-analysis model necessitated a constant hazard of clinical events over time. However, the same assumption also applies within the main simulation model, and therefore the NMA is consistent with the overall approach. It does however represent a restriction of the analysis to keep in mind. A posterior estimate of heterogeneity - the between trial standard deviation – and total residual deviance for each NMA is reported below. In general, estimates of this magnitude indicates a large amount of variation in treatment effects calculated from different trials

Table 186: Summary of posterior estimate of heterogeneity and total residual deviance

NMA	Posterior estimate of heterogeneity	Total residual deviance
All-cause mortality	0.06131	44.12
Ischaemic stroke	0.1593	48.24
Haemorrhagic stroke	0.4141	43.92
Major bleeding	0.8905	56.45
Thromboembolic Complications	0.371	39.02

To note, the NMA includes studies which looked at populations who had a previous stroke and those who have not. There were insufficient secondary prevention studies to create a full network for all of the outcomes, meaning that if they were removed the treatment effect applied to simulated patients with prior stroke in the model would have been estimated using mixed population and primary prevention studies alone. Indeed as many of the studies were mixed populations, this was felt to be reasonable in order to obtain coherent estimates of treatment effect for the model. It

could be in part responsible for the heterogeneity observed in these network met analysis, however, in many instances the estimates retrieved for primary and secondary prevention were the same on many outcomes – and in all cases the confidence intervals of estimates for primary and secondary prevention crossed suggesting that the true mean could be the same.

To note that the NMA estimated hazard ratios whereby different follow up time is accounted for, whereas the pairwise meta-analysis calculated risk ratios. This means the magnitude of effect is not directly comparable; having said this, we would expect the same direction of effect. In comparison to the pairwise comparisons, there was one instance when the best estimate from the NMA suggested a different direction of effect to the pairwise meta-analysis. This was for the outcome of thromboembolic complications between single and dual antiplatelets, where the pairwise relative risk of 0.97 (95% 0.67-1.40) was estimated from one trial (ACTIVE 2009{ACTIVE Investigators, 2009 ACTIVE2009 /id}). This compares to an estimate found by the NMA of 1.198 (95%CI: 0.563 to 3.203). Given the proximity of the former estimate to the line of no effect, and the small number of studies informing this relative effect in comparison to the larger number of studies for other arms in the network, it is not surprising that the direction of effect could change in this instance. In fact the NMA further highlights the uncertainty surrounding the estimate with the calculation of a wider confidence interval.

More of note is the treatment effect that anticoagulation may have on haemorrhagic stroke. For this outcome the absolute rate of events in the control arm is very low, and in some trials no events were observed. Although the hazard ratio falls within the confidence interval of the effect found by the pairwise meta-analysis in the review, and therefore given the data retrieved, a relative risk of this magnitude is a credible estimate. However, the low event rate is a limitation and potentially may lead to overestimation of the risk of haemorrhagic stroke should it be applied to higher baseline event rates.

Another limitation with both the pairwise and network analyses is that they were subject to poor reporting and potential misclassification of events in the trials. In particular, many trials reported difficulties in confirming whether a stroke was haemorrhagic or ischaemic in nature, with some studies also reporting unclassified stroke. The analyses used only confirmed cases, which may mean slight inaccuracies arsing due to the number of unclassified cases not incorporated. Further, some events may not be mutually exclusive. For example, an intracranial bleed may lead to haemorrhagic stroke, and trials differed in how they grouped such events. In some cases intracranial bleed may be reported as a major bleed, and in others it may be classified in the same group as haemorrhagic stroke.

Given the above limitations with the data, the GDG felt it important that the economic model tested the possibility that both bleeding and haemorrhagic stroke rates with anticoagulation could be lower than the trials suggested. For this reason an additional analysis whereby the low relative risk of bleeding and haemorrhagic stroke found for anticoagulation was adopted for anticoagulation to evaluate impact this could have on results.

Table 187: Comparisons between direction of effect found with NMA and the two way meta-analysis for chapter 9 (see antithrombotic review)

Outcome	Comparison	Intervention	Hazard ratio (NMA)	Relative risk found by pairwise meta-analysis (Primary/ secondary prevention subgroups)
All cause	AP	control	0.847	0.80/0.96

Outcome	Comparison	Intervention	Hazard ratio (NMA)	Relative risk found by pairwise meta-analysis (Primary/ secondary prevention subgroups)
mortality	DAP	control	0.825	NA
	AC	control	0.769	0.70/0.93
Ischaemic stroke	AP	control	0.775	0.74
	DAP	control	0.585	NA
	AC	control	0.311	0.32/0.60
Haemorrhagic stroke	AP	control	1.876	1.68
	DAP	control	2.104	NA
	AC	control	3.438	1.87/NA
Bleeding	AP (b)	control	1.550	1.47/1.40
	DAP	control	2.883	NA
	AC	control	2.721	1.06/4.12
Thromboembolic complications (Systemic emboli)	AP	control	0.696	0.67/0.62
	DAP	control	0.834	NA
	AC	control	0.305	0.45/0.28
Outcome	Strategy	Ref	Hazard ratio (NMA)	Risk ratio (Pairwise MA) Primary/ secondary
All cause mortality	AP	AC	0.908	0.90/0.78
	AP	DAP	0.974	0.99/NA
	AC	DAP	1.072	1.02/NA
Ischaemic stroke	AP	AC	0.401	0.48/0.37
	AP	DAP	0.755	0.70/NA
	AC	DAP	1.884	2.17/NA
Haemorrhagic stroke	AP	AC	1.833	1.92/0.27
	AP	DAP	1.122	1.40/NA
	AC	DAP	0.612	0.34/NA
Bleeding	AP	AC	1.755	1.23/2.03
	AP	DAP	1.861	1.57/NA

Outcome	Comparison	Intervention	Hazard ratio (NMA)	Relative risk found by pairwise meta-analysis (Primary/ secondary prevention subgroups)
	AC	DAP	1.06	1.10/NA
Thromboembolic complications	AP	AC	0.439	0.60/0.14
	AP	DAP	1.198	0.97/NA
	AC	DAP	2.729	4.55/NA

M.5 Conclusions of the network meta-analysis for antithrombotic therapy.

For the following outcomes, a strategy of anticoagulation is:

All cause mortality

- highly likely to be the optimal strategy (73% likelihood), and a control strategy is likely to be least optimal. There is a great deal of certainty that anticoagulation is effective in comparison to a control strategy, however the relative effects between the other comparisons are less clear.

Ischaemic stroke

- almost certain to be the optimal strategy (100% likelihood). If anticoagulation is not possible, then on the whole dual antiplatelet ranked second best, followed by antiplatelet, with a high probability that control is the least optimal strategy, ranking fourth.

Haemorrhagic stroke

- highly likely that control will rank optimal (81% likelihood) and anticoagulation least optimal. Antiplatelets are more likely to rate higher than dual platelets in regards to avoiding haemorrhagic stroke.

Major bleeding

- a do nothing or strategy of antiplatelet is most likely to be optimal (45% likelihood), and the strategy of dual antiplatelet is likely to be least optimal. However, there is a high degree of uncertainty as to which strategy would be optimal in this outcome.

Thromboembolic complications

- a strategy of anticoagulation is extremely probable to be the optimal strategy (95% likelihood). Control has a high chance of being the least optimal. In regards to prevention of thromboembolic complications, it is likely that an antiplatelet strategy is optimal if anticoagulation is not possible.

Table 188: Summary of Hazard ratios per outcome in comparison to control (as adverse events, HR below 1 indicates that the strategy is effective in avoiding the event)

Outcome	Strategy	Hazard ratio	LCI	UCI
All cause mortality	AP	0.847	0.709	1.012
	DAP	0.825	0.661	1.037
	AC	0.769	0.641	0.926
Ischaemic stroke	AP	0.775	0.550	1.089
	DAP	0.585	0.377	0.940
	AC	0.311	0.217	0.445
Haemorrhagic stroke	AP	1.876	0.617	6.521
	DAP	2.104	0.533	9.593
	AC	3.438	1.122	12.5
Bleeding	AP	1.55	0.652	3.931
	DAP	2.883	0.728	12.566
	AC	2.721	1.214	6.623
Thromboembolic complications	AP	0.696	0.289	1.543
	DAP	0.834	0.271	2.714
	AC	0.305	0.122	0.733

M.6 Winbugs Model

The Winbugs code for the network meta-analysis is as follows:

```
# Binomial likelihood, cloglog link

# Random effects model for multi-arm trials

model{                          # *** PROGRAM STARTS

for(i in 1:ns){                 # LOOP THROUGH STUDIES

   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm

   delta[i,1] <- 0           # treatment effect is zero for control arm

   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines

   for (k in 1:na[i]) {           # LOOP THROUGH ARMS

      r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood

# model for linear predictor

      cloglog(p[i,k]) <- log(time[i]) + mu[i] + delta[i,k]
```

```
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {           # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
  }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0      # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
lhr[c,k] <- (d[k]-d[c])
log(hr[c,k]) <- lhr[c,k]
}
```

```
}
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
}
}                                # *** PROGRAM ENDS
```

Appendix N: Unit costs of pharmacological agents considered in the guideline

In the absence of recent UK economic evidence, the unit cost and resource implications of various pharmacological strategies were considered. Whenever possible the drug tariff was used, however the BNF was consulted if list prices were not reported. These are given in the below table, with a brief summary of additional resource implications associated with implementation and monitoring. The unit cost of £145 (£98-£182) was given for electrocardiogram monitoring and stress testing (EA47Z) as an example of an additional cost of associated with some rhythm and rate control pharmacological strategies.[276]

Table 189: Unit cost of pharmacological agents used for stroke prevention and control of AF

	Dosage	Pack size	Net price pack	Price per tablet/unit	Daily dose	Price per day	Price per year	Source: Drug tariff August 2013, except where indicated.[692]	Additional notes, including monitoring/prevention of complications
Stroke Prevention									
Aspirin			**0.83**	**0.03**		**0.03**	**11**	**Calculated average of list prices below**	
Dispersible tablets (mg) (Non-proprietary)	75	28	0.84	0.03	75	0.03	11	Part VIIIA - Basic Prices of Drugs Product List	
Tablets (mg) (Non-proprietary)	75	28	0.82	0.03	75	0.03	11	Part VIIIA - Basic Prices of Drugs Product List	
Dual antiplatelets			**2.66**	**0.095**		**0.095**	**34.68**	**Calculated average of list prices below**	
Clopidogrel	75	28	1.83	0.07	75	0.07	24	Part VIIIA - Basic Prices of Drugs Product List - M	
Aspirin			0.83	0.03		0.03	10.82	Average of list prices	
Warfarin Sodium			1.08	0.04		0.23	85	Average of list prices	Warfarin requires anticoagulation quality of

	Dosage	Pack size	Net price pack	Price per tablet/unit	Daily dose	Price per day	Price per year	Source: Drug tariff August 2013, except where indicated.[692]	Additional notes, including monitoring/prevention of complications
Tablets (mg) (Non-proprietary)	0.5	28	1.48	0.05	6	0.63	232	BNF August 2013[489]	control monitoring. Using NHS reference cost for code 324 the annual cost of the Anticoagulant Service with monthly visits is estimated at £254.74[276]
	1	28	0.9	0.03	6	0.19	70	Part VIIIA products W	
	3	28	0.94	0.03	6	0.07	25	Part VIIIA products W	
	5	28	0.99	0.04	6	0.04	15	Part VIIIA products W	
ANTIARRHYTHMIC DRUGS									
Class Ic									
Flecainide Acetate			**5.4**	**0.09**		**0.09**	**34**	**Calculated average of list prices below**	**Rhythm control** Pill in the pocket strategy for PAF or infrequent recurrent AF: 200-300mg **To maintain** sinus rhythm for patients without LV dysfunction: 100-200mg twice daily. Should be Initiated in hospital – requires ECG monitoring, U&E, LFT prior to initiation.
Tablets (mg) (Non-proprietary)	50	60	4.24	0.07	75	0.11	39	Part VIIIA products F	
	100	60	6.56	0.11	75	0.08	30	Part VIIIA products F	
Flecainide Acetate Injection (mg/mL) (3M)	1500	1	4.4	4.4	375	1.1	N/A as used in acute AF	BNF August 2013[489]	**Rhythm control** for acute recent onset AF (given IV or orally): 2mg/kg iv dose via slow iv over 10-30mins. Oral dose 200-300mg. Should be Initiated in hospital – requires ECG monitoring, U&E, LFT prior to initiation.
Propafenone Hydrochloride			**8.36**	**0.12**		**0.08**	**29**	**Calculated average of list prices below**	**Rhythm maintenance:** Is unlikely to be used as a long term strategy. **Rhythm restoration:** Initiated in hospital only – require ECG monitoring and BP measurement during dose titration. This is done at intervals of 3-4 days, until optimum dose is achieved. However, it is unlikely UK patients are *admitted* for initiation and dose titration
Tablets (mg) (Abbott)	150	90	7.37	0.08	150	0.08	30	Part VIIIA products P	
	300	60	9.34	0.16	150	0.08	28	Part VIIIA products P	

	Dosage	Pack size	Net price pack	Price per tablet/unit	Daily dose	Price per day	Price per year	Source: Drug tariff August 2013, except where indicated.[692]	Additional notes, including monitoring/prevention of complications
									•Acute AF (given IV or orally).: 2mg/kg iv dose given over 10min. oral dose: 450-600mg po •Plus additional cost of ECG monitoring
Class II									
Esmolol Hydrochloride Injection (mg/mL) (Baxter)	**10**	**1**	**7.79**	**7.79**	**0.125**	**0.1 per min per Kg NA**		BNF August 2013[489]	**Acute rate control.** By intravenous infusion, usually within range 50–200 micrograms/kg/minute
Atenolol			**0.9**	**0.03**		**0.06**	**20**	**Calculated average of list prices below**	**For rate or rhythm maintenance**: 50-100mg daily
Tablets (mg) (Non-proprietary)	25	28	0.87	0.03	75	0.09	34	Part VIIIA - Basic Prices of Drugs Product List	
	50	28	0.89	0.03	75	0.05	17	Part VIIIA - Basic Prices of Drugs Product List	
	100	28	0.94	0.03	75	0.03	9	Part VIIIA - Basic Prices of Drugs Product List	
Injection (mg/mL) (AstraZeneca)	0.5	10	3.45	0.35	6.25	4.31	1574	BNF August 2013[489]	**Acute rhythm control:** 2.5 mg at a rate of 1 mg/minute, repeated at 5-minute intervals to a max. of 10 mg)
Labetalol Hydrochloride			**11.73**	**0.21**		**0.43**	**158**	**Calculated average of list prices below**	Labetalol [Trandate], Timolol [Betim] , Celiprolol [Celectol], and Nadolol [Corgard] are in the same class. However were thought not commonly used for AF control.
Tablets (mg) (Non-proprietary)	100	56	6.67	0.12	450	0.54	196	Part VIIIA products L	
	200	56	9.57	0.17	450	0.38	140	Part VIIIA products L	
	400	56	18.94	0.34	450	0.38	139	Part VIIIA products L	
Injection (mg/mL) (UCB Pharma)	5	20	4.91	0.25	125	6.14	2240	BNF August 2013[489]	

	Dosage	Pack size	Net price pack	Price per tablet/unit	Daily dose	Price per day	Price per year	Source: Drug tariff August 2013, except where indicated.[692]	Additional notes, including monitoring/prevention of complications
Bisoprolol Fumarate			**1.11**	**0.04**	**5.63**	**0.03**	**12**	**Calculated average of list prices below**	**For rate or rhythm maintenance:** 2.5-10mg od
Tablets (mg) (Non-proprietary)	5	28	1.07	0.04	5.63	0.04	16	Part VIIIA products B	
	10	28	1.14	0.04	5.63	0.02	8	Part VIIIA products B	
Metoprolol Tartrare			**1.17**	**0.04**		**0.12**	**45**	**Calculated average of list prices below**	**For rate or rhythm maintenance**: usually 50 mg 2–3 times daily; up to 300 mg daily in divided doses if necessary
Tablets (mg) (Non-proprietary)	50	28	1.1	0.04	200	0.16	57	1. Part VIIIA products M	
	100	28	1.23	0.04	200	0.09	32	1. Part VIIIA products M	
Injection (mg/mL) (AstraZeneca)	1	5	1	0.2	12.5	2.5	913	BNF August 2013[489]	**Acute rate control:** up to 5 mg at rate 1–2 mg/minute, repeated after 5 minutes if necessary, total dose 10–15 mg
Class II & III									
Sotalol hydrochloride			**2.73**	**0.1**		**0.37**	**136**	**Calculated average of list prices below**	**Rhythm maintenance:** dose initially 80 mg daily in 1–2 divided doses increased gradually at intervals of 2–3 days to usual dose of 160–320 mg daily in 2 divided doses. Needs to be initiated and doses increased in a facility capable of monitoring and assessing cardiac rhythm due to possibility of pro-arrhythmic events. Renal function and electrolyte balance also needs to be assessed at initiation.
Tablets (mg) (Non-proprietary)	40	28	1.35	0.05	360	0.43	158	Part VIIIA products S	
Tablets (mg) (Non-proprietary)	80	28	1.63	0.06	360	0.26	96	Part VIIIA products S	
Tablets (mg) (Non-proprietary)	160	28	5.22	0.19	360	0.42	153	Part VIIIA products S	
Class III									
Amiodarone hydrochloride			**1.68**	**0.06**		**0.17**	**63**	**Calculated average of list prices below**	Amiodarone can cause serious adverse

	Dosage	Pack size	Net price pack	Price per tablet/unit	Daily dose	Price per day	Price per year	Source: Drug tariff August 2013, except where indicated.[692]	Additional notes, including monitoring/prevention of complications
Tablets (mg) (Non-proprietary)	100	28	1.45	0.05	400	0.21	76	Part VIIIA - Basic Prices of Drugs Product List	reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system. Because these reactions may be delayed, patients on long-term treatment should be carefully supervised and not used for chronic rate control. Monitoring includes regular ECG **Maintenance rhythm control:** dose: 200 mg 3 times daily for 1 week reduced to 200 mg twice daily for a further week; maintenance, usually 200 mg daily
Tablets (mg) (Non-proprietary)	200	28	1.9	0.07	400	0.14	50	Part VIIIA - Basic Prices of Drugs Product List	
Injection (mg/mL) (Non-proprietary)	0.03	10	13.5	1.35	0.6025	27.11	9896	BNF August 2013[489]	**Acute rate and rhythm control:** By intravenous infusion initially 5 mg/kg over 20–120 minutes with ECG monitoring; subsequent infusion given if necessary according to response up to max. 1.2 g in 24 hours
Dronedarone			**67.5**	**1.13**		**2.25**	**821**	**Calculated average of list prices below**	**Maintenance rhythm control:** dose 400mg bd •Need regular monitoring of LFT– BNF recommends: before treatment, 1 week and 1 month after initiation of treatment, then monthly for 6 months, then every 3 months for 6 months and periodically thereafter •Initiated in hospital as need specialist input. •Need ECG monitoring every 6 months. •Multiple side effects and deem intensive monitoring.
Tablets (mg) (Sanofi Aventis)	400	20	22.5	1.13	800	2.25	821	BNF August 2013[489]	
	400	60	67.5	1.13	800	2.25	821	BNF August 2013[489]	

	Dosage	Pack size	Net price pack	Price per tablet/unit	Daily dose	Price per day	Price per year	Source: Drug tariff August 2013, except where indicated.[692]	Additional notes, including monitoring/prevention of complications
Class IV									
Diltiazem hydrochloride Tablets(modified release)	**60**	**84**	**10.16**	**0.12**	**270**	**0.54**	**199**	**Part VIIIA products D**	**Maintenance rate control: Calcium rate limiting antagonist:** Comes in modified-release formulation – mainly modified release prescribed as improve compliance. Brands are not interchangeable – brand must be specified when prescribing.
Verapamil hydrochloride			**8.46**	**0.15**		**0.27**	**98**	**Calculated average of list prices below**	**Maintenance rate control: Calcium rate limiting antagonist:** Comes in modified release formulation – mainly modified release used as improve compliance. Dose may be 40-120mg tds (long-acting/ modified release formulation can be used).
Tablets (mg) (Non-proprietary)	40	84	1.73	0.02	240	0.12	45	Part VIIIA products V	
	80	84	2.23	0.03	240	0.08	29	Part VIIIA products V	
	120	28	1.68	0.06	240	0.12	44	Part VIIIA products V	
	160	56	28.2	0.5	240	0.76	276	Part VIIIA products V	
Verapamil hydrochloride injection			**1.1**	**0.55**		**1.64**	**600**	**Calculated average of list prices below**	Not commonly used for acute rate control in UK, used iv for this purpose in USA . Dose = 0.25mg/Kg
Injection (mg/mL) (Dexcel)	2.5	2	1.11	0.56	7.5	1.67	608	BNF August 2013[489]	
Injection (mg/mL) (Abbott)	2.5	2	1.08	0.54	7.5	1.62	591	BNF August 2013[489]	
POSITIVE INOTROPIC DRUGS									
Digoxin			**1.22**	**0.04**		**0.08**	**30**	**Average of below**	**Maintenance rate control:** average dose of 125-250mcg daily Digoxin levels may be requested if digoxin toxicity is suspected. Regular U&E monitoring required. Lots of drug interaction.
Tablets (mg) (Non-proprietary)	0.0625	28	1.49	0.05	0.188	0.16	58	Part VIIIA products D	
	0.125	28	1.09	0.04	0.188	0.06	21	Part VIIIA products D	

	Dosage	Pack size	Net price pack	Price per tablet/unit	Daily dose	Price per day	Price per year	Source: Drug tariff August 2013, except where indicated.[692]	Additional notes, including monitoring/prevention of complications
	0.250	28	1.07	0.04	0.188	0.03	10	Part VIIIA products D	
Injection (mg/mL) (Non-proprietary)	0.25	2	0.66	0.33	0.88	1.16 for first 2 hours, and then as maintenance.		BNF August 2013[489]	**For acute rate control:** Emergency loading dose, by intravenous infusion: 0.75–1 mg over at least 2 hours then maintenance dose by mouth on the following day. Alternatively can load with oral formulation . Use 250 to 500 micrograms 8hrly over 24 hours then 125-250 micrograms daily thereafter

Abbreviations: BNF = British National Formulary; BD=Twice daily; BP=Blood pressure; ECG=Electro-cardiogram; LFT= Lung function test; LV=Left ventricular; OD=Once daily; Tds= Three times daily; U&E= Urea and electrolytes

Appendix O: How this clinical guideline was updated

O.1 Recommendations that have been deleted

Recommendation in 2006 guideline	Comment
1.2.1.1 In patients with AF without haemodynamic instability for whom cardioversion is indicated: • the advantages and disadvantages of both pharmacological and electrical cardioversion should be discussed with patients before initiating treatment • where AF onset was within 48 hours previously, either pharmacological or electrical cardioversion should be performed • for those with more prolonged AF (onset more than 48 hours previously) electrical cardioversion should be the preferred initial treatment option.	Replaced by: 1.6.7 For people having cardioversion for atrial fibrillation that has persisted for longer than 48 hours, offer electrical (rather than pharmacological) cardioversion. [new 2014]
1.2.2.1 In patients with persistent AF[2], where the decision to perform pharmacological cardioversion using an intravenous antiarrhythmic agent has been made: • in the absence of structural heart disease[3], a Class 1c drug (such as flecainide or propafenone) should be the drug of choice • in the presence of structural heart disease[3], amiodarone should be the drug of choice. [2]Persistent AF does not self-terminate, or lasts longer than 7 days (without cardioversion). [3]Coronary artery disease or left ventricular dysfunction.	Replaced by: 1.6.8 Consider amiodarone therapy starting 4 weeks before and continuing for up to 12 months after electrical cardioversion to maintain sinus rhythm, and discuss the benefits and risks of amiodarone with the person. [new 2014]
1.2.3.1 When patients with AF are to undergo elective electrical cardioversion and there is cause for heightened concern about successfully restoring sinus rhythm (such as previous failure to cardiovert or early recurrence of AF), concomitant amiodarone or sotalol[4] should be given for at least 4 weeks before the cardioversion. [4]Sotalol to be progressively titrated from 80 mg twice daily up to 240 mg twice daily.	Replaced by: 1.6.8 Consider amiodarone therapy starting 4 weeks before and continuing for up to 12 months after electrical cardioversion to maintain sinus rhythm, and discuss the benefits and risks of amiodarone with the person. [new 2014]
1.3.1.1 As some patients with persistent AF will satisfy criteria for either an initial rate-control or rhythm-control strategy (for example, age over 65 but also symptomatic): • the indications for each option should not be regarded as mutually exclusive and the potential advantages and disadvantages of each strategy should be explained to patients before agreeing which to adopt • any comorbidities that might indicate one approach rather than the other should be taken	Replaced by: 1.6.1 Offer rate control as the first-line strategy to people with atrial fibrillation, except in people: • whose atrial fibrillation has a reversible cause • who have heart failure thought to be primarily caused by atrial fibrillation • with new-onset atrial fibrillation • with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm

Recommendation in 2006 guideline	Comment
into account • irrespective of whether a rate-control or a rhythm-control strategy is adopted in patients with persistent AF, appropriate antithrombotic therapy should be used.	• for whom a rhythm control strategy would be more suitable based on clinical judgement. [new 2014]
1.3.1.2 A rate-control strategy should be the preferred initial option in the following patients with persistent AF: • over 65 • with coronary artery disease • with contraindications to antiarrhythmic drugs • unsuitable for cardioversion[5] • without congestive heart failure. [5]Patients unsuitable for cardioversion include those with: contraindications to anticoagulation; structural heart disease (e.g. large left atrium more than 5.5 cm, mitral stenosis) that precludes long-term maintenance of sinus rhythm; a long duration of AF (usually more than 12 months); a history of multiple failed attempts at cardioversion and/or relapses, even with concomitant use of antiarrhythmic drugs or non-pharmacological approaches; an on-going but reversible cause of atrial fibrillation (e.g. thyrotoxicosis).	Replaced by: 1.6.1 Offer rate control as the first-line strategy to people with atrial fibrillation, except in people: • whose atrial fibrillation has a reversible cause • who have heart failure thought to be primarily caused by atrial fibrillation • with new-onset atrial fibrillation • with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm • for whom a rhythm control strategy would be more suitable based on clinical judgement. [new 2014]
1.3.1.3 A rhythm-control strategy should be the preferred initial option in the following patients with persistent AF: • those who are symptomatic • younger patients • those presenting for the first time with lone AF • those with AF secondary to a treated/corrected precipitant • those with congestive heart failure.	Replaced by: 1.6.1 Offer rate control as the first-line strategy to people with atrial fibrillation, except in people: • whose atrial fibrillation has a reversible cause • who have heart failure thought to be primarily caused by atrial fibrillation • with new-onset atrial fibrillation • with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm • for whom a rhythm control strategy would be more suitable based on clinical judgement. [new 2014]
1.3.2.1 An antiarrhythmic drug is not required to maintain sinus rhythm in patients with persistent AF in whom a precipitant (such as chest infection or fever) has been corrected and cardioversion has been performed successfully, providing there are no risk factors for recurrence.	Replaced by: 1.6.10 Assess the need for drug treatment for long-term rhythm control, taking into account the person's preferences, associated comorbidities, risks of treatment and likelihood of recurrence of atrial fibrillation. [new 2014]
1.3.2.2 In patients with persistent AF who require antiarrhythmic drugs to maintain sinus rhythm and who have structural heart disease[3]: • a standard beta-blocker should be the initial treatment option • where a standard beta-blocker is ineffective, contraindicated or not tolerated amiodarone should be used.	Replaced by: 1.6.12 If beta-blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account. [new 2014] 1.6.15 Consider amiodarone for people with left ventricular impairment or heart failure. [new 2014] 1.6.16 Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with

Recommendation in 2006 guideline	Comment
[3]Coronary artery disease or left ventricular dysfunction.	ischaemic or structural heart disease. [new 2014]
1.3.2.3 In patients with persistent AF who require antiarrhythmic drugs to maintain sinus rhythm and who do not have structural heart disease[3] • a standard beta-blocker should be the initial treatment option • where a standard beta-blocker is ineffective, contraindicated or not tolerated - a Class 1c agent or - sotalol[6] should be given. • where other drug classes are ineffective, contraindicated or not tolerated amiodarone should be administered. [3]Coronary artery disease or left ventricular dysfunction. [6]Progressively titrated from 80 mg twice daily up to 240 mg twice daily.	Replaced by: 1.6.10 Assess the need for drug treatment for long-term rhythm control, taking into account the person's preferences, associated comorbidities, risks of treatment and likelihood of recurrence of atrial fibrillation. [new 2014] 1.6.11 If drug treatment for long-term rhythm control is needed, consider a standard beta-blocker (that is, a beta-blocker other than sotalol) as first-line treatment unless there are contraindications. [new 2014] 1.6.12 If beta-blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account. [new 2014]
1.3.3.2 Following successful cardioversion, patients should remain on therapeutic anticoagulation with warfarin (INR 2.5, range 2.0 to 3.0) for a minimum of 4 weeks.	This recommendation has been deleted because the 2014 guideline adopts a different care pathway. The Guideline Development Group did not review this question and are not confident that the evidence remains the same.
1.3.3.3 In patients with persistent AF where cardioversion cannot be postponed for 3 weeks: • heparin should be given and the cardioversion performed, and • warfarin should then be given for a minimum of 4 weeks post cardioversion.	This recommendation has been deleted because the 2014 guideline adopts a different care pathway. The Guideline Development Group did not review this question and are not confident that the evidence remains the same.
1.3.3.4 Anticoagulation should be continued for the long term in patients with AF who have undergone cardioversion where there is a high risk of AF recurrence[7] or where it is recommended by the stroke risk stratification algorithm (see full guideline appendix E, page 47). [7]Factors indicating a high risk of AF recurrence include: a history of failed attempts at cardioversion; structural heart disease (mitral valve disease, left ventricular dysfunction or an enlarged left atrium); a prolonged history of AF (>12 months); previous recurrences of AF.	Replaced by: 1.4.1 Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following: • symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation • atrial flutter • a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. [new 2014] 1.5.3 Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk onto account. [new 2014]
1.3.3.5 In patients with AF of confirmed duration of less than 48 hours undergoing cardioversion, anticoagulation following successful restoration of sinus rhythm is not required.	Replaced by: 1.4.1 Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following: • symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation • atrial flutter • a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. [new 2014]

Recommendation in 2006 guideline	Comment
	1.5.3 Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk onto account. [new 2014]
1.3.3.6 Patients with atrial flutter should be given antithrombotic therapy in the same manner as those with AF.	Replaced by: 1.4.1 Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following: • symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation • atrial flutter • a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. [new 2014] • 1.5.3 Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk onto account. [new 2014]
1.4.1.1 In patients with permanent AF, who need treatment for rate-control: • beta-blockers or rate-limiting calcium antagonists should be the preferred initial monotherapy in all patients • digoxin should only be considered as monotherapy in predominantly sedentary patients.	Replaced by: 1.6.2 Offer either a standard beta-blocker (that is, a beta-blocker other than sotalol) or a rate-limiting calcium-channel blocker as initial monotherapy to people with atrial fibrillation who need drug treatment as part of a rate control strategy. Base the choice of drug on the person's symptoms, heart rate, comorbidities and preferences when considering drug treatment. [new 2014] 1.6.3 Consider digoxin monotherapy for people with non-paroxysmal atrial fibrillation only if they are sedentary (do no or very little physical exercise). [new 2014]
1.4.1.2 In patients with permanent AF, where monotherapy is inadequate: • to control the heart rate only during normal activities, beta-blockers or rate-limiting calcium antagonists should be given with digoxin • to control the heart rate during both normal activities and exercise, rate-limiting calcium antagonists should be given with digoxin.	Replaced by: 1.6.4 If monotherapy does not control symptoms, and if continuing symptoms are thought to be due to poor ventricular rate control, consider combination therapy with any 2 of the following: • a beta-blocker • diltiazem • digoxin. [new 2014]
1.4.2.1 In patients with permanent AF a risk–benefit assessment should be performed and discussed with the patient to inform the decision whether or not to give antithrombotic therapy.	Replaced by: 1.4.3 When discussing the benefits and risks of anticoagulation, explain to the person that: • for most people the benefit of anticoagulation outweighs the bleeding risk • for people with an increased risk of bleeding the benefit of anticoagulation may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important. [new 2014]
1.4.2.2 In patients with permanent AF where antithrombotic therapy is given to prevent strokes and/or thromboembolism (see section 1.8.6): • adjusted-dose warfarin should be given as the most effective treatment • adjusted-dose warfarin should reach a target INR	Replaced by: 1.4.1 Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following: • symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation

Recommendation in 2006 guideline	Comment
of 2.5 (range 2.0 to 3.0) • where warfarin is not appropriate, aspirin should be given at 75 to 300 mg/day • where warfarin is appropriate, aspirin should not be co-administered with warfarin purely as thromboprophylaxis, as it provides no additional benefit.	• atrial flutter • a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. [new 2014] 1.5.3 Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk onto account. [new 2014]
1.5.1.2 In patients with symptomatic paroxysms (with or without structural heart disease[3], including coronary artery disease) a standard beta-blocker should be the initial treatment option. [3]Coronary artery disease or left ventricular dysfunction.	Replaced by: 1.6.11 If drug treatment for long-term rhythm control is needed, consider a standard beta-blocker (that is, a beta-blocker other than sotalol) as first-line treatment unless there are contraindications. [new 2014]
1.5.1.3 In patients with paroxysmal AF and no structural heart disease[3]: • where symptomatic suppression is not achieved with standard beta-blockers, either - a Class 1c agent (such as flecainide or propafenone) or - sotalol[6] should be given • where symptomatic suppression is not achieved with standard beta-blockers, Class 1c agents or sotalol, either - amiodarone or - referral for non-pharmacological intervention (see section 1.9.3) should be considered. [3]Coronary artery disease or left ventricular dysfunction. [6]Progressively titrated from 80 mg twice daily up to 240 mg twice daily.	Replaced by: 1.6.12 If beta-blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account. [new 2014]
1.5.1.4 In patients with paroxysmal AF and coronary artery disease: where standard beta-blockers do not achieve symptomatic suppression, sotalol should be given6 • where neither standard beta-blockers nor sotalol achieve symptomatic suppression, either - amiodarone or - referral for non-pharmacological intervention (see section 1.9.3) should be considered. [6]Progressively titrated from 80 mg twice daily up to 240 mg twice daily.	Replaced by: 1.6.15 Consider amiodarone for people with left ventricular impairment or heart failure. [new 2014]
1.5.1.5 In patients with paroxysmal AF with poor left ventricular function: • where standard beta-blockers are given as part of the routine management strategy and adequately suppress paroxysms, no further treatment for paroxysms is needed • where standard beta-blockers do not adequately suppress paroxysms, either	Replaced by: 1.6.15 Consider amiodarone for people with left ventricular impairment or heart failure. [new 2014]

Recommendation in 2006 guideline	Comment
- amiodarone or - referral for non-pharmacological intervention (see section 1.9.3) should be considered.	
1.5.1.6 Patients on long-term medication for paroxysmal AF should be kept under review to assess the need for continued treatment and the development of any adverse effects.	This recommendation has been deleted because, although the Guideline Development Group reviewed the evidence, they agreed that a recommendation about a specific review for this patient group is not necessary. They agreed that people having long-term drug treatment for atrial fibrillation should already be having regular reviews.
1.5.3.1 Decisions on the need for antithrombotic therapy in patients with paroxysmal AF should not be based on the frequency or duration of paroxysms (symptomatic or asymptomatic) but on appropriate risk stratification, as for permanent AF (see section 1.8.6).	Replaced by: 1.4.1 Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following: • symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation • atrial flutter • a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. [new 2014] • 1.5.3 Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk onto account. [new 2014]
1.6.1.1 In patients with a life-threatening deterioration in haemodynamic stability following the onset of AF, emergency electrical cardioversion should be performed, irrespective of the duration of the AF.	Replaced by: 1.7.1 Carry out emergency electrical cardioversion, without delaying to achieve anticoagulation, in people with life-threatening haemodynamic instability caused by new-onset atrial fibrillation. [new 2014]
1.6.1.2 In patients with non-life-threatening haemodynamic instability following the onset of AF: • electrical cardioversion should be performed • where there is a delay in organising electrical cardioversion, intravenous amiodarone should be used • for those with known Wolff–Parkinson–White syndrome: - flecainide may be used as an alternative for attempting pharmacological cardioversion - atrioventricular node-blocking agents (such as diltiazem, verapamil or digoxin) should not be used.	Replaced by: 1.7.4 If pharmacological cardioversion has been agreed on clinical and resource grounds for new-onset atrial fibrillation, offer: • flecainide or amiodarone if there is no evidence of structural or ischaemic heart disease or • amiodarone if there is evidence of structural heart disease. [new 2014]
1.6.1.3 In patients with known permanent AF where haemodynamic instability is caused mainly by a poorly controlled ventricular rate, a pharmacological rate-control strategy should be used.	Replaced by: 1.7.2 In people with atrial fibrillation presenting acutely with haemodynamic instability, offer rate or rhythm control if the onset of the arrhythmia is less than 48 hours, and commence with rate control in those in whom the duration is greater than 48 hours or is uncertain. [new 2014]
1.6.1.4 Where urgent pharmacological rate-control is indicated, intravenous treatment should be with one	Replaced by: 1.7.2 In people with atrial fibrillation presenting

Recommendation in 2006 guideline	Comment
of the following: • beta-blockers or rate-limiting calcium antagonists • amiodarone, where beta-blockers or calcium antagonists are contraindicated or ineffective.	acutely with haemodynamic instability, offer rate or rhythm control if the onset of the arrhythmia is less than 48 hours, and commence with rate control in those in whom the duration is greater than 48 hours or is uncertain. [new 2014]
1.6.2.4 In cases of acute AF where the patient is haemodynamically unstable, any emergency intervention should be performed as soon as possible and the initiation of anticoagulation should not delay any emergency intervention.	Replaced by: 1.7.1 Carry out emergency electrical cardioverion, without delaying to achieve anticoagulation, in people with life-threatening haemodynamic instability caused by new-onset atrial fibrillation. [new 2014]
1.8.1.1 In patients with newly diagnosed AF for whom antithrombotic therapy is indicated (see section 1.8.6), such treatment should be initiated with minimal delay after the appropriate management of comorbidities.	Replaced by: 1.4.1 Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following: • symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation • atrial flutter • a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. [new 2014] • 1.5.3 Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk onto account. [new 2014]
1.8.2.1 In all patients with AF who have had an acute stroke, any uncontrolled hypertension should be appropriately managed before antithrombotic therapy is started.	Replaced by: 1.8.1 For guidance on the initial management of stroke and atrial fibrillation see recommendation 1.4.3.1 in 'Stroke' (NICE clinical guideline 68). [new 2014]
1.8.2.2 In patients with AF and an acute stroke: • imaging (CT scan or MRI) should be performed to exclude cerebral haemorrhage • in the absence of haemorrhage, anticoagulation therapy should begin after 2 weeks • in the presence of haemorrhage, anticoagulation therapy should not be given • in the presence of a large cerebral infarction, the initiation of anticoagulation therapy should be delayed.	Replaced by: 1.8.1 For guidance on the initial management of stroke and atrial fibrillation see recommendation 1.4.3.1 in 'Stroke' (NICE clinical guideline 68). [new 2014]
1.8.2.3 In patients with AF and an acute TIA: • imaging (CT scan or MRI) should be performed to exclude recent cerebral infarction or haemorrhage • in the absence of cerebral infarction or haemorrhage, anticoagulation therapy should begin as soon as possible.	Replaced by: 1.8.1 For guidance on the initial management of stroke and atrial fibrillation see recommendation 1.4.3.1 in 'Stroke' (NICE clinical guideline 68). [new 2014]
1.8.3.1 In patients with AF who are either post-stroke, or have had a TIA: • warfarin should be administered as the most effective thromboprophylactic agent • aspirin or dipyridamole should not be administered as thromboprophylactic agents	Replaced by: 1.8.1 For guidance on the initial management of stroke and atrial fibrillation see recommendation 1.4.3.1 in 'Stroke' (NICE clinical guideline 68). [new 2014]

Recommendation in 2006 guideline	Comment
unless indicated for the treatment of comorbidities or vascular disease.	
1.8.3.2 Treatment of post-stroke or post-TIA patients with warfarin should only begin after treatment of relevant comorbidities (such as hypertension) and assessment of the risk–benefit ratio.	Replaced by: 1.8.1 For guidance on the initial management of stroke and atrial fibrillation see recommendation 1.4.3.1 in 'Stroke' (NICE clinical guideline 68). [new 2014]
1.8.4.1 Patients with asymptomatic AF should receive thromboprophylaxis as for symptomatic AF (refer to section 1.3.3 for persistent AF, section 1.4.2 for permanent AF and section 1.5.3 for paroxysmal AF).	Replaced by: 1.4.1 Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following: • symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation • atrial flutter • a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. [new 2014] • 1.5.3 Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk onto account. [new 2014]
1.8.5.1 Both the antithrombotic benefits and the potential bleeding risks of long-term anticoagulation should be explained to and discussed with the patient.	Replaced by: 1.4.3 When discussing the benefits and risks of anticoagulation, explain to the person that: • for most people the benefit of anticoagulation outweighs the bleeding risk • for people with an increased risk of bleeding the benefit of anticoagulation may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important. [new 2014]
1.8.5.2 The assessment of bleeding risk should be part of the clinical assessment of patients before starting anticoagulation therapy. Particular attention should be paid to patients who: • are over 75 years of age • are taking antiplatelet drugs (such as aspirin or clopidogrel) or non-steroidal anti-inflammatory drugs • are on multiple other drug treatments (polypharmacy) • have uncontrolled hypertension • have a history of bleeding (for example, peptic ulcer or cerebral haemorrhage) • have a history of poorly controlled anticoagulation therapy.	Replaced by: 1.4.2 Use the HAS-BLED score to assess the risk of bleeding in people who are starting or have started anticoagulation. Offer modification and monitoring of the following risk factors: • uncontrolled hypertension • poor control of international normalised ratio (INR) ('labile INRs') • concurrent medication, for example concomitant use of aspirin or a non-steroidal anti-inflammatory drug (NSAID) • harmful alcohol consumption. [new 2014]
1.8.6.1 The stroke risk stratification algorithm (full guideline appendix E) should be used in patients with AF to assess their risk of stroke and thromboembolism, and appropriate thromboprophylaxis given.	Replaced by: 1.4.1 Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following: • symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation • atrial flutter • a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. [new 2014]

Recommendation in 2006 guideline	Comment
	1.5.2 Offer anticoagulation to people with a CHA_2DS_2-VASc score of 1 and take bleeding risk onto account. [new 2014]
1.8.6.2 Risk stratification should be reconsidered whenever individual risk factors are reviewed.)	Replaced by: 1.5.17 For people who are not taking an anticoagulant because of bleeding risk or other factors, review stroke and bleeding risks annually, and ensure that all reviews and decisions are documented. [new 2014]
1.9.1.1 In patients with AF who require long-term anticoagulation, self-monitoring should be considered if preferred by the patient and the following criteria are met: the patient is both physically and cognitively able to perform the self-monitoring test, or in those cases where the patient is not physically or cognitively able to perform self-monitoring, a designated carer is able to do so an adequate supportive educational programme is in place to train patients and/or carers the patient's ability to self-manage is regularly reviewed the equipment for self-monitoring is regularly checked via a quality control programme.	This recommendation has been deleted and the following cross reference added: NICE is developing diagnostics guidance Self-monitoring coagulation status in people on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease: point-of-care coagulometers (the CoaguChek XS system and the INRatio2 PT/INR monitor) (publication expected August 2014)
1.9.2.1 Following successful cardioversion of AF routine follow-up to assess the maintenance of sinus rhythm should take place at 1 month and 6 months.	This recommendation has been deleted because the Guideline Development Group reviewed a question on monitoring and made new recommendations on review.
1.9.2.2 At the 1-month follow-up the frequency of subsequent reviews should be tailored to the individual patient taking into account comorbidities and concomitant drug therapies.	This recommendation has been deleted because the Guideline Development Group reviewed a question on monitoring and made new recommendations on review.
1.9.2.3 At each review the clinician should take the opportunity to re-assess the need for, and the risks and benefits of, continued anticoagulation.	This recommendation has been deleted because the Guideline Development Group reviewed a question on monitoring and made new recommendations on review.
1.9.2.4 At 6 months, if patients remain in sinus rhythm and have no other need for hospital follow-up, they should be discharged from secondary care with an appropriate management plan agreed with their GP.	This recommendation has been deleted because the Guideline Development Group reviewed a question on monitoring and made new recommendations on review.
1.9.2.5 Patients should be advised to seek medical attention if symptoms recur.	This recommendation has been deleted because the Guideline Development Group reviewed a question on monitoring and made new recommendations on review.
1.9.2.6 Any patient found at follow-up to have relapsed into AF should be fully re-evaluated for a rate-control or rhythm-control strategy (see section 1.3.1).	This recommendation has been deleted because the Guideline Development Group reviewed a question on monitoring and made new recommendations on review.
1.9.3.1 Referral for further specialist intervention (for example, pulmonary vein isolation, pacemaker therapy, arrhythmia surgery, atrioventricular	Replaced by: 1.2.1 Offer people with atrial fibrillation a personalised package of care. Ensure that the

Recommendation in 2006 guideline	Comment
junction catheter ablation or use of atrial defibrillators) should be considered in the following patients: • those in whom pharmacological therapy has failed • those with lone AF • those with ECG evidence of an underlying electrophysiological disorder (such as Wolff–Parkinson–White syndrome).	package of care is documented and delivered, and that it includes: • stroke awareness and measures to prevent stroke • rate control • assessment of symptoms for rhythm control • who to contact for advice if needed • psychological support if needed • up-to-date and comprehensive education and information on: • cause, effects and possible complications of atrial fibrillation • management of rate and rhythm control • anticoagulation • practical advice on anticoagulation in line with recommendation 1.3.1 in 'Venous thromboembolic diseases' (NICE clinical guideline 144) • support networks (for example, cardiovascular charities). [new 2014] 1.2.2 NICE has produced guidance on the components of good patient experience-in adult NHS services. Follow the recommendations in Patient experience in adult NHS services (NICE clinical guidance 138). [new 2014] 1.3.1 Refer people promptly[2] at any stage if treatment fails to control the symptoms of atrial fibrillation and referral for more specialised management is needed. [new 2014] [2]The Guideline Development Group defined 'promptly' as no longer than 4 weeks after the final failed treatment or no longer than 4 weeks after recurrence of atrial fibrillation following cardioversion when further specialised management is needed.
1.9.3.2 The reasons for referral for specialist intervention should be explained and discussed with the patient.	Replaced by: 1.2.1 Offer people with atrial fibrillation a personalised package of care. Ensure that the package of care is documented and delivered, and that it includes: • stroke awareness and measures to prevent stroke • rate control • assessment of symptoms for rhythm control • who to contact for advice if needed • psychological support if needed • up-to-date and comprehensive education and information on: ○ cause, effects and possible complications of atrial fibrillation ○ management of rate and rhythm control ○ anticoagulation ○ practical advice on anticoagulation in line with recommendation 1.3.1 in 'Venous

Recommendation in 2006 guideline	Comment
	thromboembolic diseases' (NICE clinical guideline 144) ○ support networks (for example, cardiovascular charities). [new 2014] 1.2.2 NICE has produced guidance on the components of good patient experience-in adult NHS services. Follow the recommendations in Patient experience in adult NHS services (NICE clinical guidance 138). [new 2014] 1.3.1 Refer people promptly[2] at any stage if treatment fails to control the symptoms of atrial fibrillation and referral for more specialised management is needed. [new 2014] [2]The Guideline Development Group defined 'promptly' as no longer than 4 weeks after the final failed treatment or no longer than 4 weeks after recurrence of atrial fibrillation following cardioversion when further specialised management is needed.

O.2 Amended recommendation wording (change to meaning)

The evidence has not been reviewed but changes have been made to the recommendation wording that change the meaning. These changes are marked with yellow shading below.

Recommendation in 2006 guideline	Recommendation in current guideline	Reason for change
1.1.4.1 Transthoracic echocardiography (TTE) should be performed in patients with AF: for whom a baseline echocardiogram is important for long-term management, such as younger patients • for whom a rhythm-control strategy that includes cardioversion (electrical or pharmacological) is being considered • in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management (for example, choice of antiarrhythmic drug) • in whom refinement of clinical risk stratification for antithrombotic therapy is needed (see section 1.8.6).	1.1.4 Perform transthoracic echocardiography (TTE) in people with atrial fibrillation: • for whom a baseline echocardiogram is important for long-term management • for whom a rhythm-control strategy that includes cardioversion (electrical or pharmacological) is being considered • in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management (for example, choice of antiarrhythmic drug) • in whom refinement of clinical risk stratification for antithrombotic therapy is needed (see anticoagulation). [2006, amended 2014]	'Such as younger patients' has been removed to ensure that all people with atrial fibrillation are included and not just younger patients, for equality purposes. The cross-reference to section 1.8.6 has been amended to cross-refer to the recommendations on assessment of stroke and bleeding risks and interventions to prevent stroke in the 2014 guideline.
1.1.4.2 Do not routinely perform TTE solely for the purpose of further	1.1.5 Do not routinely perform TTE solely for the purpose of further	The cross-reference to the stroke risk stratification

Recommendation in 2006 guideline	Recommendation in current guideline	Reason for change
stroke risk stratification in people with atrial fibrillation for whom the need to initiate anticoagulation therapy has already been agreed on appropriate clinical criteria (see stroke risk stratification algorithm in the full guideline).	stroke risk stratification in people with atrial fibrillation for whom the need to initiate anticoagulation therapy has already been agreed on appropriate clinical criteria (see anticoagulation). [2006, amended 2014]	algorithm has been amended to cross-refer to the recommendations on assessment of stroke and bleeding risk and interventions to prevent stroke in the 2014 guideline.
1.2.6.1 In people with acute atrial fibrillation who are receiving no, or sub therapeutic, anticoagulation therapy: • in the absence of contraindications, heparin should be started at initial presentation • continue heparin until a full assessment has been made and appropriate antithrombotic therapy has been started, based on risk stratification (see section 1.8.6).	1.7.7 In people with new-onset atrial fibrillation who are receiving no, or sub therapeutic, anticoagulation therapy: • in the absence of contraindications, offer heparin at initial presentation • continue heparin until a full assessment has been made and appropriate antithrombotic therapy has been started, based on risk stratification (see anticoagulation). [2006, amended 2014]	'Acute' has been amended to 'new-onset' for clarification and consistency. In the 2006 guideline 'acute' denotes new-onset atrial fibrillation. In the 2014 guideline 'acute' refers to the nature of the presentation of atrial fibrillation. The cross-reference to section 1.8.6 has been amended to cross-refer to the recommendations on assessment of stroke and bleeding risk and interventions to prevent stroke in the draft 2014 guideline.
1.6.2.2 In patients with a confirmed diagnosis of acute AF of recent onset (less than 48 hours since onset), oral anticoagulation should be used if: • stable sinus rhythm is not successfully restored within the same 48-hour period following onset of acute AF; or • there are factors indicating a high risk of AF recurrence; or • it is recommended by the stroke risk stratification algorithm (see appendix E, page 47).	1.7.8 In people with a confirmed diagnosis of acute atrial fibrillation of recent onset (less than 48 hours since onset), offer oral anticoagulation if: • stable sinus rhythm is not successfully restored within the same 48-hour period following onset of atrial fibrillation or • there are factors indicating a high risk of atrial fibrillation recurrence[8] or • it is recommended in anticoagulation [2006, amended 2014] [8]Factors indicating a high risk of atrial fibrillation recurrence include: a history of failed attempts at cardioversion; structural heart disease (mitral valve disease, left ventricular dysfunction or an enlarged left atrium); a prolonged history of atrial fibrillation (more than 12 months); previous recurrences of atrial fibrillation	'Acute' has been deleted for clarification and consistency. In the 2006 guideline 'acute' denotes new-onset atrial fibrillation. In the 2014 guideline 'acute' refers to the nature of the presentation of atrial fibrillation. The cross-reference to the stroke risk stratification algorithm has been amended to cross-refer to the recommendations on assessment of stroke and bleeding risk and interventions to prevent stroke in the 2014 guideline.
1.3.3.1 Before cardioversion,	1.7.5 In people with atrial fibrillation	The 2006 recommendation

Recommendation in 2006 guideline	Recommendation in current guideline	Reason for change
patients should be maintained on therapeutic anticoagulation with warfarin (INR 2.5, range 2.0 to 3.0) for a minimum of 3 weeks.	in whom the duration of the arrhythmia is greater than 48 hours or uncertain and considered for long term rhythm control, delay cardioversion until they have been maintained on therapeutic anticoagulation for a minimum of 3 weeks. During this period offer rate control as appropriate. [2006, amended 2014]	has been updated to make the recommendation more consistent with the pathway of the updated 2014 guideline.
1.6.2.3 In patients with acute AF where there is uncertainty over the precise time since onset, oral anticoagulation should be used, as for persistent AF (see section 1.3.3).	1.7.9 In people with new-onset atrial fibrillation where there is uncertainty over the precise time since onset, offer oral anticoagulation as for persistent atrial fibrillation (see recommendation 1.4.3). [2006, amended 2014]	'Acute' has been amended to 'new-onset' for clarification and consistency. In the 2006 guideline 'acute' denotes new-onset atrial fibrillation. In the 2014 guideline 'acute' refers to the nature of the presentation of atrial fibrillation. The cross-reference to the stroke risk stratification algorithm has been amended to cross-refer to the recommendations on assessment of stroke and bleeding risk and interventions to prevent stroke in the draft 2014 guideline.
1.7.1.1 In patients undergoing cardiothoracic surgery: • the risk of postoperative AF should be reduced by the administration of one of the following: - amiodarone - a beta-blocker - sotalol - a rate-limiting calcium antagonist • digoxin should not be used.	1.9.1 In people undergoing cardiothoracic surgery: • reduce the risk of postoperative atrial fibrillation by offering 1 of the following: - amiodarone - a standard beta-blocker (that is, a beta-blocker other than sotalol) - a rate-limiting calcium antagonist. • do not offer digoxin. [2006, amended 2014]	Deleted option of sotalol in the 2014 guideline recommendation because it is no longer recommended as an option.
1.7.1.2 In patients undergoing cardiac surgery on pre-existing beta-blocker therapy, this treatment should be continued unless contraindications develop (such as post-operative bradycardia or hypotension).	1.9.2 In people undergoing cardiothoracic surgery on pre-existing beta-blocker therapy, continue this treatment unless contraindications develop (such as postoperative bradycardia or hypotension). [2006, amended 2014]	'Cardiac' has been amended to 'cardiothoracic' for clarification and consistency. The Guideline Development Group assumes that no distinction between the 2 terms was

Recommendation in 2006 guideline	Recommendation in current guideline	Reason for change
		intended in the 2006 guideline.
1.7.2.2 Unless contraindicated, post-operative AF following non-cardiothoracic surgery should be managed as for acute-onset AF with any other precipitant.	1.9.4 Unless contraindicated, manage postoperative atrial fibrillation following non-cardiothoracic surgery as for new-onset atrial fibrillation with any other precipitant. [2006, amended 2014]	'Acute' has been deleted for clarification and consistency. In the 2006 guideline 'acute' denotes new-onset atrial fibrillation. In the 2014 draft guideline 'acute' refers to the nature of the presentation of atrial fibrillation.

O.3 Changes to recommendation wording for clarification only (no change to meaning)

Recommendation numbers in current guideline	Comment
All recommendations except those labelled [new 2014]	Recommendations have been edited into the direct style (in line with current NICE style for recommendations in clinical guidelines) where possible. Yellow highlighting has not been applied to these changes.
1.6.17	A footnote defining a "pill-in-the-pocket" strategy has been added for clarity.
1.7.7	'in the absence of contraindications, start heparin at initial presentation' has been amended to: 'in the absence of contraindications, offer heparin at initial presentation' in line with current NICE style for recommendations in clinical guidelines.
1.7.7	'In patients with a confirmed diagnosis of acute AF of recent onset (less than 48 hours since onset), oral anticoagulation should be used if:' has been amended to: 'In people with a confirmed diagnosis of acute atrial fibrillation of recent onset (less than 48 hours since onset), offer oral anticoagulation if:' in line with current NICE style for recommendations in clinical guidelines.
1.7.8	'In patients with acute AF where there is uncertainty over the precise time since onset, oral anticoagulation should be used as for persistent AF (see section 1.3.3).' has been amended to: 'In people with new-onset atrial fibrillation where there is uncertainty over the precise time since onset, offer oral anticoagulation as for persistent atrial fibrillation (see section 1.3.3).' in line with current NICE style for recommendations in clinical guidelines.
1.7.9	'In patients with acute AF where there is uncertainty over the precise time since onset, oral anticoagulation

Recommendation numbers in current guideline	Comment
	should be used as for persistent AF (see section 1.3.3).' has been amended to: 'In people with new-onset atrial fibrillation where there is uncertainty over the precise time since onset, offer oral anticoagulation as for persistent atrial fibrillation (see section 1.4 Assessment of stroke and bleeding risks and section 1.5 Interventions to prevent).' in line with current NICE style for recommendations in clinical guidelines.
1.9.1	'the risk of post-operative AF should be reduced by the administration of one of the following' has been amended to: 'reduce the risk of postoperative atrial fibrillation by offering 1 of the following' in line with current NICE style for recommendations in clinical guidelines.
1.9.1	'digoxin should not be used' has been amended to: 'do not offer digoxin' in line with current NICE style for recommendations in clinical guidelines.
1.9.3	'a rhythm-control strategy should be the initial management option' has been amended to: 'offer a rhythm-control strategy as the initial management option' in line with current NICE style for recommendations in clinical guidelines.
1.9.5	'the appropriate use of antithrombotic therapy and correction of identifiable precipitants (such as electrolyte imbalance or hypoxia) is recommended' has been amended to: 'use appropriate antithrombotic therapy and correct identifiable precipitants (such as electrolyte imbalance or hypoxia)' in line with current NICE style for recommendations in clinical guidelines.

Appendix P: Research recommendations

P.1 Research question: What is the clinical and cost effectiveness of cognitive behavioural therapy (CBT) compared with usual care for people with newly diagnosed atrial fibrillation?

Why this is important

There is currently little evidence to support psychological care for people with atrial fibrillation. Assessing the effectiveness of CBT in lowering people's levels of anxiety, reducing episodes of planned or unplanned care and improving their quality of life will help determine whether CBT should be an essential component of atrial fibrillation services. [new 2014]

Criteria for selecting high-priority research recommendations:

PICO question	What is the clinical and cost effectiveness of cognitive behavioural therapy (CBT) compared with usual care for people with newly diagnosed atrial fibrillation?
Importance to patients or the population	AF is a life-complicating condition affecting patient quality of life. Currently there is a limited choice of options in reducing symptoms for persistent AF patients, and none that deal with the anxiety that can increase AF symptoms. AF symptoms intrude significantly in the everyday lives of patients. For this patient group, CBT for the management of anxiety and symptoms may offer improved quality of life, improved psychological state, reduced anxiety and depression, and a reduced consumption of healthcare.
Relevance to NICE guidance	Positive results of CBT could herald a change to NICE guidance around support for patients suffering with persistent AF, and the evidence could be used to develop support for other long-term conditions.
Relevance to the NHS	Financial advantage in time based on patients' reduced consumption of healthcare, for example reduction in resources from readmissions due to anxiety, lack of awareness of the condition and the potential for self-management.
National priorities	CBT is recommended by NHS Local in the management of anxiety, panic attacks and stress. The National Service Framework for Cardiac Conditions states that "living with AF puts patients at a greater risk of psychological problems". The NSF also recommends a range of "stepped psychologically informed care".
Current evidence base	Thrall, Lip et al (2007)[859] showed that 33% of AF patients have elevated levels of anxiety and depression. Anxiety and depression are related to increased mortality, morbidity and consumption of healthcare. McCabe[665] reported that "..psychological distress in the form of depression and/or anxiety uniquely contributed to greater AF symptoms severity, diminished HRQOL and recurrence of AF…and its presence is related to adverse outcomes". Lewin et al[589] reported a reduction in anxiety levels and depression and fewer unplanned admissions in a patient group who received CBT rehabilitation post cardioverter-defibrillator implantation. There is no research that examines the potential link between provision of CBT and improved psychological state/reduction of symptoms in patients with persistent AF, although CBT is recommended by the NHS in the management of anxiety, panic attacks and stress.
Equality	Patients with AF have very few options available to them to manage their symptoms. CBT could be available to all patients according to their choice. This is an intervention not currently available for AF patients. Patients presenting to their GP with anxiety are routinely offered CBT, but patients with AF are not, although many symptoms of AF mirror those of anxiety.
Study design	RCT/cohort study with groups selected for usual care vs programme of CBT for

	patients with newly diagnosed AF.
Feasibility	There is the potential for a well-designed study to be carried out in multiple centres across the UK.
Other comments	It would also be important to opportunistically assess AF patients for psychological problems and establish appropriate protocols for providing suitable psychological support and care – it may be that CBT is not a solution for every psychological issue presented.
Importance	There is currently little evidence to support the intensive input that is required to delivery psychological care for patients with atrial fibrillation. Assessing the impact that CBT can have on patients with AF in terms of e.g. their levels of anxiety, quality of life, and episodes of planned or unplanned care, will aid the assessment of whether such input is cost effective and therefore an essential component for the developing atrial fibrillation services.

P.2 Research question: Can routine data from UK primary care databases clarify stroke risk in people with atrial fibrillation according to baseline risk factors and treatment?

Why this is important

There are several scores available to predict stroke risk in people with atrial fibrillation. Most have been derived from secondary care populations and validated in non-UK populations. The availability of routine primary care databases such as CPRD (Clinical Practice Research database) and THIN (The Health Improvement Network) provides the opportunity to assess these risk tools, and the impact of treatment on risk, in a non-selected UK population.

A prospective cohort study should be carried out to establish baseline risk in people with atrial fibrillation, using established risk scores, and to prospectively evaluate the outcomes, of stroke and mortality, taking into account treatment and changes in risk over time.

The results would help determine the most effective means of providing stroke prevention in a non-selected general practice population and establish the discriminatory value of existing stroke risk scores. [new 2014]

Criteria for selecting high-priority research recommendations:

PICO question	Can routine data from UK primary care databases clarify stroke risk in people with atrial fibrillation according to baseline risk factors and treatment?
Importance to patients or the population	There are several scores available to predict stroke risk in patients with atrial fibrillation. These have generally been derived in secondary care populations and been validated in non-UK populations. The availability of routine primary care databases (CPRG, THIN) provides the opportunity to assess these risk tools in a non-selected UK population and can also assess the impact of treatment on modifying risk.
Relevance to NICE guidance	It will provide further evidence on the utility of stroke risk stratification.
Relevance to the NHS	It would define the need (or not) for increased use of thromoprophylaxis in atrial fibrillation. The outcome would also help to guide the most effective use of the QOF resource.
National priorities	The question is relevant to stroke prevention.
Current evidence base	The study will help to extend the current evidence base on stroke prevention to a more general primary care population.

Equality	None.
Study design	Prospective cohort study to establish baseline risk of patients with atrial fibrillation according to established risk scores, and to prospectively evaluate outcomes, specifically stroke and mortality, taking into account treatment and change is risk with time.
Feasibility	The study is feasible based on existing primary care database systems.
Other comments	This would be the first prospective study to evaluate existing current stroke-risk scores.
Importance	The study would help address the most effective means of providing stroke prevention in a non-selected general practice population, and establish the discriminatory value of existing stroke-risk scores.

P.3 Research question: Do people with atrial fibrillation whose anticoagulant control is poor or is predicted to be poor with warfarin benefit from changing to one of the non-vitamin K antagonists (non-VKA) oral anticoagulants?

Why this is important

Trials of the non-VKA oral anticoagulants have shown that the degree of benefit of these agents compared with warfarin may depend on the time in therapeutic range (TTR) of the warfarin group. These trials assessed the degree of benefit in relation to the mean TTR for the warfarin group in that country.

However, the inference of benefit is based on a number of assumptions. It is unclear that the population TTR can be extrapolated to decision-making in an individual. If, for example, an individual's low TTR is a result of poor compliance, it is unlikely that compliance will improve with a non-VKA oral anticoagulant and uncertain whether a non-VKA oral anticoagulant will offer any benefit. Moreover, the threshold of TTR at which a non-VKA oral anticoagulant might offer benefit is unclear. The same question can be extended to include people before they start warfarin treatment, using criteria that prospectively identify those likely to have poor control on warfarin.

A study with 2 arms should be carried out. The first arm should randomise people with atrial fibrillation, whose control is poor with warfarin, to either continue warfarin treatment or change to a non-VKA oral anticoagulant. The second arm should randomise people newly diagnosed as having atrial fibrillation, who have not previously had anticoagulant therapy and in whom poor anticoagulant control is predicted (using the SAMe-TT_2R_2 score[a]), to have treatment with either warfarin or a non-VKA oral anticoagulant. Outcomes would include stroke and other thromboembolic complications, major haemorrhage and death. [new 2014]

Criteria for selecting high-priority research recommendations:

PICO question	Do people with atrial fibrillation whose anticoagulant control is poor or is predicted to be poor with warfarin benefit from changing to one of the novel oral anticoagulants?

[a] The SAMe-TT_2R_2 score is defined as: 'Sex female, Age <60 years, Medical history (at least 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), Treatment (interacting drugs, for example, amiodarone for rhythm control): all 1 point; plus current Tobacco use (2 points) and Race (non-Caucasian, 2 points)'.

Apostolakis S, Sullivan RM, Olshansky B et al. (2013) Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score. Chest 144: 1555–63.

Importance to patients or the population	Approximately one third of patients receiving warfarin have poor anticoagulant control, defined as a TTR < 65%. Potentially these patients might benefit from changing to a non-VKA oral anticoagulant through more effective stroke prevention and also through reduction in bleeding complications. Moreover recent research has shown that patients likely to have poor control can be identified even prior to commencing warfarin
Relevance to NICE guidance	Existing NICE guidance on non-VKA oral anticoagulants states that non-VKA oral anticoagulants "…..should be considered in light of their level of international normalised ratio (INR) control", but with no additional information on thresholds or potential benefits. This research protocol would address both issues.
Relevance to the NHS	The non-VKA oral anticoagulants represent an additional expense over conventional anticoagulation. This protocol would help to inform the cost effectiveness of switching people from conventional anticoagulation to a non-VKA oral anticoagulant
National priorities	No
Current evidence base	There is evidence at the population level that populations of patients with poor anticoagulant control on warfarin derive more benefit from non-VKA oral anticoagulants than those with good control. However, one cannot firmly extrapolate from this to deduce that individual patients will benefit from changing therapy or at what level of anticoagulant control. Hence the protocol will expand on recommendation xxx, of what options to consider in patients with poor anticoagulant control on warfarin therapy. It will also help to identify whether patients identified to be likely to have poor control prior to commencing warfarin would benefit from a non-VKA oral anticoagulant.
Equality	There are no equality issues
Study design	The protocol proposes a parallel RCT. In one limb, patients with AF and known poor anticoagulant control whilst on warfarin (TTR <65%) would be randomised to continue warfarin or to switch to a non-VKA oral anticoagulant. In the second limb, newly diagnosed patients with AF who have not previously received warfarin therapy would undergo risk scoring (using the validated SAMe-TT2R2 score*) and those predicted to have poor INR control on warfarin would undergo randomisation to warfarin or a non-VKA oral anticoagulant.
Feasibility	The protocol would require a large multi-centre study involving many thousands of patients. It could be based on a single non-VKA oral anticoagulant and run in conjunction with a pharmaceutical company, or could be based on generic non-VKA oral anticoagulant therapy and run independently of the pharmaceutical industry.
Other comments	*SAMe-TT2R2 is an acronym for female Sex, Age (<60 years), Medical history (at least two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), Treatment (interacting drugs, e.g. amiodarone for rhythm control) (all one point), as well as current Tobacco use (two points) and Race (non-white people; two points). Apostolakis et al Chest. 2013;144(5):1555-63.
Importance	We view that his protocol would be of high importance. In England alone approximately half a million patients are anticoagulated for AF, the vast majority taking warfarin. Of these one third will have poor anticoagulant control and might potentially benefit from changing to a non-VKA oral anticoagulant.

P.4 Research question: What is the comparative effectiveness of the 3 main drug classes used for rate control (beta-blockers, calcium-

channel blockers and digoxin) in people aged 75 years and over with atrial fibrillation in controlling symptoms, improving quality of life and reducing morbidity and mortality?

Why this is important

Atrial fibrillation is the most common arrhythmia in people aged 75 and over, with a prevalence of more than 15%. This guideline recommends rate control of atrial fibrillation as the treatment of choice. However, there are no good-quality randomised controlled trials (RCTs) comparing the 3 main drug classes (beta-blockers, calcium-channel blockers and digoxin) used for rate control, and no studies specifically addressing people aged 75 and over.

Drug treatment for rate control in people aged 75 and over with atrial fibrillation is particularly challenging because of comorbidities. For example, heart failure is prevalent in this age group but RCTs comparing beta-blockers with digoxin in people aged over 70 are of low quality. Although these RCTs suggest no advantage of beta-blockers compared with digoxin for rate control, and an increased incidence of hospitalisations with heart failure, current guidelines propose beta-blockers as first-line therapy for rate control. Other conditions such as chronic kidney disease, ischaemic heart disease, valvular heart disease, concomitant heart conduction disorders, dementia, pulmonary disease, hypo- and hypertension and frailty might also affect the choice of drugs for this age group. Optimal treatments for people with these comorbidities are not known.

Optimising drug treatment for atrial fibrillation in this age group has the potential to reduce hospitalisations and the need for services such as GPs and specialist nurses to manage secondary symptoms, with consequent economic benefits. [new 2014]

Criteria for selecting high-priority research recommendations:

PICO question	What is the comparative effectiveness of the 3 main drug classes used for rate control (beta-blockers, calcium-channel blockers and digoxin) in people with atrial fibrillation aged 75 and over in controlling symptoms, improving quality of life and reducing morbidity and mortality?
Importance to patients or the population	Atrial fibrillation is the commonest arrhythmia in the over 75s with a prevalence of over 15%. The 2013 revised NICE guidelines recommend rate control of AF as the treatment of choice over rhythm control yet there are no good quality randomised controlled trials comparing the three main drug classes (B blockers, calcium channel blockers and digoxin) used for rate control. Guidelines recommending one drug group in preference to another are based on lower quality studies or studies determining the effects of these drugs in other cardiovascular conditions or from physiological studies of the effects of these drugs on humans during rest and exercise. There are no studies in this area specifically addressing older adults over 75. The optimal choice of medication for AF rate control in the over 75s is particularly challenging due to co-morbidities: heart failure is prevalent, the current very low/ low quality randomised controlled trials in patients with heart failure and AF over 70 suggest no advantage of B blockers over digoxin in rate control and an increased incidence of hospitalisations with heart failure. Yet guidelines propose B blockers as first line therapy for rate control. Other conditions such as chronic kidney disease, ischaemic heart disease, valvular heart disease, concomitant heart conduction disorders, dementia, pulmonary disease, hypo- and hypertension and frailty might also affect the optimal choice of medication for this group. The optimal treatment for people with these comorbidities is currently unknown. The advantages of getting this right go beyond symptoms, quality of life, morbidity and mortality for the individual patient; over 75s are major users of NHS services, optimising drug therapy for this condition has the potential to

	reduce hospitalisations for secondary symptoms and utilisation of community services (GPs, community specialist nurses etc.) with consequent economic benefits.
Relevance to NICE guidance	The results of such a study would provide an evidence based approach to drug treatment for rate control of AF in patients over 75 years of age (the majority of AF patients). Furthermore additional recommendations for those with co-morbidities including heart failure could be included in new guidelines.
Relevance to the NHS	1. Improved patient outcomes for a large group of patients 2. Potential economic benefits of; • cheaper first line drug being recommended • reduction in hospitalisations for secondary symptoms • utilisation of community services (GPs, community specialist nurses etc.)
National priorities	This research would be in line with • the National agenda to make health care more suitable for the older multi-morbid population rather than younger people with single conditions. • National and International emphasis to include older people and those with co-morbidities (more akin to typical patients) in research studies
Current evidence base	As described in the "importance to patients and the population" section there is no good quality evidence base to answer this question. See chapter on rate control in NICE 2013 guidelines.
Equality	This research focuses on older people a group frequently excluded from research yet the majority of patients with this condition.
Study design	Randomised controlled trial comparing drug regimes with pre-planned subgroup analyses to look at the effects of co-morbidities.
Feasibility	A large multi-centre RCT recruiting several thousand patients would be required. With the prevalence of AF in over 75s over 15% recruitment should be feasible in a reasonable time frame. However follow up might need to be for several years. There have been many large cardiological trials that have demonstrated feasibility of this type of study, in particular the Hypertension in the Very Elderly Study that looked at the management of hypertension in the over 80s. The ethical issue of including patients with dementia can be overcome by following the provision within the Mental capacity Act for those with dementia participating in research.
Other comments	This would probably require funding by a large independent research body such as NIHR or MRC.
Importance	High: The research is essential to inform future updates of key recommendations in the guideline.

P.5 Research question: What is the effect of case volume on complications and outcomes after left atrial catheter ablation?

Why this is important

As interest in left atrial catheter ablation for atrial fibrillation increases, more clinicians are taking up this procedure. Many patients want to know whether they will receive a safe and effective treatment. If increased experience and case volume are associated with improved outcomes, the case volume of a centre or a clinician is an easily measurable parameter that people with atrial fibrillation could use to help judge the quality of the procedure they are likely to receive. [new 2014]

Criteria for selecting high-priority research recommendations:

PICO question	What is the effect of case volume on complications and outcomes after left atrial

	catheter ablation?
Importance to patients or the population	Catheter ablation may be better performed in high-volume centres by high volume operators. This may however result in limited access to patients across geographies. Therefore whatever the research outcome it has high relevance to patients.
Relevance to NICE guidance	NICE guidance makes no recommendations on the skill and experience of operators performing catheter ablation because of lack of evidence.
Relevance to the NHS	At present there are no clear data to recommend skill or experience of an operator performing what is recognised as a technically challenging procedure. This has led to the establishments of new AF ablation centres which give patients greater access to therapy. If these smaller/newer centres have equal performance to larger centres, this practice should be encouraged.
National priorities	At present there is interest in rationalizing healthcare and focusing specialised services on fewer sites. This research would be important to inform whether this was justified or not.
Current evidence base	At present the only evidence available are from insurance records in the USA. Here the volume of procedures done by small centres are much lower than would be expected in the UK (<20 vs <50) and as such are not comparable to UK data. The US data does suggest significantly poorer outcomes in low volume centres.
Equality	Smaller centres encourage equality of access across geographies and as such this research will be important to eliminating variations across the country. However if smaller centres do not perform as well, patients may be significantly disadvantaged by their geographical location.
Study design	Retrospective examination of national audit data would be the most cost effective way of investigating this question.
Feasibility	Using NICOR (national institute for cardiovascular outcomes research) would be a highly efficient way of investigating this question.
Other comments	This study would be best funded by the NIHR or charities like the BHF. Industry would have no motive for funding this type of research and may be seen as potentially biasing outcome.
Importance	This research recommendation was considered a high priority research recommendation by the GDG.

Appendix Q: NICE project team

Name	Role
Philip Alderson	Guideline Lead (until October 2012)
Christine Carson	Guideline lead (until February 2013)
Sharon Summers-Ma	Guideline Lead (from March 2013)
Mark Baker	Clinical Adviser
Sarah Dunsdon	Guideline Commissioning Manager (until December 2012)
Clifford Middleton	Guideline Commissioning Manager (until May 2013)
Caroline Kier	Guideline Commissioning Manager (from May 2013)
Jennifer Heaton	Guideline Coordinator (until August 2012)
Andrew Gyton	Guideline Coordinator (until April 2013)
Margaret Ghlaimi	Guideline Coordinator (from May 2013)
Nichole Taske	Technical Lead (until March 2013)
Beth Shaw	Technical Lead (from April 2013)
Jasdeep Hayre	Health Economist
Judy McBride	Editor (until February 2014)
Gareth Haman	Editor (from February 2014)

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