National Clinical Guideline Centre

Atrial Fibrillation

Atrial fibrillation: the management of atrial fibrillation

Clinical guideline

Methods, evidence and recommendations

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Guideline update
NICE's original guideline on atrial fibrillation was published in 2006. It was updated in 2014 and 2021.
See the NICE website for the guideline recommendations and the evidence reviews for the 2021 update.
This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2021.

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Appendices A–S are in a separate file.

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1 Introduction

Atrial fibrillation (AF) is a very common problem. In England alone, approximately 835,000 people have AF.[321] Through its effects on rate and rhythm, it is a major cause of morbidity. Through increasing susceptibility to stroke, it is a major cause of both morbidity and mortality.

Despite the fact that AF is a major population problem, it is not necessarily well managed. Anecdotally, people with AF often describe the inadequate explanations they have been given at the time of first diagnosis both concerning the nature of the problem and the treatment options which are open to them.

This may partly reflect the fact that many doctors, particularly those working in primary care, do not feel confident in AF management. Anticoagulation is a case in point. The 2006 atrial fibrillation NICE Guideline[320] laid down criteria for anticoagulation – yet amongst patients with known AF, only 55% of those fulfilling the 2006 criteria for anticoagulant therapy currently receive it.[106] Research into the shortfall in anticoagulant uptake indicates that it cannot be adequately explained by either bleeding risk or co-morbidities.[395] The attitude of healthcare professionals and the perceived risk of anticoagulation could also be major factors limiting uptake.

The shortfall in the prescribing of anticoagulants to patients with AF was clearly seen in the Sentinel Stroke National Audit Programme of the Royal College of Physicians.[386] Of 11,939 patients admitted with stroke to hospitals in England, Wales and Northern Ireland in the first 3 months of 2013, approximately one fifth were in AF on admission. Of these only 36% were receiving an anticoagulant. Yet 38% were on an antiplatelet drug as sole antithrombotic therapy and 26 % were on no antithrombotic treatment.

The rate and rhythm management of AF is also often perceived to be difficult. In discussions informing the scope of this guideline, the classification of AF into paroxysmal, persistent and permanent was considered to be a barrier to implementation of rate and rhythm care. While this classification is a natural sub-division which does help to inform management, it is important that it should not obscure the common underlying principles of heart rate and rhythm care which apply to the generality of AF patients.

This guideline seeks to address these issues. The question of how best to provide a patient with a focussed care package including patient information and treatment options is considered. Stroke prevention is considered in detail both in terms of treatment strategies, risk thresholds and risk scoring and options for treatment. Finally rate and rhythm management are considered, in as far as possible based on the totality of AF, rather than on individual sub-categories. In considering rate and rhythm management, it is emphasised that patient symptoms should be the driver to timely consideration of alternative escalating management options.

No clinical guideline can ever be complete and the constraints of the guideline process have meant that we have needed to focus on a number of specific areas. The current guideline is a partial update of the 2006 guideline. The evidence relating to some sections of the 2006 guideline, most particularly AF diagnosis, has not been updated and the original recommendations have been incorporated unchanged. It is also the case that there has been very rapid progress in a number of areas relating to AF in recent years. This has been reflected in recent NICE technology appraisals on dronedarone,[323] dabigatran,[324] rivaroxaban[327] and apixaban.[327] The evidence and the recommendations relating to these drugs have not been reconsidered in the current guideline. The existing technology appraisal recommendations have been incorporated into the updated guideline.

We have not sought to distinguish which aspects of care should take place in specific settings. We recognise that models of care vary greatly both locally and nationally and that in many places aspects of AF care which might hitherto have been regarded as most suited to secondary care are now being undertaken in primary care. It seems likely that this trend will continue. We have therefore tried to avoid imposing artificial boundaries. The target audience of the guideline is any healthcare professional working in any setting who is involved in caring for patients with AF.

The guideline has been developed by the National Clinical Guideline Centre (NCGC) working in association with a group of healthcare professionals, representing primary, secondary and tertiary

care, whose common interest lies in improving AF management. The recommendations are based on review of the evidence, but where the evidence is less than clear-cut, the guideline represents the combined opinion of the group as to best clinical practice. Delivering patient centred care has been a central theme throughout.

We very much hope that the guideline will prove of value to other workers in the field and above all that it will lead to an improvement in the education, support and management of people with AF.

1.1 Prevalence of AF

AF is becoming more prevalent.[205,379] Since the 2006 guideline, these estimates suggest a substantial increase in prevalence of AF. One way of accessing data on prevalence of AF is through the Quality and Outcomes Framework (QOF) for general practices in England. In 2011 /2012 the QOF estimate of AF prevalence was 1.48%.[194]

However, it is possible that data from QOF underestimates true prevalence due to exclusion of some patients. An alternative recent estimate of prevalence was provided by the GRASP (Guidance on Risk Assessment and Stroke Prevention) risk assessment tool of NHS Improvement, which provided an estimate of prevalence of 1.76%.[106] This was based on 1857 general practices in England, representing 21% of the population, who voluntarily uploaded data on AF management between 2009 and 2012. The GRASP tool assessed patients with AF at any time in their history. When patients with an AF resolved code were excluded from consideration, prevalence was reduced to 1.65%. The NICE Commissioning Guide for anticoagulation therapy published in 2013,[321] estimated the prevalence of AF as 1.6% of the whole population of England.

Whatever the prevalence of known AF, this is an underestimate of the true prevalence. This was illustrated in the SAFE study[201] in which targeted opportunistic screening increased the prevalence of AF by 0.5%. It seems probable, therefore, that the true prevalence of AF for the population of England is of the order of 2.0%.

1.2 Patient-centred care

This guideline offers best practice advice on the care of adults (aged 18 and over) with atrial fibrillation.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. The guidelines are based upon the best available research evidence, with the aim of improving the quality of health care. Predetermined and systematic methods are used to identify and evaluate the evidence relating to specific review questions.
Clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.
The guidelines are produced using the following steps:

- the guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process
- the scope is prepared by the National Clinical Guideline Centre (NCGC)
- the NCGC establishes a Guideline Development Group (GDG)
- a draft guideline is produced after the GDG assesses the available evidence and makes recommendations
- there is a consultation on the draft guideline
- the final guideline is published.

The NCGC and NICE produce a number of different versions of this guideline the:

- 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence
- 'NICE guideline' lists the recommendations
- 'information for the public' is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all related NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.
This is an update of 'Atrial fibrillation: the management of atrial fibrillation', NICE clinical guideline 36 (2006). See section 2.4 for details of which sections will be updated. We will also carry out an editorial review of all the recommendations to ensure that they comply with NICE's duties under equalities legislation.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researches as well as lay members developed this guideline (see the list of Guideline Development Group members and acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Dr Campbell Cowan in accordance with guidance from NICE.

The group met every 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.4 What this guideline covers

The guideline covers the following populations:

- Adults (18 years or older) with AF, including new-onset or acute AF, chronic AF (including paroxysmal, persistent and permanent), post-operative AF and atrial flutter).
- Specific consideration will be given to the needs of older people, people with left ventricular dysfunction and people with reversible causes of AF.

The guideline updates the following clinical areas from CG36:

- risk stratification for stroke or thromboembolic events and bleeding
- prevention of stroke using antithrombotic therapy and left atrial appendage occlusion
- treatment of AF (rhythm and rate control strategies)
- referral of people with AF to specialist care
- 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
- patient information and support specific to AF

For further details please refer to the scope in Appendix A and review questions in Appendix C.

2.5 What this guideline does not cover

The guideline does not cover:

- people under 18 years
- people with congenital heart disease precipitating AF

The guideline does not cover treatment of comorbidities associated with AF.

2.6 Relationships between the guideline and other NICE guidance

NICE Technology appraisals to be incorporated in this guidance:

Apixaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. NICE technology appraisal guidance 275 (2013).

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE technology appraisal guidance 249 (2012).

Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. NICE technology appraisal guidance 256 (2012).

Dronedarone for the treatment of non-permanent atrial fibrillation. NICE technology appraisal guidance 197 (2010).

Related NICE Technology appraisals:

Cardiac resynchronisation therapy for the treatment of heart failure. NICE technology appraisal guidance 120 (2007).

Implantable cardioverter defibrillators for arrhythmias. NICE technology appraisal guidance 95 (2006).

Related NICE Interventional procedures guidance:

Insertion of a subcutaneous implantable cardioverter defibrillator for prevention of sudden cardiac death. NICE interventional procedure guidance 454 (2013).

Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation. NICE interventional procedure guidance 427 (2012).

Thoracoscopic exclusion of the left atrial appendage (with or without surgical ablation) for non-valvular atrial fibrillation 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).

Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. NICE interventional procedure guidance 349 (2010).

Percutaneous (non-thoracoscopic) 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).

High-intensity focused ultrasound ablation for atrial fibrillation in association with other cardiac surgery. NICE interventional procedure guidance 184 (2006).

Percutaneous radiofrequency 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).

Non-surgical reduction of the myocardial septum. NICE interventional procedure guidance 40 (2004).

Related NICE medical technology guidance:

WatchBP Home A for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension. NICE medical technology guidance 13 (2013).

Related NICE public health guidelines:

Physical activity. NICE public health guidance 44 (2013).

Related NICE Clinical guidelines:
Patient experience in adult NHS services. NICE clinical guidance 138 (2012)
Medicines adherence. NICE clinical guidance 76 (2009).
MI – secondary prevention. NICE clinical guideline 172 (2013).
Myocardial infarction with ST-segment elevation. NICE clinical guideline 167 (2013).
Stroke rehabilitation. NICE clinical guideline 162 (2013).
Venous thromboembolic diseases. NICE clinical guideline 144 (2012).
Hypertension. NICE clinical guideline 127 (2011).
Chronic heart failure. NICE clinical guideline 108 (2010).
Alcohol-use disorders. NICE clinical guideline 100 (2010).
Type 2 diabetes – newer agents. NICE clinical guideline 87 (2009).
Stroke. NICE clinical guideline 68 (2008).
Type 2 diabetes. NICE clinical guideline 66 (2008).

Related NICE guidance currently in development:
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).
Acute heart failure. NICE clinical guideline. Publication expected September 2014.
Type 1 diabetes. NICE clinical guideline. Publication expected August 2015.
Type 2 diabetes. NICE clinical guideline. Publication expected August 2015.

3 Methods

This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2012.[326]

3.1.1 Amendments to 2006 text

All text and recommendations from the previous guideline CG36 that has not been updated (therefore review questions have not been generated and evidence has not been searched for) has been left unchanged and included in the update when the GDG agreed that the recommendations were still applicable. However, recommendations that were no longer accurate or relevant were removed from this update. Details of amendments and deleted recommendations are explained in Appendix O.

3.2 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews. This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A).

A total of 18 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
Education	Intervention	What educational and behavioural interventions are clinically and cost effective for aiding the management of antithrombotic therapy, rate, and rhythm strategies and symptoms in patients with atrial fibrillation?	Time in therapeutic range (TTR) Percentage of INR in therapeutic range Stroke and thromboembolic events Health related quality of life Anxiety Decision conflict Hospitalisations Knowledge and understanding
Referral to specialist care	Intervention	What is the clinical and cost effectiveness of referral to specialist services?	Mortality (all-cause) Stroke or thromboembolic complications Health related quality of life Disease awareness Rehospitalisation Adherence to guidelines Number of patients referred to anticoagulation clinic
Stroke risk tools	Prognostic	What is the most clinically and cost-effective risk stratification tools for stroke or thromboembolic events in atrial fibrillation?	**Patient outcomes:** Stroke Thromboembolic events

Chapter	Type of review	Review questions	Outcomes
			Mortality **Statistical outcomes:** Hazard ratio for high, moderate thresholds Sensitivity at particular thresholds Specificity at particular thresholds AUC (C indices) Calibration Net reclassification scores
Antithrombotic therapy	Intervention	What is the most clinical and cost-effective antithrombotic therapy for stroke prevention in people with atrial fibrillation?	Mortality (all mortality – time to event or latest endpoint) Ischaemic stroke (latest endpoint) Haemorrhagic stroke (latest endpoint) Major bleeding – all Hospitalisation Health related quality of life Thromboembolic complications
Bleeding risk tools	Prognostic	What is the clinical and cost effectiveness of HAS-BLED compared to other tools in assessing bleeding risk in people with atrial fibrillation?	**Patient outcomes:** Final outcome of bleeds Major bleeds (including fatal and intracranial bleeding) Mortality from bleeding Health related quality of life **Statistical outcomes:** Hazard ratio for high, moderate thresholds Sensitivity at particular thresholds Specificity at particular thresholds AUC (C indices) Calibration
Monitoring	Intervention	What is the clinical and cost effectiveness of systematic monitoring of patients with atrial fibrillation? What is the clinical and cost effectiveness of monitoring quality of control of anticoagulation compared to routine management?	Mortality Stroke or thromboembolic complications Health related quality of life Time in therapeutic range (INR) - for monitoring of anticoagulation question Persistence of atrial fibrillation Adherence to national/ international guidelines Major bleeding Rehospitalisation with a primary diagnosis of atrial fibrillation Patients developing heart failure Patient adherence to guidelines
Left atrial appendage occlusion	Intervention	What is the clinical and cost effectiveness of left atrial appendage occlusion compared to anti-thrombotic	Mortality (all mortality – latest endpoint) Ischaemic stroke (latest endpoint)

Chapter	Type of review	Review questions	Outcomes
		therapy in the prevention of stroke in people with atrial fibrillation?	Haemorrhagic stroke (latest endpoint) Major bleeding Hospitalisation Procedural complications Health related quality of life thromboembolic complications
Rate versus rhythm strategies	Intervention	What is the clinical and cost effectiveness of rhythm control (excluding ablation) compared to rate control in the treatment of atrial fibrillation in reducing stroke or improving prognosis?	Mortality Health related quality of life Stroke or thromboembolic complications Major bleeding – all Rehospitalisation with a primary diagnosis of atrial fibrillation Patients developing heart failure Restoration of sinus rhythm Recurrence of atrial fibrillation
Rate control strategies	Intervention	What is the clinical and cost effectiveness of using different rate control drug strategies in the pharmacological management of atrial fibrillation?	Mortality (long-term) Health related quality of life Rate control – heart rate (time or amount of people) Stroke or thromboembolic complications Rate of discontinuation of drug due to side effects Rehospitalisation with a primary diagnosis of atrial fibrillation or heart failure Time to response Left ventricular function – number of people / ejection fraction as percentage
Restoration of sinus rhythm	Intervention	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?	Mortality (30 days and longest endpoint) Health related quality of life Restoration of sinus rhythm/time to restoration for acute Stroke or thromboembolic events Rehospitalisation with a primary diagnosis of atrial fibrillation Patients developing heart failure Maintenance of sinus rhythm/Recurrence of atrial fibrillation
Maintenance of sinus rhythm	Intervention	What is the most clinical and cost-effective antiarrhythmic drug alone or in combination for maintaining sinus rhythm in (a) paroxysmal atrial fibrillation and (b) persistent atrial fibrillation after cardioversion?	Mortality (30 days and longest endpoint) Health related quality of life Recurrence rate Stroke or thromboembolic complications

Chapter	Type of review	Review questions	Outcomes
			Rehospitalisation with a primary diagnosis of atrial fibrillation Patients developing heart failure Drug withdrawal due to side effects Time to first relapse
Left atrial ablation	Intervention	What is the clinical and cost effectiveness of percutaneous catheter ablation compared to non- ablation therapies in people with atrial fibrillation? What is the clinical and cost effectiveness of surgical ablation compared to non- ablation therapies in people with atrial fibrillation? What is the clinical and cost effectiveness of surgical ablation compared to catheter ablation in people with atrial fibrillation?	Mortality - all-cause (reported at 30 days and longest endpoint given) Maintenance of sinus rhythm Heath related quality of life Stroke or thromboembolic complications Major bleeding including intracranial bleeding Re-hospitalisation (cardiovascular) Necessity for concomitant antiarrhythmic drug therapy Need for a pace maker (for catheter versus surgical ablation review only)
Pace and ablate	Intervention	What is the clinical and cost effectiveness of atrioventricular junction ablation and pacing compared to usual care in the treatment of atrial fibrillation?	All- cause mortality (30 days and latest endpoint) Heart failure Health related quality of life Stroke or thromboembolic complications Rehospitalisation with a primary diagnosis diagnosis of AF or heart diagnosis Left ventricular function
Atrial fibrillation presenting acutely	Intervention	What is the clinical and cost effectiveness of using different rate control drug strategies in the pharmacological management of atrial fibrillation?	Mortality (long-term) Health related quality of life Rate control – heart rate (time or amount of people) Stroke or thromboembolic complications Rate of discontinuation of drug due to side effects Rehospitalisation with a primary diagnosis of atrial fibrillation or heart failure Time to response Left ventricular function
Atrial fibrillation presenting acutely	Intervention	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	Mortality (30 days and longest endpoint) Health related quality of life Restoration of sinus rhythm/time to restoration for acute Stroke or thromboembolic events

Chapter	Type of review	Review questions	Outcomes
		antiarrhythmic drugs?	Rehospitalisation with a primary diagnosis of atrial fibrillation Patients developing heart failure Maintenance of sinus rhythm/Recurrence of atrial fibrillation

3.3 Searching for evidence

3.3.1 Clinical literature search

Systematic literature searches were undertaken to systematically identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the guidelines manual 2012.[326] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, Embase, and The Cochrane Library. Additional subject specific databases were used for some questions: CINAHL for referral and education; HMIC for referral; PsycINFO for education. Databases were searched from their date of inception, and all searches were updated on 3 October 2013. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/).

3.3.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to atrial fibrillation in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and Embase using a specific economic filter, from 2010, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

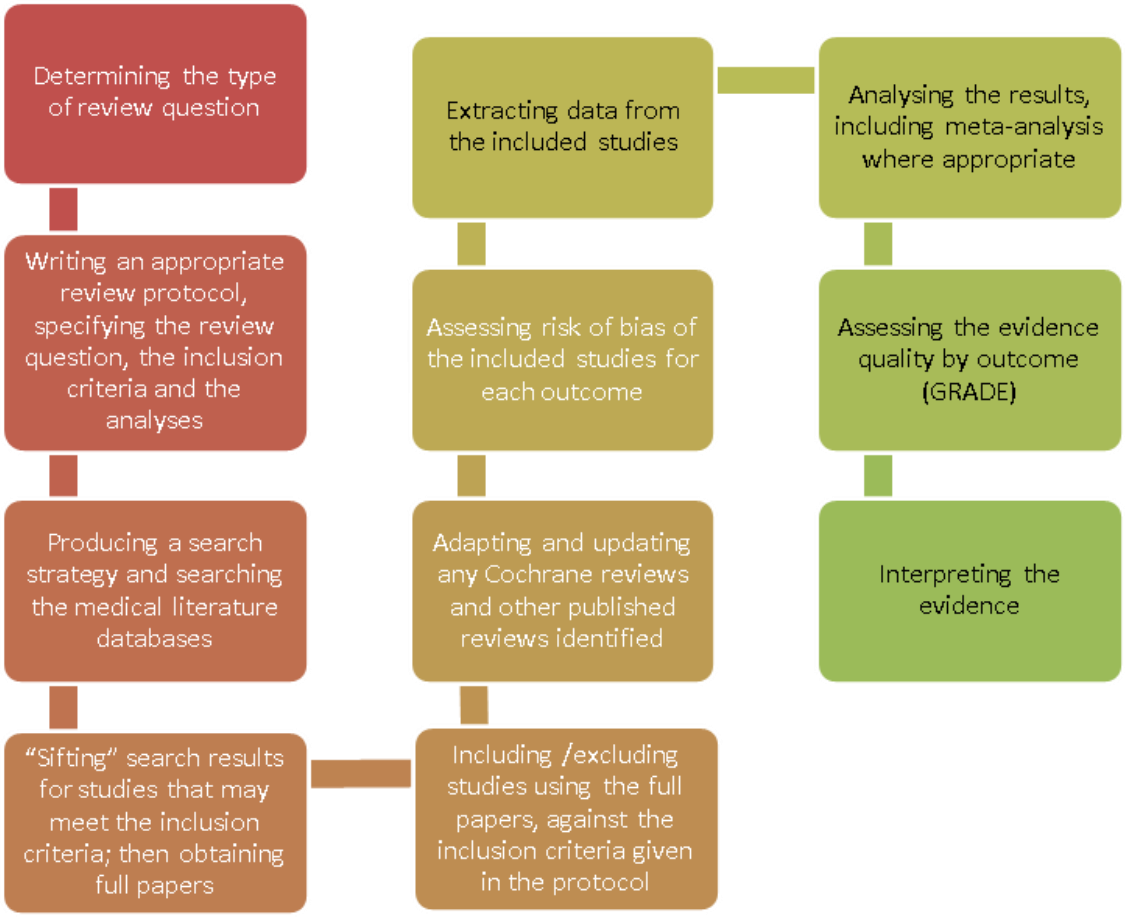
The health economic search strategies are included in Appendix F. All searches were updated on 3 October 2013. No papers published after this date was considered.

3.4 Evidence of effectiveness

The evidence was reviewed following the steps shown schematically in **Figure 1**:

- Potentially relevant studies were identified for each review question from the search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- Relevant studies were critically appraised using the appropriate checklist as specified in The guidelines manual.[326]
- Key information was extracted on the study's methods, PICO factors and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix G).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in GDG meetings:
  - Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
  - Prognostic studies: data were presented as medians and range of scores.

Figure 1: Step-by-step process of review of evidence in the guideline



3.4.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix J. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

Randomised trials, non-randomised trials, and observational studies (including prognostic studies) were included in the evidence reviews as appropriate.
Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.
The review protocols are presented in Appendix C.

3.4.2 Methods of combining clinical studies

3.4.2.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: mortality, stroke or thromboembolic complications, rehospitalisation, ischaemic stroke, haemorrhagic stroke, major bleeding, procedural complications, restoration of sinus rhythm recurrence of AF, rate of discontinuation due to adverse events, number of patients referred to anticoagulation clinics.
For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes [quality of life, time in therapeutic INR range, anxiety, and decision conflict and knowledge scores] were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.
Where reported, time-to-event data was presented as a hazard ratio.
For a number of reviews, the results were presented separately for pre-stratified groups or strata. Strata included:

- heart failure
- reversible causes of AF
- acute unstable AF

For more details on these strata refer to the protocols (see Appendix C).

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity).
The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% CIs were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in RevMan5. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as '$p\leq0.001$', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in Section 16.1.3 of the Cochrane Handbook (September 2009) 'Missing standard deviations' were applied as the last resort.
For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the

individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.
For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

3.4.2.2 Network meta-analysis

A network meta-analysis (NMA) was conducted for the review on choice of antithrombotic therapy for stroke prevention. This type of analysis simultaneously compares multiple treatments in a single meta-analysis, preserving the randomisation of RCTs included in the reviews of direct comparisons trials. The aim of the NMA was to include all relevant evidence in order both to answer questions on the clinical effectiveness of interventions when no direct comparison was available and to give a ranking of treatments in terms of efficacy. The output was expressed as the probability of each antithrombotic treatment being the best for an outcome and as effect estimates for how much each treatment is better than the other treatments included in the network.
A random effects Bayesian NMA was performed using the software WinBUGS version 1.4. That allowed inclusion of multi-arm trials and accounts for the correlation between arms in the trials with any number of trial arms.
There were 3 main outputs from the NMA:

- estimated hazard ratios (HRs) (with their 95% credible intervals) were calculated for comparisons of the direct and indirect evidence
- the probability that each treatment was best, based on the proportion of Markov chain iterations in which each treatment had the highest probability of achieving the outcomes selected in the network(s)
- a ranking of treatments compared to baseline groups (presented as the median rank and its 95% credible intervals).

A full technical account can be found in appendix M

3.4.2.3 Data synthesis for prognostic factor and risk tool reviews

Odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), with their 95% confidence intervals (95% CIs) for the effect of the pre-specified prognostic factors combined within a risk stratification tool were extracted from the papers. In addition, sensitivity and specificity for each risk stratification tool were considered if reported.
The area under the ROC curve (AUC) data for each study was reported as the c-statistic. The AUC describes the overall prognostic accuracy in regards to the tests discriminatory power across the full range of thresholds. The GDG agreed on the following criteria for AUC[207]:

- ≤0.50: worse than chance
- 0.50–0.60: very poor
- 0.61–0.70: poor
- 0.71–0.80: moderate
- 0.81–0.92: good
- 0.91–1.00: excellent or perfect test.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots where appropriate (only when there were similar thresholds).

3.4.3 Type of studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or

there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C for full details on the study design of studies selected for each review question. For example the monitoring and referral to specialist care reviews included non-randomised controlled trials if there were no RCTs available. It was considered unlikely that the search would find any RCTs.
For prognostic reviews, prospective and retrospective cohort studies were included. Case–control studies were not included. Studies of lower risk of bias were preferred, taking into account the analysis and the study design for example studies with more than 100 events. Studies which applied and assessed the different tools within the cohort were preferred to compare the tools predictive and discriminatory power Data were not combined in meta-analyses for prognostic studies.
Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

3.4.4 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and, where appropriate, observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was taken into consideration in the quality assessment and only included in the 'Clinical evidence profile' table if it was apparent from GDG members.
The evidence for each outcome was examined separately for the quality elements listed and defined in **Table 2**. Each element was graded using the quality levels listed in
Table 3. The main criteria considered in the rating of these elements are discussed below (see Section 3.4.5). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (**Table 4**).
The GRADE toolbox is currently designed only for randomised trials and observational studies but we adapted the quality assessment elements and outcome presentation for prognostic studies.

Table 2: Description of the elements in GRADE used to assess the quality of intervention studies

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

3.4.5 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High, observational studies as Low, and uncontrolled case series as Low or Very low.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality element are discussed further in the following Sections 3.4.7, 3.4.8 and 3.4.9).

3.4.6 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example, multiple replications of the same study would reach the wrong answer on average.

The risk of bias for a given study and outcome is associated with the risk of over- or underestimation of the true effect.

The risks of bias are listed in **Table 1**.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

The GDG accepted that investigator and participant blinding in surgical intervention studies was unlikely in surgical interventions for ablation and left atrial appendage occlusion.

Table 5: Risk of bias in randomised controlled trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example, allocation by day of week, birth date, chart number)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention-to-treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Recruitment bias in cluster-randomised trials

3.4.6.1 Prognostic studies

For prognostic studies, quality was assessed using the checklist for prognostic studies (Appendix I in The guidelines manual[326]). The quality rating (Low, High, and Unclear) was derived by assessing the risk of bias across 6 domains: selection bias, attrition bias, prognostic factor bias, outcome measurement bias, control for confounders and appropriate statistical analysis, with the last 4 domains being assessed for each outcome. More details about the quality assessment for prognostic studies are shown below:

- The study sample represents the population of interest with regard to key characteristics.
- Missing data are unrelated to key characteristics, sufficient to limit potential bias – reasons for missing data are adequately described.
- The prognostic factor of interest is adequately measured in study participants.
- The outcome of interest is adequately measured in study participants.
- Important potential confounders are accounted for appropriately.
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of valid results.

3.4.7 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect.

Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C).

When heterogeneity exists (chi-squared $p<0.1$, I-squared inconsistency statistic of >50%, or evidence from examining forest plots), but no plausible explanation can be found (for example, duration of intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I-squared and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

3.4.8 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. Studies with mixed populations of atrial flutter and atrial fibrillation were included in this guideline. However, studies that were only people with atrial flutter were excluded.

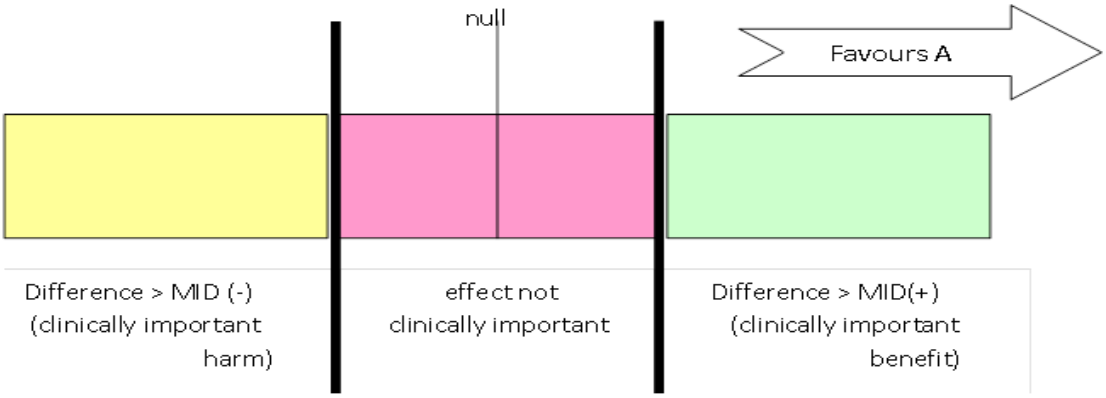
3.4.9 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate is relevant to decision-making, considering each outcome in isolation. Figure 2 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 2: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



When the confidence interval of the effect estimate is wholly contained in one of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.
The GDG was asked whether they were aware of any acceptable MIDs in the clinical community but there were none known. Therefore, the GDG agreed that the default values stated in GRADEpro were appropriate for our outcomes. The default thresholds suggested by GRADE are a relative risk reduction of 25% (relative risk of 0.75 for negative outcomes) or a relative risk increase of 25% (risk ratio 1.25 for positive outcomes) for dichotomous outcomes. For continuous outcomes, the default approach of multiplying 0.5 by the standard deviation (taken as the median of the standard deviations across the meta-analysed studies) was employed.
Finally, the GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to clinically important thresholds for a risk ratio of 0.75 and 1.25 respectively. This default MID was used for all the outcomes in the interventions evidence reviews. The default MID was used for continuous outcomes.

3.4.10 Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.
The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardised across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved (if positive) the outcome of interest in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative.
This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

3.4.11 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- a brief description of the participants
- an indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- a description of the overall quality of evidence (GRADE overall quality).

3.5 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[326] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.
Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

3.5.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The guidelines manual.[326]
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix H).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

3.5.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix E of the guidelines manual[326] and the health economics review protocol in Appendix C).

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

3.5.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The guidelines manual.[326] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See **Table 6** for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[344]

Table 6: Content of NICE economic evidence profile

Item	Description

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making • Directly applicable – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study • Minor limitations – the study meets all quality criteria, or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusions about cost effectiveness. • Very serious limitations – the study fails to meet one or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of The guidelines manual (2012)[326]

3.5.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified the prevention of stroke and decision rules to identify and select low risk patients who would benefit from anticoagulation as the highest priority area for original economic modelling. This was due to having sufficient data to parameterise the model in a clinical topic area where the health and cost implications are large. A detailed pathway model developed by Brunel University [293] was made available for the purposes of the guideline. It was felt that this model should be simplified and focus in particular on stroke prevention to avoid the potential for poorer quality data and assumptions regarding other clinical topics in the pathway to impact on the conclusions the analysis. The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[328]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.

- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

Full methods for the cost-effectiveness analysis of stroke prevention therapies for people with AF are described in Appendix L.

3.5.3 Cost-effectiveness criteria

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.[322] 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 cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[322]

3.5.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the GDG and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

3.6 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices G and H.
- Summary of clinical and economic evidence and quality (as presented in Chapters 6-19).
- Forest plots and summary ROC curves (Appendix I).
- A description of the methods and results of the cost-effectiveness analysis(ses) undertaken for the guideline (Appendix L).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on

the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, it was assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, and recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Appendix P).

The wording of recommendations was agreed by the GDG and focused on the following factors:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

3.6.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

3.6.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

3.6.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.6.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

3.6.5 Funding

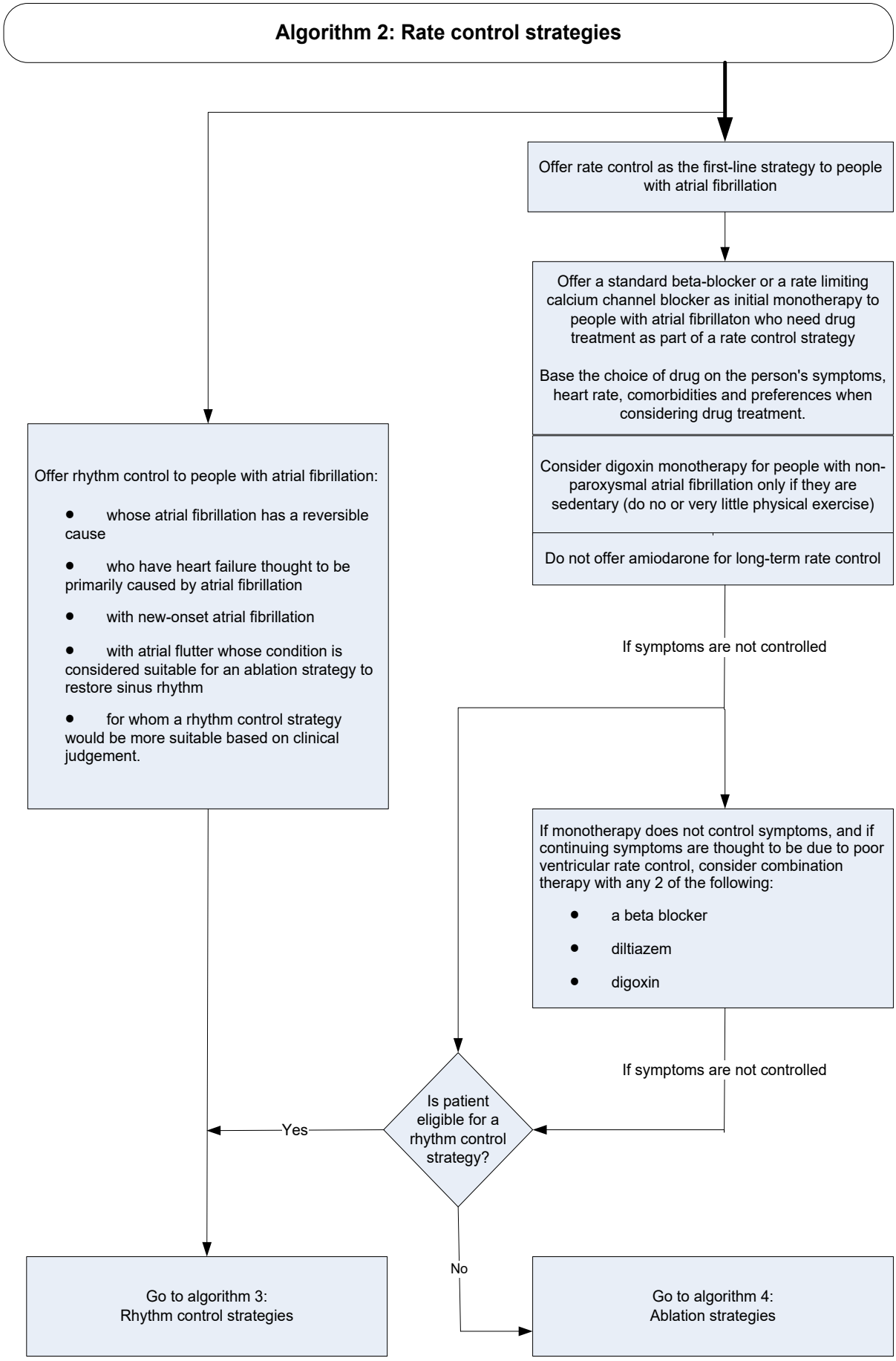
The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

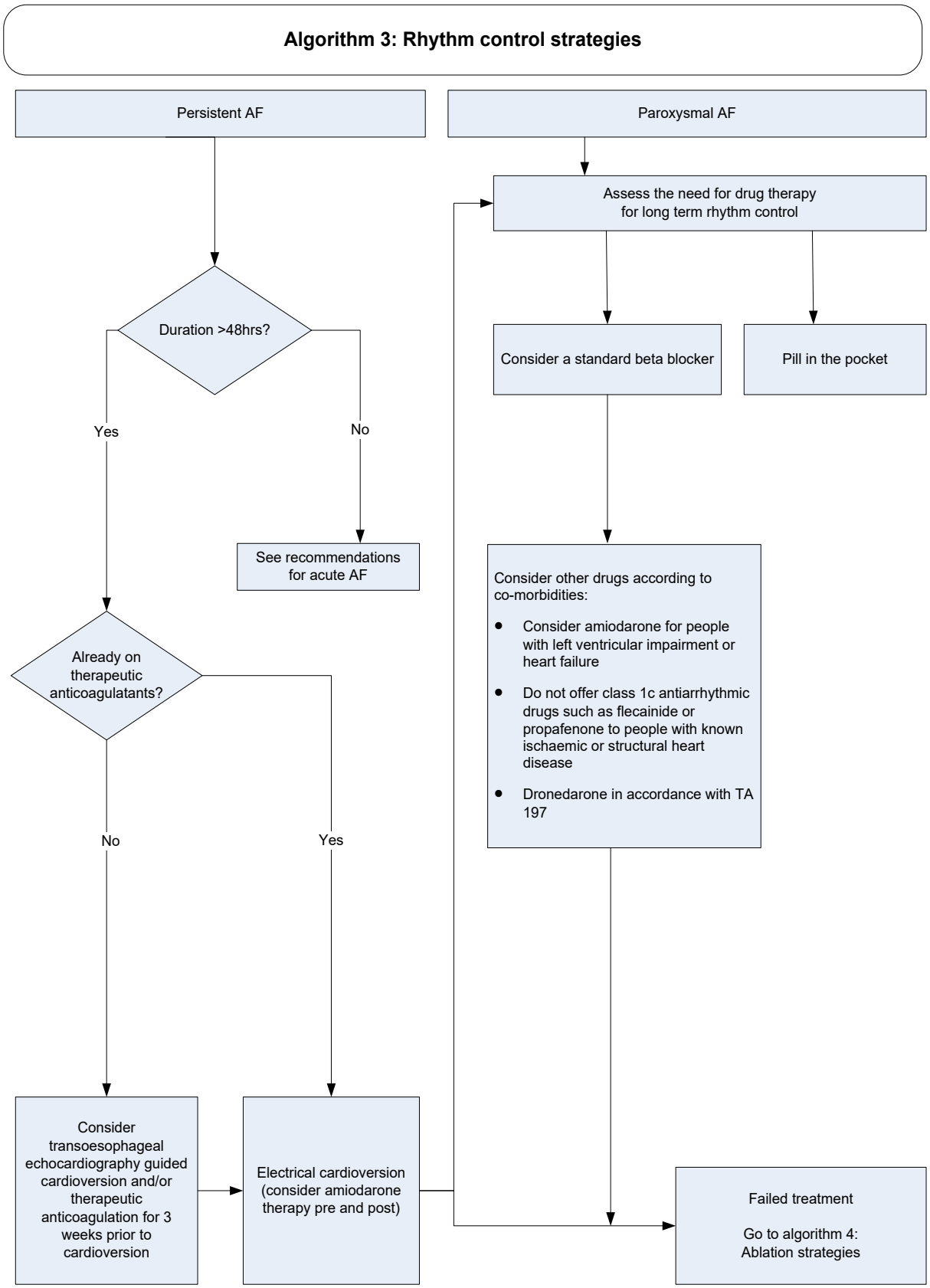
4 Guideline summary

4.1 Algorithms

The current algorithms can be found at http://www.nice.org.uk/guidance/ng196

Algorithm 1: Stoke prevention was updated in 2021. The current algorithms can be found at http://www.nice.org.uk/guidance/ng196


Algorithm 2: Rate control strategies
Offer rate control as the first-line strategy to people with atrial fibrillation
Offer a standard beta-blocker or a rate limiting calcium channel blocker as initial monotherapy to people with atrial fibrillaton 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.
Consider digoxin monotherapy for people with non-paroxysmal atrial fibrillation only if they are sedentary (do no or very little physical exercise)
Do not offer amiodarone for long-term rate control
If symptoms are not controlled
Offer rhythm control to people with atrial fibrillation:
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.
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
If symptoms are not controlled
Is patient eligible for a rhythm control strategy?
Yes
No
Go to algorithm 3: Rhythm control strategies
Go to algorithm 4: Ablation strategies


Algorithm 3: Rhythm control strategies
Persistent AF
Paroxysmal AF
Assess the need for drug therapy for long term rhythm control
Duration >48hrs?
Consider a standard beta blocker
Pill in the pocket
Yes
No
See recommendations for acute AF
Consider other drugs according to co-morbidities:
Consider amiodarone for people with left ventricular impairment or heart failure
Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with known ischaemic or structural heart disease
Dronedarone in accordance with TA 197
Already on therapeutic anticoagulatants?
No
Yes
Consider transoesophageal echocardiography guided cardioversion and/or therapeutic anticoagulation for 3 weeks prior to cardioversion
Electrical cardioversion (consider amiodarone therapy pre and post)
Failed treatment
Go to algorithm 4: Ablation strategies

Algorithm 4: Left atrial ablation was updated in 2021. The current algorithms can be found at http://www.nice.org.uk/guidance/ng196

4.2 Key priorities for implementation

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

4.3 Full list of recommendations

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

4.4 Key research recommendations

The current research recommendations can be found at http://www.nice.org.uk/guidance/ng196

5 Identification and assessment

This section was partially updated in 2021. See http://www.nice.org.uk/guidance/ng196/evidence for the 2021 evidence reviews.

5.1 Presenting symptoms/pulse palpitation

AF can present in the setting of a wide variety of cardiac and non-cardiac conditions, it is often asymptomatic and can present with vague non-specific symptoms. Too often, AF is only detected after the patient presents with serious complications of AF, such as a stroke, thromboembolism or heart failure. The initial diagnosis of AF depends on associating symptoms such as breathlessness, dyspnoea, palpitations, syncope/dizziness or chest discomfort with AF.

Most of the data on presentation of AF patients have been based on white Caucasian populations, and limited data are available in relation to ethnicity and AF.[151] Furthermore, there may be important differences between hospital-based cohorts compared with community or population-based studies, as many do not present to hospital care, and if they do, it is often in the context of associated comorbidity such as ischaemic heart disease or heart failure. Indeed, many patients with AF in general practice remain asymptomatic. However, as AF commonly occurs in association with risk factors, such as hypertension, diabetes and ischaemic heart disease, opportunistic assessment of such patients for the presence of AF may be prudent, especially since such patients are frequently seen for check-ups in primary care.

While general population screening is beyond the scope of this guideline, targeted/opportunistic screening of symptomatic patients or those with risk factors may allow identification of AF patients. One recent study[201,426] aims to determine the baseline prevalence and the incidence of AF based on a variety of screening strategies and in doing so to evaluate the incremental cost effectiveness of different screening strategies, including targeted or whole population screening, compared with routine clinical practice, for detection of AF in people aged 65 and over. This study[201] – whose publication date fell outside of the date limits of the systematic literature search – reported that the baseline prevalence of AF in subjects older than 65 was 7.2%, with a higher prevalence in men (7.8%) and among patients aged 75 or older (10.3%), and indicated that the only strategy that improved on routine practice was opportunistic screening.

5.1.1 Methodological introduction

The results of nine studies are included in this report. Seven studies were critically appraised.[114,273,278,283,290,402,465] Of these, none reported the frequency of presenting symptoms in primary care in a UK (or other) population. Patients presenting to secondary care generally present with more severe symptoms. The studies:

- did not use a consistent terminology to classify AF symptoms. 'Dizziness' was also referred to as 'near syncope'[114] and 'chest pain' was also referred to as 'chest discomfort'[290]
- were single-centre studies
- had a variable proportion of patients presenting with de novo AF versus those with a previous history of AF.

Three of the appraised studies were not based on UK populations.[114,290,402] One study[465] reported the frequency of presenting symptoms between ethnic groups (white, Asian and black groups) but the numbers were too small to perform statistical comparisons.

5.1.2 Evidence statements

Dyspnoea, chest pain and palpitations were found to be the most common presenting symptoms in emergency admissions with newly diagnosed or previously diagnosed AF in the UK[283,465] or USA.[64,313,445]

Table 7: Presenting symptoms associated with emergency AF admissions

Study	N	Dyspnoea %	Chest pain %	Palpitations %	Dizziness/ syncope %
Zarifis et al[465]	245	47.1	19.9	16.2	16.2
Lip et al[283]	170	51.8	34.1	25.9	18.8
Michael et al[313]	289	7	10	78	3
Burton et al[64]	266	12	24	40	9

Similar results were found in patients with chronic[402] (more than 7 days since onset of symptoms) and lone AF.[114]

In one study[273] (N=756) dyspnoea was the most commonly reported symptom in chronic and recent-onset AF (46.8%); palpitations were the most commonly reported symptom in paroxysmal AF (79.0%).[445]

Table 8: Presenting symptoms between paroxysmal, chronic and recent-onset AF patients

Symptom	Total	Paroxysmal	Chronic	Recent-onset
Palpitations (%)	54.1	79	44.7	51.5
Chest pain (%)	10.1	13.2	8.2	11
Dyspnoea (%)	44.4	22.8	46.8	58
Syncope/dizziness (%)	10.4	17.4	8	9.5
Fatigue (%)	14.3	12.6	13.1	18
Other (%)	0.9	0	1.8	0
None (%)	11.4	5.4	16.2	7

In two studies, stroke was reported as a presenting symptom of AF at rates of 5.1% and 3.2% respectively[278,290] and occurred at a rate of 12.7% in a study population combining both new-onset and previously diagnosed AF.[445,465]

5.1.3 From evidence to recommendations

Those with undiagnosed AF can receive treatment sooner if an opportunistic case finding is undertaken using manual pulse palpation in those presenting with symptoms commonly associated with AF. It was therefore considered good practice to check the blood pressure and pulse (manually) in all patients who present with breathlessness, dyspnoea, palpitations, syncope/dizziness or chest discomfort.

Many patients presenting with stroke are also found to be in AF, indicating a missed opportunity to diagnose the pre-existing AF and administer appropriate antithrombotic therapy.

5.1.4 Recommendation

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

5.2 Electrocardiography

As with many chronic disorders, AF may be symptomatic or asymptomatic, and episodes of either can occur in the same patient.

Most symptomatic patients with AF present with symptoms related to the arrhythmia. However, such patients can have a wide variety of other cardio-respiratory presenting symptoms and clinical features[273,283] (see section 5.1)

Many patients with AF are asymptomatic and are picked up in general practice. One study[282] found that a third of AF patients had not had hospital contact for symptoms related to AF. Asymptomatic

AF can be discovered incidentally during clinical examination by cardiac auscultation, 12-lead ECG recording, or 24-hour Holter recording that may have been performed for unrelated reasons.
The patient may also have presented with associated medical problems, such as heart failure, stroke or thromboembolism, and coincidental AF is detected. The duration of AF may be unknown in such patients, and whether AF was the cause or effect of the acute problem (e.g. stroke or heart failure) may be uncertain.
Many patients with risk factors for developing AF, such as hypertension and diabetes, do attend regular checkups with their GPs. In these cases then, there is the possibility of opportunistic case finding.

5.2.1 Methodological introduction

The two studies performed in UK primary care[316,425] evaluated the finding of an irregular pulse as a screening test for AF. Both studies included populations of over 65-year-olds and confirmed the diagnosis of AF by ECG.

5.2.2 Evidence statements

In one study,[425] the diagnostic accuracy of pulse palpation was compared between different age and gender groups in a primary care population aged 65 or over, and is summarised in **Table 9**). (II)

Table 9: Diagnostic accuracy of pulse palpitation between different age and gender groups

	Women 75+	Women 65-74	Men 75+	Men 65-74
Sensitivity	93 (66 to 100)	100 (16 to 100)	95 (75 to 100)	100 (54 to 100)
Specificity	71 (66 to 77)	86 (81 to 91)	71 (65 to 77)	79 (74 to 84)
PPV	14 (7 to 22)	8 (1 to 25)	23 (14 to 34)	12 (4 to 23)
NPV	99 (97 to 100)	100 (98 to 100)	99 (96 to 100)	100 (98 to 100)

All values are percentages with 95% confidence intervals.

One study[316] measured the diagnostic accuracy of three different methods of nurse-based screening for AF based on the presence of either continuous or intermittent pulse irregularities over a minimum of 20 seconds in a population aged over 65. The results are as shown in **Table 10**. (II)

Table 10: Comparison of the diagnostic accuracy of three different methods of pulse palpation to screen for the presence of AF

`	Method 1	Method 2	Method 3
Sensitivity	91 (82 to 97)	72 (59 to 82)	54 (41 to 66)
Specificity	74 (72 to 77)	94 (93 to 96)	98 (97 to 99)
PPV	19 (15 to 23)	44 (35 to 54)	61 (47 to 73)
NPV	99 (98 to 100)	98 (97 to 99)	97 (96 to 98)

All values are percentages with 95% confidence intervals. Method 1: diagnostic accuracy based on the detection of any pulse irregularity; method 2: diagnostic accuracy based on the detection of frequent or continuous irregularities; method 3: diagnostic accuracy based on the detection of only continuous irregularities.

5.2.3 From evidence to recommendations

An irregular pulse was found to be sensitive to the presence of AF.[425] The positive predictive value was greater in those over 75 years old, as the prevalence of AF is known to be higher in this population. The negative predictive value of a regular pulse (>96%) was also emphasised. The results of a second study[316] suggested it would be prudent to consider any pulse irregularity as requiring further investigation to determine whether AF is present.
One study[201,426] whose publication date fell outside of the date limits of the systematic literature search confirmed the above results in an elderly UK population (over 65 years old). The study also showed that opportunistic case-detection for AF is a more cost-effective strategy than systematic

screening and is associated with fewer ischaemic strokes and a greater proportion of diagnosed AF cases.
The evidence did not consider clinical indicators other than an irregular pulse and it was agreed that where there were other clinical indicators suggestive of AF, an ECG should still be performed. Nonetheless, the majority of patients presenting with AF will have an irregular pulse that may occur in the absence of any symptoms, and it is unlikely that AF will be present if the pulse is normal.
The diagnosis of AF does not require a 12-lead ECG recording. In the case of atrial flutter, however, a 12-lead ECG may be necessary, and may also occur in the presence of a regular pulse. The recommendation made below therefore applies only to AF case detection.

5.2.4 Recommendation

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

5.3 Ambulatory ECG recording

Many patients with intermittent AF have asymptomatic paroxysms. In one study[346] it was estimated that only 1 in 12 paroxysms are symptomatic. Nonetheless, these patients remain at risk of complications associated with AF.
In patients with daily paroxysms, clinical practice is to perform a 24-hour Holter monitor, but this is less useful in patients who get paroxysms at intervals of more than 24 hours. In the latter category of patients, event ECGs (including transtelephonic monitors ('cardiomemos') and some implanted systems) are commonly used to detect/diagnose AF.

5.3.1 Methodological introduction

Ambulatory-ECG was defined as any electrocardiographic recording device that continuously recorded cardiac electrical activity while the patient was able to move around relatively freely without hindrance. Ambulatory-ECG included both Holter-monitoring and implanted recorders such as programmed pacemakers that generated a continuous ECG recording.
Event-ECG was defined as any electrocardiographic recording device which recorded only particular events, identified either automatically by a software program to detect arrhythmic episodes or by the onset of symptoms (when the patient manually switches on the device for the duration of the symptomatic episode), or a combination of the two. As with ambulatory-ECGs, event-ECGs record cardiac electrical activity while the patient is able to move around relatively freely without hindrance.
Studies were included if the sample population was reported to be patients with either suspected AF or suspected atrial arrhythmia. No studies compared the diagnostic accuracy of event-ECG devices with ambulatory-ECG devices over the same duration.

5.3.2 Evidence statements

One cross-over study[238] of patients suspected of atrial arrhythmia based on palpitations compared a patient-triggered event recorder over a mean period of 70 hours with a 48-hour Holter monitor. The event recorder detected proportionately more symptomatic episodes than the Holter monitor (67% of recorded episodes associated with symptoms versus 35% respectively; $p<0.001$) (1b). Similarly, the event recorder yielded more arrhythmia diagnoses (19% versus 0% respectively; $p<0.005$). (1b)
In one study[375] which compared 24-hour Holter monitoring with automatic and patient triggered event recording (each over 30 days), the automatically-triggered event recorder had a higher diagnostic yield than the patient-triggered event recorder, which in turn had a higher diagnostic yield for diagnoses of AF than the Holter monitor (24%, 13% and 5% respectively). The automatically triggered event recorder was also more effective than the patient-triggered event recorder in detecting asymptomatic episodes of AF (52 events versus 1 event respectively).[299]
In one study[209] of 139 patients admitted with symptoms of acute stroke or transient ischaemic attack (TIA) who were ECG-negative for AF/flutter, seven (5%) were picked up in a second round of

monitoring using a 24-hour Holter monitor. A further five (6%) patients were diagnosed with AF/flutter in a third round of monitoring using a 7-day event recorder (with both patient and automated triggering).[299]

5.3.3 From evidence to recommendations

No studies were found to compare the positive diagnostic yield per unit time between an ambulatory-ECG diagnostic tool and an event-ECG tool where the recordings were interpreted in a comparable manner.

One study[209] found that the use of event-ECG detected cases of AF remained undetected by both non-ambulatory and ambulatory-ECG. In addition, the study found that the use of ambulatory-ECG detected cases of AF remained undetected by non-ambulatory-ECG.

Also, a strategy of event-ECG diagnosis detected more symptomatic episodes and more positive diagnoses of atrial arrhythmias, including AF, than the strategy of ambulatory-ECG diagnosis.

5.3.4 Recommendation

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

5.4 Echocardiography

Although most cardiologists will perform a transthoracic echocardiogram (TTE) on patients with AF referred to cardiology clinics,[285] echocardiography is not undertaken on all patients seen in primary or non-specialist secondary care.[280,282,283,465]

Regarding the use of echocardiography to identify stroke risk factors, although most stroke risk stratification criteria (see Appendix S) lay emphasis on clinical risk factors, there is a perception that TTE is mandatory to decide on antithrombotic therapy. In one study[71] echocardiography revealed cardiac abnormalities in many AF patients, although most had other clinical risk factors for thromboembolism and often echocardiography did not alter the management decision.

In clinical practice echocardiography has also been used to assess the risk of recurrent AF post cardioversion, as well as to assess the risk of developing postoperative AF. Finally, transoesophageal echocardiography (TOE) has been used to guide cardioversion (TOE-guided cardioversion (see section 15.3)), but this is a specialist investigation. TOE can also be used by specialists to assess the risk of stroke and thromboembolism.[241]

5.4.1 Methodological introduction

The results of 29 studies were included in this report. Studies were considered for inclusion if echocardiographic (TTE or TOE) variables were stratified into normal and abnormal ranges and tested, alongside clinical variables, as independent risk factors for clinically defined outcomes.

The clinical outcomes considered were:

- AF pathophysiology
- the recurrence of AF following successful cardioversion
- stroke or thromboembolism
- vascular death.

The presence of intra-cardiac thrombus was not considered as an echocardiographic measure of structural or functional heart disease. Rather, it was considered as a consequence of the disease.

5.4.2 Evidence statements

5.4.2.1 AF pathophysiology

One study[147] found a left atrial diameter greater than 50 mm to be the only significant independent echocardiographic predictor for the development of a greater AF burden, in terms of the amount of time spent in AF or the frequency of AF episodes ($p<0.05$). (2++)

One study[433] found that in patients developing AF, it is more likely to lead to haemodynamic instability in patients with an atrial filling fraction less than 40% (RR 2.7; p<0.0001), or left-ventricular dysfunction (p<0.03) during sinus rhythm. (2+)

5.4.2.2 Post-cardioversion recurrence

Left atrial haemodynamic dysfunction, as measured by a left atrial appendage velocity (LAA-V) greater than 40 cm/sec, has been found to be a significant independent predictor of maintained sinus rhythm following cardioversion in one study[23] (OR 5.2, 95% CI 2.7 to 10; p<0.0001). In another study, [381] a ratio of left atrial appendage area (LAA-V) over the left atrial area (LA area) greater than 0.009 was found to be an independent predictor of maintained sinus rhythm (OR 6.4; 95% CI 1.9 to 2.4; p=0.004). (2+)

Left atrial haemodynamic dysfunction, as measured by the presence of spontaneous echo contrast (SEC) in the left atrium, has not been found to be an independent predictor of sinus rhythm maintenance following cardioversion.[23,129] (2++)

Based on the results of four studies,[23,28,136,155] left atrial diameter is not an independent predictor of sinus rhythm maintenance following cardioversion (2+). However, two studies[129,341] did find a left atrial diameter of less than 45 mm (p=0.02) or less than 41 mm (p=0.008) to be an independent predictor. (2++)

One study,[155] while not finding left atrial diameter to be an independent predictor of sinus rhythm maintenance following cardioversion, did find a right atrial diameter of less than 37 mm to be an independent predictor (OR 5.9; 95% CI 1.4 to 25; p<0.02). (2+)

The presence of moderate or severe heart failure (NYHA>1) has been found to be an independent predictor of AF recurrence following cardioversion in one study[128] (p<0.0005) (2++). Another study,[136] found no such relationship between left ventricular dysfunction, when measured as either left ventricular end diastolic diameter (LVEDD) or left ventricular end systolic diameter (LVESD), and sinus rhythm maintenance. (2+)

One study[23] did not find the presence of mitral regurgitation to be an independent predictor AF recurrence following cardioversion (2+). Another study[349] found the presence of mitral annular abnormalities to be able to effectively predict the recurrence of AF at 12 months following cardioversion (positive predictive value (PPV) 79%, negative predictive value (NPV) 85%). (2+)

5.4.2.3 Stroke or thromboembolism

Two studies[30,272] did not find aortic stenosis to be an independent predictor of stroke or thromboembolism. (2+)

One study[404] found the presence of complex aortic plaque to be an independent predictor of stroke in those over 70 years (OR 4.0, 95% CI 1.1 to 14; p=0.03). The same study did not find the same result in those under 70. (2++)

Based on the results of four studies,[272,315,404,422] it is unclear whether left atrial haemodynamic dysfunction, as measured by the presence of SEC, is an independent predictor of stroke or thromboembolism. (2++)

Based on the results of two studies,[222,315] left atrial haemodynamic dysfunction, as measured by LAA-V less than 20 cm/sec, is an independent predictor of stroke or thromboembolism (2+). Another study[404] found a similar result in those under 70 years, but not in those over 70 years. (2++)

Based on the results of six studies,[1,30,65,251,319,422] it is unclear whether an enlarged left atrium, measured either in terms of area or diameter, is an independent predictor of stroke or thromboembolism. (2+)

Based on the results of three studies,[1,2,29] (echocardiographically detected) left ventricular dysfunction is an independent predictor of stroke or thromboembolism: (2++)

- RR = 2.5 (1.5 to 4.4), p<0.001[2]
- RR = 2.6 (1.4 to 4.9), p=0.003[1]
- OR = 1.8 (1.2 to 2.7), p=0.003.[29]

Two other studies[272,422] did not find left ventricular dysfunction to be an independent predictor. (2+)
Based on the results of two studies,[29,30] left ventricular hypertrophy is an independent predictor of stroke or thromboembolism: (2+)

- OR = 2.8 (1.8 to 4.4), p=0.0001[29]
- OR = 6.56, p<0.01.[30]

Another study[272] did not find left ventricular hypertrophy to be an independent predictor. (2+)
Two studies[30,272] did not find mitral annular calcification to be an independent predictor of stroke or thromboembolism. (2+)
A meta-analysis of three clinical trials[2] (N=1,066) failed to find either mitral valve prolapse or regurgitation (of any degree) to be independent predictors of stroke or thromboembolism (2++). However, the results of a smaller study (N=290)[319] suggested that moderate-to-severe mitral regurgitation may be an independent negative predictor of stroke (OR 0.45, 95% CI 0.20 to 0.97) in a population at a low risk of stroke. (2++)

5.4.2.4 Vascular death

One study[117] found that left-atrial haemodynamic dysfunction, as indicated by spontaneous echo contrast, was an independent predictor of vascular death in patients with AF, defined as either fatal non-haemorrhagic stroke, MI, congestive heart failure (CHF), systemic embolism or sudden cardiac death syndrome (RR 7.96, 95% CI 1.6 to 41; p=0.013) (2++). The study did not find the presence of structural, valvular or aortic cardiovascular disease to be independent predictors. (2++)

5.4.3 From evidence to recommendations

Echocardiography is able to identify factors that are independently predictive of successfully maintaining sinus rhythm following cardioversion. In particular, LAA-V measured by TOE is able to independently predict the successful maintenance of sinus rhythm following cardio-version.[23,381] TOE may therefore be used, in addition to other clinical variables, in determining the appropriateness of pursuing a rhythm-control strategy involving cardioversion.
In most cases risk stratification for stroke or thromboembolism and the decision to administer appropriate thromboprophylaxis can be made on purely clinical (non-echocardiographic) characteristics. However, the stroke risk may be unclear in some patients, in which case echocardiography may be useful in refining the risk. In particular, TOE may be used to identify the presence of complex aortic plaque[404] and impaired left atrial haemodynamics.[222,315,404] TTE may be used to identify left ventricular dysfunction or hypertrophy,[1,2,29] that may not be associated with overt heart failure.[29,30]
In many patients with AF, there may be indications other than the AF itself that make it necessary to perform an echocardiographic examination. For example, it may be used to identify suspected co-present heart disease. TOE may further be used to detect cardiac abnormalities not identified through TTE (e.g. patent foramen ovale).
The recommendations made here are specifically for those instances where echocardiography is used in relation to AF and how the results may influence the choice of treatment strategy or antiarrhythmic drug.

5.4.4 Recommendations

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

6 Patient information and education

6.1 Introduction

For many patients the first onset of atrial fibrillation (AF) is a very frightening experience. They become aware of an irregular and often rapid heart rhythm, which may be accompanied by symptoms of shortness of breath, chest discomfort or dizziness. For some it is their first encounter with serious illness. For others it adds yet another problem to a list of existing debilities.
Whatever the circumstances, many patients recount the importance of receiving timely explanation as to the cause of AF and the available treatment options. It helps for them to receive reassurances that however irregular their rhythm, their heart is not going to suddenly stop. At the same time the potential serious consequence of stroke needs to be openly discussed and information given about their stroke risk together with the benefits and risk of anticoagulation and its lifestyle consequences. The role of AF rate and rhythm management in alleviating symptoms should similarly be considered. Addressing patient concerns and providing them with the knowledge to make informed choices about their condition, whilst time-consuming, is good clinical practice and should be the goal for all health care professionals.
The GDG wanted to know whether provision of education, specifically in relation to anticoagulation and management of symptoms, influenced patient outcomes and asked the following question.

6.2 Review question: What educational and behavioural interventions are clinically and cost effective for aiding the management of anticoagulation therapy, rate and rhythm strategies and symptoms in patients with AF?

For full details see review protocol in Appendix C.

Table 11: PICO characteristics of review question

Population	People with atrial fibrillation
Intervention/s	Educational and behavioural interventions for the management of anticoagulation therapy, rate and rhythm strategies and symptoms including: Educational: Literature, videos, talking interventions, decision aids and self-monitoring with education
Comparison/s	Usual care
Outcomes	Time in therapeutic range (TTR) / % of INR in therapeutic range Stroke and thromboembolic complications Quality of life Anxiety Decision conflict Hospitalisation Knowledge and understanding
Study design	Randomised controlled trials (RCTs) Systematic reviews of RCTs

6.2.1 Clinical evidence

One Cochrane review[94] of 8 RCTs[45,92,156,300,309,363,431,450] and one other study[95] were included in the review. This other study[95] only reported outcomes as median and interquartile ranges (IQRs) for time in therapeutic range (TTR). As evidence had already been retrieved for mean TTR and been meta-analysed, this median TTR outcome could not be combined with the analysis. Quality of life was reported but the groups were not comparable at baseline therefore accurate conclusions could not

be drawn. Anxiety and depression were reported and these have been included due to lack of evidence from other studies; however these have been reported in GRADE tables only as forest plots could not be generated with median and IQR values.
Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 13**, **Table 14** and **Table 15**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 12: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Beyth 2000[45] RCT, USA Follow up: 6 months	**Intervention:** multicomponent comprehensive program for management of warfarin therapy aimed at improving control. Patient education, coaching and self-monitoring (n=27) **Comparison:** usual care consisting of medical care, including management, dosing and medical information according to the discretion and practices of their personal physician (n=27)	Patients hospitalised who were 65 years or older and for whom treatment with warfarin was planned for 10 days or more. N=325 (AF patients: n=54) Unpublished AF data in Cochrane review.	Stroke and thromboembolic complications	Stratified according to baseline risk for major bleeding before randomisation
Christensen 2007[92] RCT, Denmark Primary observation period 6 months	**Intervention**: self-management and teaching lesson; included patient practicing analysis of blood specimens. Patient gradually assumed management of oral anticoagulation. Exam at 27 weeks then patients went on to self-manage (n=11). **Comparison:** usual care – continued treatment with physician or hospital (n=9)	Patients over 18 years of age and treatment with oral anticoagulants for at least 8 months and referred for patient self-management. N=92 (AF patients n=20) Unpublished AF data in Cochrane review.	TTR	No comments
Clarksmith 2013[95] UK Follow-up 12 months	**Intervention:** 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 oral anticoagulation (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	All patients over 18 years of age attending a specialist AF clinical or local anticoagulation outpatient clinic; documented AF; warfarin naive; accepting of OAC therapy. N= 97 Not all outcomes reported in the paper were able to	Anxiety Quality of life TTR	No comments

Study	Intervention/comparison	Population	Outcomes	Comments
	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 (n=46) **Comparison:** 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 (n=51)	be included in this report.		
Gadisseiur 2003[158] RCT (4 arms), Netherlands Mean follow up time 24.5 weeks	Intervention: information about the study, oral anticoagulation, effects of some substances, instructed on oral self-dosing. Provided with written information (n=6) **Group A**: self-monitoring and education. Weekly INR self-measurement, but dosing performed by anticoagulation clinics (n=9). **B**: Self-management and education (n=10) **C**: education: patients trained for inclusion into groups A or B but stayed in the routine care system. **Comparison**: usual care (n=43) Groups A-C: 3 training sessions 90-120 minutes	More than 3 months oral anticoagulation experience need for long-term anticoagulation, aged 18-75 years. N=161, AF patients n=68	TTR	Unpublished AF data in Cochrane review
Man-Son-Hing 1999[300] RCT US Hospital 6 month follow up	**Intervention**: decision aid group consisted of a 29 page booklet, a personal worksheet and a 20 minute audiotape that guides the participants through the material (n=139) **Comparison**: usual care – no change was made to the usual manner in which each centre communicated the results of the study or the way in which the decision regarding type of antithrombotic was made (n=148)	All AF participants were in the SPAF III aspirin cohort study and were eligible unless they had high risk criteria or had a major haemorrhage during the study.	Knowledge Decision conflict	No comments
McAlister 2005[309] RCT, Canada Follow-up 1 year	**Intervention**: self-administered booklet and audiotape decision aid tailored to their personal stroke risk profile (n=219) **Comparison**: usual care – no further information provided (n=215)	Non valvular AF from 102 community based primary care practices.	TTR Decision conflict	No comments
Polek 2012[363] RCT, USA	**Intervention**: enhanced educational follow-up: face-to-face warfarin	Patients discharged to home on oral	Knowledge and	No comments

Study	Intervention/comparison	Population	Outcomes	Comments
Follow-up 12 weeks	education, printed materials, instruction, and medical alert bracelet. Aim to improve self-efficacy. Four post-discharge phone calls assessing knowledge post intervention and correcting incorrect answers (n=5). **Comparison**: face to face warfarin education, printed materials, instruction, and medical alert bracelet with one post discharge phone call at 12 weeks (n=9)	anticoagulation, alert and orientated. N=53, AF n= 14 Unpublished AF data in Cochrane review.	understanding	
Thomson 2007[431] RCT, UK Follow up 3 months	**Intervention**: Decision aid – taken through a presentation of the individualised benefits and potential harms of warfarin before coming to a shared decision with the clinic doctor. Includes personalised stroke risk assessment and bleeding risk from a systematic review (n=53) **Comparison**: Guidelines based consultation (n=56)	Patients recruited if they were already taking warfarin or if they were considering taking warfarin for the first time. Chronic non-valvular AF or paroxysmal AF and aged 60 or over. Participants recruited from 40 general practices throughout primary care trusts.	Knowledge and understanding Anxiety Hospitalisation	2 different decision aids – an observational study running alongside found one of decision aids to be difficult so this was discontinued. This RCT compares the other decision aid with usual care
Voller 2005[431,450] RCT, Germany Self-management was 37 and family doctor was 40 years follow up (retrospective)	**Intervention**: self-management: educational session including anticoagulation in general, INR self-monitoring, preventing bleeding, effects of diet and other medication, reducing or increasing dose, problems that may be encountered with operations, illness, exercise and pregnancy. 60-90 minute duration and over 3 consecutive weekly training sessions. (n=101) **Comparison**: guideline based consultation (n=101)	Long-term anticoagulation indicated due to permanent non-valvular AF	Time within range Stroke and thromboembolic complications	

Table 13: Clinical evidence profile: self-monitoring and education versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SM + education	Control	Relative (95% CI)	Absolute		
TTR (measured with: % of time in therapeutic range; range of scores: 0-100; Better indicated by higher values)[92,157]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	not calculated	none	17	52	-	MD 6.31 higher (5.63 lower to 18.25 higher)	MODERATE	CRITICAL
Stroke or thromboembolic events [45,450]												
2	randomised trials	serious[b]	no serious inconsistency	no serious indirectness	very serious[c]	none	1/128	3/128	RR 0.43 (0.07 to 2.81)	24 fewer per 1000 (from 39 fewer to 76 more)	VERY LOW	CRITICAL
Anxiety (HADS) at 6 months (score 0-21; higher score indicating increased anxiety)[95]												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	N/A	none	9	14		Median (IQR) Int: 12 (11-14) Control: 12 (10-13.7)	MODERATE	IMPORTANT
Anxiety (HADS) at 12 months (score 0-21; higher score indicating increased anxiety)[95]												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	N/A	none	9	14		Median (IQR) Int: 9 (7-12) Control: 11 (9-12.7)	MODERATE	IMPORTANT

a. One study had a high risk of selection bias and both studies had unclear blinding
b. One study had unclear selection bias and blinding whereas the other study had high risk of attrition bias.
c. Confidence intervals crosses two MIDS (0.75 and 1.25)
d. One study [95] reported TTR, but only as a median and IQR. As the mean plus SD provide more accurate information only these data have been fully reported.

Table 14: Clinical evidence profile: education versus usual care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Education	Control	Relative (95% CI)	Absolute	Quality	Importance
TTR (measured with: % of time in therapeutic range; range of scores: 0-100; Better indicated by higher values)[159]												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	not calculated	none	10	43	-	MD 7.9 higher (6.02 lower to 21.82 higher)	VERY LOW	CRITICAL
Knowledge (follow-up mean 12 weeks; measured with: Survey questions modified from Cheah and Martens tool; range of scores: 0-14; Better indicated by higher values)[363]												
1	randomised trials	very serious [b]	no serious inconsistency	no serious indirectness	not calculated	none	5	9	-	MD 1.1 higher (0.69 lower to 2.89 higher)	VERY LOW	IMPORTANT

a. High risk of selection and attrition bias and blinding was unclear.
b. Unclear randomisation and blinding with high risk of attrition bias.

Table 15: Clinical evidence profile: decision aids versus usual care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decision aids	Control	Relative (95% CI)	Absolute	Quality	Importance
Hospitalisation[431]												
1	randomised trials	serious [a]	no serious inconsistency	no serious indirectness	very serious [b]	none	3/53 (5.7%)	4/56 (7.1 %)	RR 0.79 (0.19 to 3.38)	15 fewer per 1000 (from 58 fewer to 169 more)	VERY LOW	IMPORTANT
Decision conflict (measured with: decision conflict scale ; range of scores: 1-5; Better indicated by lower values)[300,309]												
2	randomised trials	serious [c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	363	-	MD 0.1 lower (0.17 to 0.02 lower)	MODERATE	IMPORTANT
Knowledge - warfarin related (measured with: invalidated score - % of correct answers; range of scores: 0-100; Better indicated by higher values)[300]												
1	randomised trials	serious [d]	no serious inconsistency	no serious indirectness	very serious [b]	none	139	148	-	MD 14.9 higher (4.6 to 25.2 higher)	VERY LOW	IMPORTANT
Stroke or thromboembolic events												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decision aids	Control	Relative (95% CI)	Absolute		
0	No available evidence											CRITICAL
TTR												
0	No available evidence											CRITICAL

a. High risk of section bias and unclear blinding.
b. Confidence interval crossed both MIDs (0.75 and 1.25)
c. Both studies had a high risk of selection bias and one study had unclear blinding.
d. High risk of selection bias and unclear blinding.

6.2.2 Economic evidence

Published literature

No relevant economic evaluations were identified. There were no excluded studies.
See also the economic article selection flow chart in Appendix E.

6.2.3 Evidence statements

Clinical

Self-monitoring and education compared to usual care

Evidence from two studies showed that there may be no clinical difference for:

- improving TTR (Moderate quality evidence, N= 69)
- reducing stroke and thromboembolic complications (Very low quality evidence, N= 256)

In both cases the direction of the estimate of effect favoured self-monitoring with education.

Education compared to usual care

Very low quality evidence from one study showed that there may be no clinical difference for improving:

- TTR (N= 53)
- knowledge (N= 14)

In both cases the direction of the estimate of effect favoured education.

Decision aids compared to usual care:

One study, of very low quality evidence showed no clinical difference for:

- reducing hospitalisations (N= 109).
- improving knowledge (N= 287).

In both cases the direction of the estimate of effect favoured decision aids.

Moderate quality evidence from two studies showed that there may be no clinical difference for:

- improving decision conflict, the (N= 721).

The direction of the estimate of effect favoured decision aids

Economic

No relevant economic evaluations were identified.

6.2.4 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	Time in therapeutic range (TTR), quality of life and stroke and thromboembolic complications were considered the critical outcomes for this review. TTR or % of INR in therapeutic range was considered acceptable to determine the control of anticoagulation.

Trade-off between clinical benefits and harms	There was one RCT[95] and one Cochrane review[94] (which included 8 RCTs). There was no clinical difference between TTR and stroke and thromboembolic complications for 2 RCTs comparing self-monitoring and education with usual care. There was no clinical difference between education and usual care for knowledge and TTR. Decision aids found a benefit for knowledge but no difference for hospitalisation or decision conflict when compared to usual care. Despite the lack of evidence that education improved anticoagulant control, the GDG agreed that it was still important to provide patients with information on treatment strategies. Provision of information enables informed decision making. The benefits of education will enable the patients to understand their treatment and make appropriate choices that are suitable for them to improve outcomes. The GDG identified the components of an evidence package which they thought of greatest importance to patients with AF. This package should include: • a basic understanding of the nature of the problem and the different ways in which AF can affect the function of the heart • an explanation of the types of problem which can cause AF including the fact that in some individuals there may be no obvious precipitating cause • an explanation of the types of symptoms which can arise in patients with AF • an explanation of potential complications, especially stroke • an explanation of the objective of treatment in rate and rhythm control strategies and the role of cardioversion in a rhythm control strategy • a consideration of the benefits and risks of anticoagulant therapy • practical guidance on anticoagulation • direction to support networks to enable patients to obtain further information The GDG agreed that patients considering treatment with vitamin K antagonists should be provided with information at the start of their treatment. They agreed that information was an on-going requirement with regular updates needed particularly as their treatment changed at different stages of their lives.
Economic considerations	There was no economic evidence that informed this question. The GDG acknowledged that patient education programmes and tools have healthcare resource implications in terms of staff time and production of materials. Due to no proven effect in favour of a given educational intervention, the recommendations formed are qualitative and advise on the type of information which should be given to AF patients rather than advice on a specific interventional package. As such the resource implications and cost effectiveness will be dependent on local circumstances in how this support is delivered.
Quality of evidence	Overall there were few studies included with small numbers of predominately low quality evidence on education for anticoagulation therapy. None of the trials were cluster randomised and hence contamination effects may be apparent. As the evidence was considered to be poor with major limitations the GDG drafted recommendations using GDG opinion and experience. No evidence was found pertaining to information or education for rate or rhythm strategies.
Other considerations	The GDG noted that the NICE patient experience guideline recommendations highlight well the need to explain the risk and benefits of treatment to patients (Patient experience in adult NHS services, NICE clinical guideline 138) and hence wished to cross refer readers to the guideline.

7 Referral to specialist atrial fibrillation services

7.1 Introduction

Atrial fibrillation (AF) is a chronic disease which has an impact on important health outcomes, particularly heart failure, stroke, and mortality. For this reason it is important that patients identified with atrial fibrillation, of whatever aetiology or classification, are monitored in terms of their underlying condition, the atrial fibrillation itself (particularly in terms of symptoms) and antithrombotic therapy.

Management of AF is now increasingly patient centred and symptom directed.[284] The management cascade for such patients includes stroke prevention, rate and rhythm control, and treatment of associated comorbidities.[66] Guideline-adherent management of AF results in improved clinical outcomes compared to non-adherence with guidelines,[175,331] and specialist referral may improve such a guideline-adherent approach.

Nonetheless, it is uncertain if routine referral to specialist AF services would be clinically beneficial and cost-effective to patient management.

7.2 Review question: What is the clinical and cost effectiveness of referral to specialist AF services?

For full details see review protocol in Appendix C.

Table 16: PICO characteristics of review question

Population	People with atrial fibrillation
Intervention/s	Specialist atrial fibrillation services
Comparison/s	Routine services
Outcomes	Mortality Stroke or thromboembolic complications Health related quality of life Disease awareness Rehospitalisation Adherence to guidelines Number of patients referred to anticoagulation clinic
Study design	Randomised controlled trials (RCT) Systematic reviews of RCTs Non RCTs – prospective cohort studies

7.2.1 Clinical evidence

One RCT study[199] was included in the review with additional information on quality of life and knowledge outcomes from the thesis by the author.[199] Evidence from this is summarised in the clinical GRADE evidence profile below (**Table 18**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 17: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Hendriks 2012[199]	**Intervention:** Specialist care provided in the AF clinic based on the chronic	Adults referred for newly diagnosed AF	Cardiovascular mortality Stroke and	Additional data from thesis by

Study	Intervention/comparison	Population	Outcomes	Comments
	care model, consisting of nurse led outpatient care steered by decision support software based on guidelines (ACC/AHA/ESC) and supervised by a cardiologist. **Comparison**: usual care by a cardiologist in the outpatient clinic		thromboembolic events Quality of life Cardiovascular hospitalisation Adherence to guidelines Knowledge	Hendriks

Table 18: Clinical evidence profile: Referral to specialist AF services versus usual care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Referral to specialist AF services	Control	Relative (95% CI) or p-values reported by author with median SF36 scores	Absolute	Quality	Importance
Mortality - cardiovascular (follow-up mean 22 months)[199]												
1	RCT	no serious risk of bias	no serious inconsistency	serious	serious[a]	none	4/356 (1.1%)	14/356 (3.9%)	HR 0.28 (0.09 to 0.86)	28 fewer per 1000 (from 5 fewer to 35 fewer)	LOW	CRITICAL
Stroke or thromboembolic complications (follow-up mean 22 months)[199]												
1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	4/356 (1.1%)	11/356 (3.1%)	RR 0.36 (0.12 to 1.13)	20 fewer per 1000 (from 27 fewer to 4 more)	MODERATE	CRITICAL
SF36 – physical functioning: change over time, median (IQR) - (follow-up mean 12 months; Better indicated by lower values):												
1	RCT	very serious[b]	no serious inconsistency	no serious indirectness	not calculated[c]	none	0 (-7-10) 286	0 (-10-15) 248	P=0.336[d]	-	LOW	CRITICAL
SF36 – social functioning: change over time, median (IQR) - (follow-up mean 12 months; range of scores 0-100; Better indicated by higher values)												
1	RCT	very serious[b]	no serious inconsistency	no serious indirectness	not calculated[c]	none	0 (-12-12) 286	0 (-12-12) 248	P=0.882[d]	-	LOW	CRITICAL
SF36 – role physical: change over time, median (IQR) - (follow-up mean 12 months; range of scores 0-100; Better indicated by higher values)												
1	RCT	serious[b]	no serious inconsistency	no serious indirectness	not calculated[c]	none	0 (0-25) 286	0 (0-25) 248	P=0.701[d]	-	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Referral to specialist AF services**	**Control**	**Relative (95% CI) or p-values reported by author with median SF36 scores**	**Absolute**	**Quality**	**Importance**
SF36 – role emotional: change over time, median (IQR) - (follow-up mean 12 months; range of scores 0-100; Better indicated by higher values)												
1	RCT	very serious[b]	no serious inconsistency	no serious indirectness	not calculated[c]	none	0 (0-0) 286	0 (0-0) 248	P=0.040[d]	-	LOW	CRITICAL
SF36 – mental health: change over time, median (IQR) - (follow-up mean 12 months; range of scores 0-100; Better indicated by higher values)												
1	RCT	very serious[b]	no serious inconsistency	no serious indirectness	not calculated[c]	none	2 (-4-12) 286	0 (-8-12) 248	P=0.437[d]	-	LOW	CRITICAL
SF36 – vitality: change over time, median (IQR) - (follow-up mean 12 months; range of scores 0-100; Better indicated by higher values)												
1	RCT	very serious[b]	no serious inconsistency	no serious indirectness	not calculated[c]	none	5 (-6-15) 286	5 (-5-15) 248	P=0.65[d]	-	LOW	CRITICAL
SF36 – bodily pain: change over time, median (IQR) - (follow-up mean 12 months; range of scores 0-100; Better indicated by higher values)												
1	RCT	very serious[b]	no serious inconsistency	no serious indirectness	not calculated[c]	none	0 (-10-10) 286	0 (0-22) 248	P=0.024[d]	-	LOW	CRITICAL
SF36 – general health: change over time, median (IQR) - (follow-up mean 12 months; range of scores 0-100; Better indicated by higher values)												
1	RCT	very serious[b]	no serious inconsistency	no serious indirectness	not calculated[c]	none	0 (-10-10) 286	0 (-10-10) 248	P=0.575[d]	-	LOW	CRITICAL
Cardiovascular hospitalisation (follow-up mean 22 months)[199]												
1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	48/356 (13.5%)	68/356 (19.1%)	RR 0.71 (0.5 to 0.99)	55 fewer per 1000 (from 2 fewer to 95 fewer)	MODERATE	IMPORTANT
Adherence to guidelines (follow-up mean 22 months)[199]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Referral to specialist AF services	Control	Relative (95% CI) or p-values reported by author with median SF36 scores	Absolute		
1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	292/356 (82%)	135/356 37.9%	RR 2.16 (1.88 to 2.49)	440 more per 1000 (from 334 more to 565 more)	HIGH	IMPORTANT
Disease awareness (follow-up mean 12 months; range of scores: 0-11; Better indicated by higher values)												
1	RCT	serious[b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	286	248	-	MD 0.57 higher (0.21 to 0.93 higher)	MODERATE	IMPORTANT

a Confidence interval crossed one MID.
b Serious study limitations as only 75% of study population completed the quality of life questionnaire which was reported within the thesis by the author. The majority of the SF-36 functions were not comparable at baseline so change score over time has been reported.
c Imprecision could not be assessed because non-parametric statistics were reported.
d As stated by the authors.
e The evidence had an indirect outcome.

7.2.2 Economic evidence

Published literature

One economic analysis that included a relevant comparison was identified.[197,199] This is summarised in the economic evidence profile below (Table 19) and the economic evidence tables in Appendix H.

Two economic evaluations relating to this review question were identified but were excluded due to limited applicability.[53 427] These are summarised in Appendix K, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Table 19: Economic evidence profile: specialist nurse led care versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost (c)	Incremental effects QALY	Cost effectiveness	Uncertainty
Hendriks et al 2013 [198](Netherlands) [197]	Partially applicable (a)	Potentially serious limitations (b)	Within trial economic analysis Intervention 1: Nurse led care Intervention 2: Usual care by a cardiologist in the outpatient clinic	-£623 (95% CI: -£1,569 to £661)	0.009 (95% CI: -0.007 to 0.024)	Nurse led care is more effective and less costly than usual care	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.

(a) Non UK setting. Unclear if usual care in Dutch setting is applicable comparator as not well described. Various questionnaires used to estimate quality of life which was translated to the SF36, method of mapping of SF36 to EQ5D reported.

(b) 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.

(c) Converted using 2011 purchasing power parities[344]

7.2.3 Evidence statements

Clinical

One study (N= 712) showed that referral to specialist care may be more clinically effective than usual care at:

- reducing cardiovascular hospitalisation (Moderate quality evidence)
- improving adherence to guidelines (High quality evidence)
- reducing cardiovascular mortality (Low quality evidence)
- improving disease awareness (Moderate quality evidence)

The same study showed there may be no clinical difference between referral to specialist care and usual care at:

- reducing stroke or thromboembolic complications (Moderate quality evidence)
- improving quality of life (Low quality evidence)

Economic

One cost utility analysis found specialist nurse led care to be more effective and less costly than usual care, with a 99% probability of being cost effective at the £20,000 threshold. This evidence was partially applicable and had potentially serious limitations.

7.2.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	Mortality, stroke or thromboembolic complications and health related quality of life were considered to be the critical outcomes for this review. Other outcomes reported were disease awareness, rehospitalisation, adherence to guidelines and patients referred to anticoagulation clinics.
Trade-off between clinical benefits and harms	One RCT compared referral to specialist care with usual care and described specialist care as being provided in the AF clinic based on a chronic care model. It consisted of nurse led outpatient care steered by decision support software based on guidelines and supervised by a cardiologist. The usual care was described as a cardiologist in an outpatient clinic. One RCT found a clinical benefit for mortality, hospitalisation, adherence to guidelines and disease awareness favouring referral to specialist care compared to usual care. There was no difference between stroke and thromboembolic diseases and quality of life. This RCT was limited by its applicability to UK general practice as it was based on a Dutch healthcare system which has a different approach to oral anticoagulation. It was noted that 35% of the study population had a $CHADS_2$ score greater than 1 and the GDG felt that this was a lower risk population than an AF population in primary care in the UK. Although this RCT promotes benefits to specialist AF care in some aspects the GDG were cautious in interpreting the evidence due to these limitations. The GDG agreed that some level of specialist care was important for AF patients but did not feel that a computer assisted programme of specialist care used in this study should be recommended based on one small study. The GDG took into account the various limitations including lack of applicability, small event numbers and no consistent trial evidence. However, GDG consensus was to make recommendations for a tailored initial package of care that precedes onward referral to specialist AF service if AF symptoms remain uncontrolled (see recommendation in previous chapter). The GDG debated the potential harms of not referring some rapidly for specialist AF care when standard AF treatments had failed compared to over burdening a specialist AF referral service. Through consensus, the GDG described the component of a specialist service and that these could be provided through a package of care which covered key elements of service provision tailored to the AF patient as was enforced through formal documentation that key elements had been delivered. For this reason they recommended that there should be timely onward referral of patients who remain symptomatic despite their initial care package. The GDG wanted to ensure that patients were promptly being referred if their initial care package had not controlled their symptoms or when further management requires onward referral. The GDG defined prompt referral as within four weeks of the final failed therapy (or for cardioversion when AF recurrence occurred) and this was based on the experience and opinion of the GDG. The GDG considered that it was important to include patient education and information within the care package. The GDG agreed that psychological support was a factor that needed to be included as it is important to raise awareness of this issue within the AF population. It was thought that some AF patients may not be aware that their anxiety is due to AF which in turn could be making their symptoms worse.

Economic considerations	One cost-effectiveness analysis found that specialist nurse led care was a dominant strategy when compared to usual care. Nurse led care involved dedicated software and a higher volume of diagnostics (inclusive of laboratory costs) due to guideline adherent management. Therefore it is unclear whether it was the components of the integrated care system which was nurse led, or the involvement of the specialist nurse, that specifically led to improved outcomes. Nurse led care was found to be cost saving due to a reduction in the mean cost per patient of inpatient hospitalisation, whereby an average of 0.21 (SD: 0.54) hospitalisations per patient was found with usual care, and a 0.11 (SD: 0.37) hospitalisations per patient was found with nurse led care, resulting in an average saving of €775.06 per patient in hospital inpatient costs. The outcome of hospitalisation was found to have moderate quality in the clinical review. The GDG discussed the potential limitations of the study which are further summarised below. Overall it was felt that whilst this study did not disprove cost effectiveness of the intervention, it did not give firm evidence for cost effectiveness of referral to specialist services. Cost effectiveness therefore remains unproven in the UK setting. The GDG felt that having a dedicated service to AF patients would greatly improve health outcomes through symptom management, timely monitoring, and treatment plans. Through consensus, the GDG described the components of a specialist service and that these could be provided through a package of care which covered key elements of service provision tailored to the AF patient, and was enforced through formal documentation that key elements had been delivered. As these aspects are already recommended in this guideline, the additional resource use in implementing this recommendation above and beyond that of the guideline would primarily be that in documenting and implementing the referral system. Local circumstance would dictate the most cost-effective and pragmatic means of delivering this recommendation. Overall, reinforcement of the cost-effective practice as recommended in the guideline is likely to offset costs in delivering this recommendation.
Quality of evidence	There was only one randomised controlled trial included in this review that had predominately moderate quality outcomes. The outcome quality of life and patient knowledge were reported within the author's thesis but not published within the RCT. The quality of life and patient knowledge was questionnaire based information and 75% of the target population responded. There were significant differences between baseline scores for different criteria within the SF-36 questionnaire (quality of life) which was why we reported difference over time rather than 12 month results. The economic analysis was assessed to have partial applicability and potentially serious limitations, sharing the same limitations as the randomised control trial. The GDG noted that the mean cost per inpatient hospitalisation, a key aspect in leading to the conclusion that the intervention was cost saving, appeared different between the study groups. Due to the reporting of costs, it was unclear whether this was due to a potential difference in the complexity and complications between the two groups. Given the differences in baseline quality of health domains regarding physical function and bodily pain, the GDG interpreted the conclusion of the analysis with caution. The GDG defined an "AF specialist" as a cardiologist or nurse with an interest in arrhythmias.
Other considerations	The recommendations were based on the evidence and the experience and opinion

	of the GDG.

8 Stroke risk tools

This section was updated and replaced in 2021. See http://www.nice.org.uk/guidance/ng196/evidence for the 2021 evidence reviews.

8.1 Introduction

Atrial fibrillation (AF) increases the risk of stroke and thromboembolism by five-fold, but this risk is not homogeneous, and is dependent upon the presence of various stroke risk factors. These stroke risk factors have recently been part of a systematic review.[359] They have been used to formulate stroke risk stratification tools, which have been used in clinical practice to aid decision making.[281] Approaches to stroke risk stratification are evolving. The focus of older risk stratification tools was to divide patients into low, moderate and high risk strata, so that 'high risk' patients could be targeted for oral anticoagulation. However, numerous studies have shown that a focus on identifying 'high risk' patients still leads to substantial undertreatment with oral anticoagulants in these populations.[335]

Stroke risk is a continuum, and the presence of AF with even a single stroke risk factor (some of which carry more weight) confers an increased risk of stroke. Thus the focus of contemporary stroke risk assessment has shifted towards the initial identification of 'low risk' patients who have such a low absolute risk that no antithrombotic therapy (whether anticoagulant or antiplatelet therapy) is necessary.[66] Subsequent to this step, AF patients with one or more stroke risk factors can be offered effective stroke prevention.

The objective of this chapter is to review the clinical utility and cost effectiveness of various stroke risk scores in AF. Two scores were considered, $CHADS_2$ and CHA_2DS_2-VASc.

8.2 Review question: What is the most clinically and cost-effective risk stratification tool for stroke or thromboembolic events in people with AF?

For full details see review protocol in Appendix C.

Table 20: PICO characteristics of review question

Population	People with atrial fibrillation
Risks tools (must be validated – in different population and by different author)	$CHADS_2$ ACCP (8th edition) ACC/AHA/ESC (2006) CHA_2DS_2-VASc
Patient outcomes	Stroke Thromboembolic events Mortality (stroke or thrombosis)
Statistical outcomes	Hazard ratios for high, moderate thresholds Sensitivity/specificity Area under the curve (AUC)/ c indices Calibration Net reclassification scores
Study design	Cohort studies

8.2.1 Clinical evidence

Eleven studies were included in the review.[37,104,142,154,161,262,275,287,340,444] Evidence from these are summarised in summary of included studies below. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

The clinical evidence profile in **Table 22** was completed only using the studies with over 100 events as fewer events was considered a major study limitation.

Table 21: Summary of studies included in the review

Study	Stroke risk score	Population	Outcomes
Baruch 200737 Prospective cohort (based on randomised parallel-group trials) N = 7329 This study is the same as Lip 2010, but at 1.5 year mean follow up, rather than up to 9 years.	CHADS2 CHA2DS2-VASc ACC/AHA/ESC NICE 2006	Patients with AF enrolled in SPORTIF III and SPORTIF V trials. Received anticoagulation (warfarin or ximelagatran)	Stroke (c statistics and hazard ratios based on continuous scores and 3 strata risk scores)
Coppens 2013104 Prospective cohort N = 4670	CHADS2 CHA2DS2-VASc	Patients with AF and a CHADS2 score of 1 enrolled in AVERROES, ACTIVE-W and ACTIVE-A trials, treated with aspirin or clopidogrel.	Thromboembolism (c statistics and hazard ratios based on dichotomised risk scores)
Fang 2008142 Prospective cohort N = 13559 (5588 not on warfarin).	CHADS2 ACCP 2004	Patients with AF enrolled in ATRIA study.	Thromboembolism (c statistics based on continuous scores and 3 strata risk scores)
Friberg 2012B154 Retrospective cohort N = 170291 (90490 not on warfarin)	CHADS2 CHA2DS2-VASc ACC/AHA/ESC NICE 2006	Patients with AF	Stroke and thromboembolism (c statistics based on continuous and 3 strata risk scores) NRI for CHADS2, ref = CHA2DS2-VASc
Gage 2004161 Data from 6 trials (AFASAK-I, PATAF, EAFT, low risk SPAF III, AFASAK -2 and high risk SPAF III. N = 2580 (2/6 trials included warfarin)	CHADS2 ACCP 2001	Patients with non valvular AF - all received aspirin.	Stroke (c statistic based on 3 strata risk scores).
Larsen 2012262 Prospective cohort N = 1603 (not on warfarin)	CHADS2 CHA2DS2-VASc	Patients with AF	Stroke and mortality (continuous data).
Li 2012275 Prospective cohort N = 1297 (1112 without anticoagulants)	CHADS2 CHA2DS2-VASc	Patients hospitalised with acute stroke and non valvular AF.	Stroke recurrence and mortality (c statistic).
Lip 2010A287 Prospective cohort (SPORTIF III and V trials) N = 7329	CHADS2 CHA2DS2-VASc 8th ACCP NICE 2006	Patients with non-valvular AF. Received anticoagulation (warfarin or ximelagatran)	Thromboembolism (c statistics and hazard ratios based on 3 strata risk scores)
Olesen 2011336	CHADS2	Patients with AF not	C-statistics for

Study	Stroke risk score	Population	Outcomes
Retrospective cohort N=73538	CHA2DS2-VASc	treated with vitamin K antagonists	thromboembolism
Olesen 2012B340 Retrospective cohort N = 47576 (without anticoagulants)	CHADS2 CHA2DS2-VASc	Patients with non-valvular AF or atrial flutter.	Thromboembolism (hazard ratio by dichotomised scores, c statistic and NRI)
Vanstaa 2011444 Prospective cohort N = 79844 (20% received anticoagulants)	ACCP (2001, 2004, 2008) CHADS2 CHA2DS2-VASc NICE 2006 ACC/AHA/ESC	AF patients identified in general practice.	Stroke and mortality (c statistics for continuous and 3 strata risk factors).

Table 22: Clinical evidence profile: Stroke risk scores

Quality assessment							No of events/patients		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Absolute risk difference	Hazard ratios [95% CI] c	Quality
Hazard ratio for stroke (categorical variables) – CHA_2DS_2-VASc[340] -No anticoagulant										
CHA_2DS_2-VASc 1 versus 0										
1	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	1: 159/8880 (1.79%) 0: 58/6919 (0.83%)	9 more per 1000 (from 5 more to 15 more)	2.10 [1.56 - 2.81	MODERATE
CHA_2DS_2-VASc 2 versus 0										
1	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	2: 435/11863 (3.67%) 0: 58/6919 (0.83%)	27 more per 1000 (from 20 more to 35 more	4.22 [3.40 - 5.24]	MODERATE
CHA_2DS_2-VASc 3 versus 0										
1	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	3: 660/11473 (5.75%) 0: 58/6919 (0.83%)	46 more per 1000 (from 32 more to 64 more)	6.49 [4.84 - 8.71]	MODERATE
CHA_2DS_2-VASc 4 versus 0										

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
1	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	4: 93/1137 (8.18%) 0: 58/6919 (0.83%)	67 more per 1000 (from 46 more to 97 more)	9.12 [6.53 - 12.72]	MODERATE
Hazard ratio for stroke (continuous variables) – $CHADS_2$[37]										
$CHADS_2$ 1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 0/238 (0%) Moderate: 72/7286 (1.0%) High: 87/3721 (2.3%)	-	1.48 [1.31 - 1.66]	HIGH
Hazard ratio for stroke (3 strata continuous variables) – $CHADS_2$[37]										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 0/238 (0%) Moderate: 72/7286 (1.0%) High: 87/3721 (2.3%)	-	2.44 [1.78 - 3.33]	HIGH
Hazard ratio for thromboembolism (categorical variables) – CHA_2DS_2-VASc[104]										
CHA_2DS_2-VASc 2 versus 1										
1	Cohort studies	no serious limitations	no serious inconsistency	Serious indirectness (b)	no serious imprecision	none	1: 27/1224 (2.20%) 2: 92/1984 (4.64%)	26 more per 1000 (from 9 more to 53 more)	2.2 [1.43 - 3.39]	MODERATE

Quality assessment							No of events/patients		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Absolute risk difference	Hazard ratios [95% CI] c	Quality
CHA_2DS_2-VASc 2-4 versus 1										
1	Cohort studies	no serious limitation	no serious inconsistency	serious indirectness (b)	no serious imprecision	none	1: 27/1224 (2.20%) 2 - 4: 178/3446 (5.16%)	37 more per 1000 (from 16 more to 69 more)	2.69 [1.75 - 4.14]	MODERATE
CHA_2DS_2-VASc 3-4 versus 1										
1	Cohort studies	no serious limitation	no serious inconsistency	serious indirectness (b)	no serious imprecision	none	1: 27/1224 (2.20%) 3 - 4: 86/1462 (5.88)	33 more per 1000 (from 15 more to 61 more)	2.51 [1.66 - 3.79]	MODERATE
Hazard ratio for thromboembolism (3 strata continuous variables) – $CHADS_2$[287]										
$CHADS_2$ (1 = moderate)										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 0/238 (0 %) Moderate: 87/7276 (1.19%) High: 97/3716 (2.61%)	-	2.51 [1.73 - 3.64]	HIGH
$CHADS_2$ (1-2 = moderate)										

Quality assessment							No of events/patients		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor	Absolute risk difference	Hazard ratios [95% CI] c	Quality
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 0/238 (0 %) Moderate: 31/3563 (0.87%) High: 153/7431 (2.05%)	-	2.27 [1.73 - 2.99]	HIGH
NICE 2006										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 0/238 (0 %) Moderate: 32/3651 (0.87%) High: 152/7580 (2.00%)	-	2.27 [1.56 - 3.29]	HIGH
ACC/AHA/ESC 2006										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 0/212 (0 %) Moderate: 29/3469 (0.83%) High: 155/7551 (2.05%)	-	2.59 [1.75 - 3.83]	HIGH
ACCP 2008										

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 0/212 (0%) Moderate: 29/3479 (0.83%) High: 155/7541 (2.05%)	-	2.59 [1.75 - 3.83]	HIGH
CHA_2DS_2-VASc										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[f]	none	Low: 0/2 (0%) Moderate: 3/65 (4.61%) High: 181/10578 (1.71%)	-	3.75 [1.20, 11.73]	MODERATE
C statistic for stroke (3 strata continuous variables) NICE 2006[154] No anticoagulants										
1	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	Event rate/100 years Low:0.2 Intermediate: 2.2 High: 6.4	-	C statistic: 0.61 [0.60 - 0.62]	MODERATE
C statistic for stroke (3 strata continuous variables) – CHA_2DS_2-VASc[154] No anticoagulants										
1	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	Event rate/100 years Low:0.2 Intermediate: 0.6 High: 6.2	-	C statistic: 0.56 [0.56 - 0.57]	MODERATE
C statistic for stroke (3 strata continuous variables) – $CHADS_2$ [154] No anticoagulants										

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
$CHADS_2$ (1-2 = moderate)										
1	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	Event rate/100 years Low:0.6 Intermediate: 3.0 High: 6.6	-	C statistic: 0.62 [0.61 - 0.62]	MODERATE
$CHADS_2$ (1 = moderate)										
1	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	Event rate/100 years Low:0.6 Intermediate: 3.6 High: 9	-	C statistic: 0.65 [0.64 - 0.65]	MODERATE
C statistic for stroke (3 strata continuous variables) – $CHADS_2$[37,161] All patients										
1	Cohort studies	serious limitations (c)	no serious inconsistency	no serious indirectness	not assessed	none	Event rate/100 years Low:0.8 Intermediate: 2.7 High: 5.3	-	C statistic: 0.7 (CI not reported)	MODERATE
C statistic for stroke (3 strata continuous variables) – ACCP 2001[161]										
1	Cohort studies	serious limitations (c)	no serious inconsistency	no serious indirectness	not assessed	none	N/R	-	C-statistic: 0.58 (CI not reported)	MODERATE

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
C statistic for stroke (3 strata continuous variables) – ACC/AHA/ESC[154]										
1	Cohort studies	serious limitations (a)	no serious inconsistency	Serious indirectness (b)	no serious imprecision	none	Event rate/100 years Low:0.6 Intermediate: 2.8 High: 6.6	-	C statistic: 0.62 [0.61 - 0.62]	MODERATE
C statistic for stroke (continuous) – ACCP[37]										
1	Cohort studies	serious limitations (c)	no serious inconsistency	no serious indirectness	not assessed	none	ACCP 2001: Low: 2/173 (1.2 %) Moderate: 1/271 (0.4%%) High: 156/10800 (1.4%) ACCP 2004: Low: 0/29 (0%) Moderate: 0/250 (0%) High: 159/10965 (1.5%)	-	C statistic: 0.51 (CI not reported)	MODERATE
C statistic for stroke (continuous) – $CHADS_2$, all patients[37,161,275]										

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
2	Cohort studies	serious limitations (c)	no serious inconsistency	no serious indirectness	not assessed	none	Baruch 2007 Low: 0/238 (0 %) Moderate: 72/7286 (0.99%) High: 87/3721 (2.34%) Li: N/R	-	Median c-statistic [95% CI]: 0.53 0.65 Range: 0.53-0.65	MODERATE
C statistic for stroke (continuous) – $CHADS_2$, no anticoagulation[154,262]										
2	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	Serious imprecision(d)	none	Friberg 2012: Event rate/100 years Low:0.6 Intermediate: 3.6 High: 9.0 Larsen 2012: N/R	-	Median c-statistic [95% CI]: 0.64 [0.56-0.71] 0.66 [0.66-0.67] Range0.64 - 0.66	LOW
C statistic for stroke (continuous) – CHA_2DS_2-VASc, all patients[275]										
1	Cohort studies	serious limitations (c)	no serious inconsistency	no serious indirectness	not assessed	none	N/R	-	C statistic: 0.53 (CI not reported)	MODERATE

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
C statistic for stroke (continuous) – CHA_2DS_2-VASc, no anticoagulation[154,262]										
2	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	Serious imprecision(d)	none	Friberg 2012: Event rate/100 years Low:0.2 Intermediate: 0.6 High: 6.2 Larsen 2012 N/R	-	Median c-statistic [95% CI]: 0.66 [0.59-0.72] 0.67 [0.66-0.68] Range: 0.66-0.67	LOW
C statistic for thromboembolism (3 strata)– ACC/AHA/ESC[154,287]										
2	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Friberg 2012: Event rate/100 years Low:0.8 Intermediate: 3.9 High: 9.2 Lip 2010: Low: 0/212 (1.8%) Moderate: 29/3469 (30.3%) High: 155/7551 (67.9%)	-	Median c-statistic [95% CI]: 0.59 [0.56-0.61] 0.62 [0.61-0.62] Range: 0.59-0.62	HIGH

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
C statistic for thromboembolism (3 strata) – ACCP, all patients[142,287]										
2	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Fang 2008: Low: 11.7% Moderate: 7.9% High: 80.4% Lip 2010: Low: 0/212 (%) Moderate: 29/3479 (0.83%) High: 155/7541 (2.05%)	-	Median c-statistic [95% CI]: 0.56 0.59 [0.56-0.61] Range of HR: 0.56-0.59	HIGH
C statistic for thromboembolism (3 strata) – ACCP, no anticoagulation[142]										
1	Cohort studies	serious limitations (c)	no serious inconsistency	no serious indirectness	not assessed	none	N/R	-	C statistic 0.6 (CI not reported)	MODERATE
C statistic for thromboembolism (3 strata)– $CHADS_2$, all patients[142,287]										

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
2	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Fang 2008: Low: 18.8% Moderate: 61.2% High: 20.1% Lip2010: Low: 0/238 (0 %) Moderate (1): 31/3563 (0.87%) High: 153/7431 (2.05%) Lip2010: Low: 0/238 (0 %) Moderate (1 - 2) : 87/7276 (1.19%) High: 97/3716 (2.61%)	-	Median c-statistic [95% CI]: 0.58 0.64 [0.61-0.67] Range: 0.58-0.64	HIGH
C statistic for thromboembolism (3 strata) – $CHADS_2$, no anticoagulation[142,154,339,340]										

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
4	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	Fang 2008: Event rate not given. Friberg 2012: Event rate/100 years Low:0.9 Intermediate: 5.2 High: 12.3 Olesen 2012: 1: 159/8880 (1.79%) 0: 58/6919 (0.83%) Olesen 2011: Event rate/100 person years Low: 1.67 Intermediate: 4.75 High: 12.27	-	Median c-statistic [95% CI]: 0.61 [0.61-0.62] 0.66 [0.65-0.68] 0.67 [CI not reported] 0.72 [0.69-0.75] Range: 0.61-0.72	MODERATE
C statistic for thromboembolism (continuous) – $CHADS_2$, all patients[142]										
1	Cohort studies	serious limitations (c)	no serious inconsistency	no serious indirectness	not assessed	none	Fang 2008: Event rate not given.	-	C statistic 0.6 (CI not reported)	MODERATE

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
C statistic for thromboembolism (continuous) – $CHADS_2$, no anticoagulation[154,339]										
2	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	serious imprecision(d)	none	Friberg 2012: Event rate/100 years Low:0.3 Intermediate: 1.0 High: 8.9 Olesen 2011: Event rate/100 person years Low: 1.67 Intermediate: 4.75 High: 12.27		Median c-statistic [95% CI]: 0.66 [0.65-0.66] 0.72 [0.69 - 0.75] Range: 0.66-0.72	LOW
C statistic for thromboembolism (3 strata) – CHA_2DS_2-VASc , all patients[104,287]										
2	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 0/2 (%) Moderate: 3/65 (4.61%) High: 181/10578 (1.71%) Coppens 2013: 1: 27/1224 (2.20%) 2: 92/1984 (4.64%) 3 - 4: 86/1462 (5.88)	-	Median c-statistic [95% CI]: 0.57 [0.54-0.59] 0.65 [0.61-0.68] Range: 0.57-0.65	HIGH

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
C statistic for thromboembolism (3 strata) – CHA_2DS_2-VASc , no anticoagulation[154,339,340]										
3	Cohort studies	serious limitations (a)	serious inconsistency(e)	no serious indirectness	no serious imprecision	none	Friberg 2012: Event rate/100 years Low:0.3 Intermediate: 1.0 High: 8.9 Olesen 2011 Event rate per 100 years Low: 0.78 Intermediate: 2.01 High: 8.82 Olesen 2012 Event rate/100 years 0= 0.84 1= 1.79 2= 3.67 3= 5.75 4= 8.18	-	Median c-statistic [95% CI]: 0.56 [0.56-0.57] 0.63 [0.62-0.65] 0.85 [0.83-0.87] Range: 0.56-0.85	LOW
C statistic for thromboembolism (continuous) – CHA_2DS_2-VASc , no anticoagulation[154,339]										

Quality assessment							No of events/patients		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of events/people (%) with and without risk factor**	**Absolute risk difference**	**Hazard ratios [95% CI] c**	**Quality**
2	Cohort studies	serious limitations (a)	serious inconsistency (e)	no serious indirectness	no serious imprecision	none	Friberg 2012: Event rate/100 years Low:0.3 Intermediate: 1.0 High: 8.9 Olesen 2011 Event rate per 100 years Low: 0.78 Intermediate: 2.01 High: 8.82	-	Median c-statistic [95% CI]: 0.67 [0.67-0.68] 0.85 [0.83-0.87] Range: 0.67-0.85	LOW
C statistic for thromboembolism – NICE 2006, no anticoagulation and all patients[154,287]										
2	Cohort studies	serious limitations (a)	no serious inconsistency	no serious indirectness	no serious imprecision	none	Friberg 2012: Event rate/100 years Low:0.3 Intermediate: 0.5 High: 9.0 Lip 2010: Low: 0/238 (0 %) Moderate: 32/3651 (0.87%) High: 152/7580 (2.00%)	-	Median c-statistic [95% CI]: 0.58 [0.55-0.60] 0.61 [0.60-0.62] Range: 0.58-0.61	MODERATE

(a) Retrospective cohort. Data obtained through database searching. Unknown if patients were selected randomly or consecutively.

(b) Indirectness - selected patients with a $CHADS_2$ score of 1.
(c) Missing data, point estimate for c statistic given and no confidence intervals provided.
(d) Wide confidence intervals make it difficult to know the true effect size for this outcome.
(e) Inconsistency detected across studies
(f) Confidence interval crossed one MID

Quality assessment							No of patients/events		Effect	
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Number of people with an event reclassified to a higher risk**	**Number of people without an event were reclassified to a higher risk**	**Net reclassification index (95% CI)**	**Quality**
Net reclassification index using CHA_2DS_2-VASc instead of $CHADS_2$[262,340]										
2	Cohort studies	serious limitations [(a)]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Olesen: 1307/1405 (93%)	Olesen: 36410/46171 (78.9%)	Larsen: -3% (-6% to -1%) Olesen: 14.2%	MODERATE

(g) Retrospective cohort. Data obtained through database searching. Unknown if patients were selected randomly or consecutively.

8.2.2 Economic evidence

Published literature

One economic evaluation relating to this review question was identified but excluded due to the availability of more applicable evidence through new cost-effectiveness modelling. [430] This is summarised in Appendix K, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

New cost-effectiveness analysis

In the absence of published cost-effectiveness studies on this topic, an original cost-effectiveness analysis to evaluate the most appropriate stroke risk score to initiate anticoagulation was prioritised for the guideline. In particular, the comparison of the $CHADS_2$ and CHA_2DS_2-VASc scoring methods were prioritised as these are most commonly used in UK practice. Further it was unclear from the clinical evidence review which of these scoring systems was most likely to be cost effective when used to decide appropriate stroke preventive therapy. This analysis was embedded in a model looking at stroke prevention treatments for people in AF, the results are summarised in the table below. Please also see chapter 9 for an overview of the full analysis and appendix L or a full technical report.

Table 23: Economic evidence profile: Use of $CHADS_2$ and CHA_2DS_2-VASc scoring methods to decide treatment with antithrombotic therapy

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects	Cost effectiveness	Uncertainty
NCGC adaption of the MAPGuide model (2013), UK. Please see appendix [M] for full details.	Directly applicable (a)	Potentially serious limitations (b)	An extended analysis of a model assessing cost effectiveness of alternative antithrombotic treatments to prevent stroke assessed two stroke risk scoring systems to determine most cost-effective threshold to give anticoagulation (following a do nothing, single or a dual antiplatelet strategy) for people with AF but at low risk of stroke. The analysis compared the following groups of strategies: 1. Give anticoagulation at CHA_2DS_2-VASc score of 2 2. Give anticoagulation at $CHADS_2$ score of 1 3. Give anticoagulation at CHA_2DS_2-VASc score of 1 4. Give anticoagulation according to bleeding risk score (stroke risk score = NA) The above four strategies were further stratified by	**Extended analysis of using risk scoring tools** A strategy to give anticoagulation after a do nothing strategy (as compared giving single or dual antiplatelets) achieved the highest net monetary benefit for any given combination of bleeding and stroke risk scores. The results of initiating anticoagulation after a do nothing strategy when at or above a given stroke risk score, or at or below a given HAS-BLED score, are given below. Non dominated options were to "not give antithrombotic therapy" or to "give anticoagulation at CHA_2DS_2-VASc score of 2 or above and a HAS-BLED score of 0, otherwise do nothing" Incremental cost = £1.84 Incremental QALY gain = 0.00125 Cost per QALY gain = £1467.94 **Probabilistic Results — Value for outcome: QALY (discounted)** Intervention if under a given stroke risk score / Do not give AC / Give anticoagulation if at, or under, bleeding risk specified by HASBLED score of…: 0, 1, 2, 3, 4, 5, NA Control — NA: 5.24 | 5.24 | 5.21 | 5.15 | 5.08 | 5.03 | 5.03 | 5.15 CHADSVASC1: 5.24 | 5.21 | 5.16 | 5.09 | 5.04 | 5.03 | 5.14 CHADS1: 5.24 | 5.21 | 5.17 | 5.10 | 5.05 | 5.03 | 5.15 CHADSVASC2: 5.25 | 5.23 | 5.18 | 5.12 | 5.07 | 5.07 | 5.16 **Probabilistic Results — Value for outcome: Cost (discounted)** Intervention if under a given stroke risk score / Do not give AC / Give anticoagulation if at, or under, bleeding risk specified by HASBLED score of…: 0, 1, 2, 3, 4, 5, NA Control — NA: 19318.56 | 19429.43 | 20480.27 | 23542.50 | 26399.53 | 27630.82 | 27892.94 | 25590.77 CHADSVASC1: 19392.64 | 20361.53 | 23425.38 | 26339.68 | 27568.94 | 27709.90 | 25777.68 CHADS1: 19324.04 | 20480.27 | 23130.05 | 26015.04 | 27239.32 | 27892.94 | 25590.77 CHADSVASC2: 19320.40 | 20096.32 | 22968.27 | 25858.03 | 27065.57 | 27260.27 | 25444.92 **Probabilistic Results — Value for outcome: NB (discounted)** Strategy / Do not give AC / Give anticoagulation if at, or under, bleeding risk specified by HASBLED score of…: 0, 1, 2, 3, 4, 5, NA Control — NA: 85560.78 | 85371.18 | 83656.90 | 79503.35 | 75288.93 | 73046.02 | 72650.60 | 77385.50 CHADSVASC 1: 85487.54 | 83890.64 | 79702.80 | 75461.88 | 73204.02 | 72941.99 | 77014.59 CHADS 1: 85556.30 | 83656.90 | 80230.95 | 75965.13 | 73814.80 | 72650.60 | 77385.50 CHADSVASC 2: 85584.01 | 84531.98 | 80724.20 | 76618.37 | 74393.75 | 74065.16 | 77803.23			The probabilistic analysis shows increasing uncertainty around the QALY gain (in comparison to a do nothing strategy) with increasing numbers of patients put on anticoagulation with higher bleeding risk thresholds. Of all strategies assessed, including those using combinations of bleeding and stroke risk thresholds to determine management, the three highest ranking strategies with highest probability of being optimal were: a) Give anticoagulation at CHA_2DS_2-VASc score of 2 or above and a HAS-BLED score of 0, otherwise do nothing = 16% probability b)Give anticoagulation at $CHADS_2$ score of 1 or above and a HAS-BLED score of 0, otherwise do nothing = 14% probability c)Give anticoagulation at CHA_2DS_2-VASc score of 1 or above and a HAS-BLED score of 0, otherwise do nothing = 14% probability Small absolute differences between the strategies, in particular in the QALY gain, means small differences in effect could have a large impact on

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects	Cost effectiveness	Uncertainty
			bleeding risk as measured by the HAS-BLED score.	[NA indicates that no stroke risk or bleeding risk scoring system was used to initiate treatment with anticoagulation).			the incremental cost-effectiveness ratio between the optimal strategies, including the optimal score at which to give treatment. In deterministic analysis, lowering haemorrhagic adverse event risk of anticoagulation changed the overall conclusions of the most cost-effective decision rule, with conclusions matching those of the probabilistic analysis. Lowering case fatality rates of bleeding did not change the conclusion on the deterministic analysis.

a) *UK dataset used to populate model, with NICE reference case followed. Not all comparators listed in the review protocol explored.*
b) *Analysis considers downstream management options to evaluate cost and benefit of using the risk scoring tools to inform management. Probabilistic analysis performed, effectiveness informed by systematic review and network meta-analysis. Exploration of risk scoring on management decisions. Assumptions and parameters validated as reasonable for decision making, with deterministic sensitivity analysis on parameter estimates of concern.*

8.2.3 Evidence statements

Clinical

Moderate quality evidence from one study showed hazard ratios for stroke ranging from 2.10 – 9.12 (increases with for CHA_2DS_2-VASc (hazard ratio increases with increasing risk group).
Moderate quality evidence reported a hazard ratio of:

- stroke of 1.48 (continuous) and 2.44 (3 strata continuous) for $CHADS_2$ score (High quality evidence)
- 2.20 – 2.69 for thromboembolism for CHA_2DS_2-VASc score in patients with a $CHADS_2$ score of 1.

High quality evidence reported a hazard ratio of:

- stroke of 1.48 (continuous) and 2.44 (3 strata continuous) for $CHADS_2$ score
- thromboembolism of 2.59 for ACCP score, 2.59 for ACC/AHA/ESC score, 2.27-2.51 for $CHADS_2$ score and 3.74 for CHA_2DS_2-VASc.

Moderate quality evidence was found for thromboembolism c-statistic with patients not on anticoagulation for ACCP (8th) of 0.60 which is poor at discriminating between risk groups.
Low to moderate quality evidence was found for:

- CHA_2DS_2-VASc score ranging from 0.56 to 0.85 which crosses the category of fair to good discrimination of risk groups (7 studies)
- CHA_2DS_2 score ranging from 0.61 to 0.72 which crosses the category of poor to fair discrimination between risk group (9 studies).

Economic

No relevant economic evaluations were identified.

One original cost utility analysis (NCGC 2013) found in a probabilistic sensitivity analysis that use of the CHA_2DS_2-VASc score to determine when to give anticoagulation resulted in a marginally higher mean net monetary benefit than use of the $CHADS_2$ score (when holding the bleeding risk threshold within the decision rule constant). For example, the incremental net monetary benefit between initiation at CHA_2DS_2 score of 1 versus a CHA_2DS_2-VASc score of 2 for patients with the lowest HAS-BLED: £28 per patient. This analysis was assessed as directly applicable with minor limitations.

8.2.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	Hazard ratios of stroke and thromboembolic events between risk groups stratified by the same tool were considered critical outcomes for this prognostic review. The higher the hazard ratio, the greater the difference was in observed risk of these between the risk groups identified by the tool. In particular, outcomes reported using patient cohorts not on anticoagulation were considered important as these outcomes were reflective of the population that the GDG would be making the recommendation for. Ideally, outcomes to assess predictive as well as discriminatory power of the prognostic tools are desired; however, no study reported on such outcomes. The comparisons between prognostic outcomes are most useful where they have been calculated using risks estimated by stratifying the same population by different risk scores. The C-statistic is a measure of how good a test is, and can be considered to be the average probability that the test can discriminate between people at high risk and low risk. However, knowing whether it is a good test or not is not always helpful. The GDG want to use the test to inform treatment options for people with different risks for which hazard ratios, odds ratios or risk ratios at a particular threshold are needed. In addition, C-statistics are insensitive to changes in the risk model (when new prognostic factors are added to an existing model). However, the C-statistic is useful in deciding if the prognostic model is better than chance, but the fine tuning differences between tests are not so easily distinguished. The GDG included this statistic as an outcome as it is commonly reported in these studies and adds some useful information to the review in the absence of hazard ratios. Reclassification measures were also reported and although informative about how well the tool may differentiate a given population according to risk, reclassification does not give much information on the tools predictive power. Assuming accurate prediction, the most useful tool will be able to discriminate and classify the most accurately groups which would benefit most from cost-effective treatments. The GDG also emphasised that the recommendations on anticoagulation applied to all patients with AF irrespective of whether they were symptomatic, to all categories of AF (paroxysmal, persistent and permanent), to patients following cardioversion considered at continuing risk of arrhythmia recurrence, and to patients with atrial flutter.
Trade-off between clinical benefits and harms	The GDG highlighted that 'high risk' AF populations were already known to be undertreated and for this reason the GDG agreed that the default should be to treat all AF patients unless they were clearly defined as truly 'low risk'. Because of this the GDG were more concerned with identifying the very low risk groups of patients and hence those who did not require pharmacological treatment to prevent stroke. Overall the stroke risk scores, the hazard ratio scores for stroke were reporting a 3% increase on top of a 2% absolute risk at baseline. The GDG agreed that there was a clinical benefit in using a stroke risk score to identify patients at risk. The review

	found that there may be a slight benefit of CHA_2DS_2-VASc over the other scores considered ($CHADS_2$, ACCP and the ACC/AHA/ESC). The c-statistics suggested that the scores were not very good at discriminating between risk groups. The GDG considered a number of studies that showed how the CHA_2DS_2-VASc score further refined stroke risk in patients categorised as low risk using the $CHADS_2$ score. One study[104] used a clinical trial population with a $CHADS_2$ score of 1 and reclassified patients into CHA_2DS_2-VASc scores showing that CHA_2DS_2-VASc was better at identifying the low risk groups of patients. This indicated that $CHADS_2$ score of 1 was not necessarily 'low risk' and could include some patients that were at high risk of stroke. The nationwide cohort study by Olesen 2012[340] found that of >17,000 patients with a $CHADS_2$ score of 0, the rate of stroke could range between 0.8% to 3.25/year, when patients were sub stratified using the CHA_2DS_2-VASc score. Hence the CHA_2DS_2-VASc score has been shown to refine stroke risk stratification even in those previously defined as 'low risk' [Olesen 2012[340]]. The GDG agreed that all people with AF and a CHA_2DS_2-VASc score of 2 should be offered anticoagulation. However, anticoagulation should be considered for men with a CHA_2DS_2-VASc score of 1. The SPORTIF, RELY, ARISTOTLE and AVERROES trials all include AF patients with a single risk factor (some had CHA_2DS_2-VASc=1). Female gender is in general[154] an independent risk factor for stroke amongst patients with AF. In a population of over 100,000 Swedish patients, after multivariate adjustment for other risk factors for stroke, female gender retained an increased risk ratio of 1.18 (confidence limits 1.12-1.24). However, considering the sub-group of patients under 65 with no additional risk factors for stroke (lone AF), the influence of gender was not statistically significant. Amongst patients with a $CHADS_2$ score of 0 aged under 65, the annual stroke rate was slightly higher in women than in men (0.7% versus 0.5%) but this difference was not statistically significant (p=0.09). A recent study[338] of 6438 French patients with AF similarly found that female gender was not a significant predictor of risk amongst patients aged less than 65 years. The GDG considered the role of gender in risk stratification of patients with no other risk factors. They were of the opinion that any effect of gender in this group was small. A CHA_2DS_2-VASc score of 1 in women (that is women under the age of 65 with no other risk factors) should both be regarded as indicating low risk, not meriting anticoagulation. In summary, the GDG agreed that the initial clinical decision step should use the CHA_2DS_2-VASc score to determine the low risk patients who do not require antithrombotic therapy. Subsequent to this step, stroke prevention could be offered to those AF patients with one or more stroke risk factors.
Economic considerations	There was no published economic evidence to inform this question. The cost effectiveness of recommending a particular risk tool over another is dependent on its ability to categorise a population into groups who would most benefit from a particular treatment. It therefore is dependent on the population's epidemiology (i.e. the proportion of people with a given absolute risk of ischaemic stroke within the population), the extent to which a treatment modifies the risk of ischaemic stroke (enhancing health benefit and reducing costs) and further, the extent to which the treatment causes harm. The tool which comes closest to the threshold whereby the benefits of treatment (i.e. ischaemic stroke reduction) outweigh the harms for the majority of people with AF will be the most cost effective. The most cost-effective tool for stroke prevention cannot be assessed using stroke risk in isolation. The risk of bleeding (the key adverse event of treatment) as well as placing the tools within the epidemiological context of the AF population is critical in determining the optimal tool. It was agreed that the majority of the AF population

	would have low to medium risk of ischaemic stroke, and the most cost-effective tool would be that which was able to distinguish between these groups. In the absence of published evidence, the economic model undertaken to find the optimal stroke prevention treatment also undertook extensive sensitivity analysis to find out at which stroke and bleeding risk score treatment became most cost effective. In the model, a person's risk score was calculated based on their individual risk factors. For example a CHA_2DS_2-VASc score of 0 was given if they had no risk factors, or a CHA_2DS_2-VASc score of 1 was given if female and no other risk factors. If a patient had another risk factor, they would have a CHA_2DS_2-VASc score of 1 if they were male or a CHA_2DS_2-VASc score of 2 if female. In this way the model took into account different patient characteristics such as gender. The associated risk of ischaemic stroke for each score was derived from a large Swedish cohort study [154] Further detail of methods is given in appendix L. The model found the optimal threshold to reduce thromboembolic events was to give anticoagulation to people with AF with a CHA_2DS_2-VASc score of 1 or above (see Appendix L), without consideration of bleeding risk at all. This supports the argument that the CHA_2DS_2-VASc scoring system could be optimal in stratifying low risk AF patients according to their risk of thromboembolic events. However, this strategy resulted in higher bleeding event rates, and in higher costs, than use of alternative strategies using a different risk threshold. The highest net monetary benefit found in probabilistic analysis was reserving anticoagulation only for the lowest risk groups of bleeding and at a CHA_2DS_2-VASc score of 2 or over. The conclusions regarding the optimal strategy for QALY and life year gain were very sensitive to the adverse bleeding event rates associated with anticoagulation. Using best estimates from the trials in the review, the highest QALY and life year gain was evident when anticoagulation use was restricted to only those groups at lowest risk of bleeding and in the lower stroke risk groups. If it is assumed though, that with improved quality of anticoagulation control the adverse effect of anticoagulation is the same as that found with antiplatelets, the optimal QALY and life year gains are found when all but the highest bleeding risk groups have anticoagulation. However once costs were taken into account, the optimal strategy in terms of cost effectiveness remained unchanged. The GDG noted limitations in the data which drove the bleeding event rate associated with anticoagulation in the model (please see antithrombotic review and appendix L and M for details). For example, the quality of anticoagulation control was likely to be improved since the time when some of the older trials were conducted. Further, there are wide confidence intervals around the best estimate derived for the hazard ratio of this parameter meaning there is uncertainty whether anticoagulation is beneficial or harmful for patients of high risk of bleeding. The probabilistic analysis reflects this uncertainty showing greater variation in expected cost effectiveness with higher proportions taking anticoagulation instead of control through an extended offer of anticoagulation to high patients of high risk of bleeding is cost effective. The findings of the probabilistic analysis, and the limitations of the data informing the model, led to a cautious approach when specifying a bleeding risk threshold. None the less, it was agreed that the model offers supportive evidence that bleeding risk should be taken into account alongside ischaemic stroke risk when determining the optimal score to initiate anticoagulation.
Quality of evidence	The outcomes were low to high quality across 11 studies included in the review. It was noted that caution should be taken when comparing c-statistics, or indeed other

	prognostic outcomes, as one study cannot be directly compared to those reported in a different study, given population and various treatment differences. The paper by Friberg 2012[154] was deemed to be of highest quality and used to support the economic model. It looked at bleeding and stroke risk tools using the same large European cohort and was sufficiently applicable to be used in the economic model in the absence of UK data. Expected rates of bleeding and thromboembolic events could be estimated for treatment naive patients by adjusting for aspirin use. However, this does mean that the economic model within this guideline is based on observed event rates from one cohort only. Some of the early stroke risk stratification studies are based on the placebo/control (i.e. non-warfarin) arms of the historical trials performed >10 years ago. These trials have been criticised for randomising <10% of patients screened, and many stroke risk factors were not recorded or systematically looked for, nor consistently defined (for example, peripheral artery disease).[227,230] More recently, information on stroke risk factors has been obtained from large nationwide cohort studies that have provided information on common stroke risk factors.[339] The economic analysis was judged to be directly applicable to the NHS context, however the limitation that it only assessed two tools contained within the review protocol was noted. Its strengths were that it could look at risk in a dynamic way, with risk factors being updated throughout the patient's lifetime and treatment options amended accordingly. Uncertainty within the data inputs were explored through sensitivity analysis deterministically and probabilistically. It was noted that the model did not take into account that risk factors for bleeding may be modifiable.
Other considerations	The recommendations were derived from the evidence and the experience and opinion of the GDG. The GDG noted that by using the CHA_2DS_2-VASc score they were recommending a change in practice based on the (outdated) 2006 NICE guidelines, although it was noted that the CHA_2DS_2-VASc score was a refinement of the 2006 NICE stroke risk algorithm. This change could be supported by carefully controlled implementation and training programs to assist in using the new score. There are computer programs that are able to calculate these risk scores that would make it easier to apply. The role of anticoagulation post ablation is a difficult and unresolved question. The GDG did not specifically review the evidence on this question, but we believe that there is no definitive evidence and did not think it appropriate to include post ablation patients in the recommendation. We believe that common clinical practice is to continue to treat patients in accordance with their pre-ablation stroke risk score.

9 Antithrombotic therapy

This section was partially updated in 2021. See http://www.nice.org.uk/guidance/ng196/evidence for the 2021 evidence reviews.

9.1 Introduction

Stroke prevention is of crucial importance in the management of atrial fibrillation. Historically vitamin K antagonists (mainly warfarin in the UK) have played the major role in stroke prevention. However, aspirin and other anti-platelet agents provide a theoretical alternative and are also widely used.

The decision to commence a drug for stroke prevention involves consideration of a balance between the benefits in stroke reduction, the adverse effects of increased bleeding risk and particularly the increased risk of haemorrhagic stroke. The use of risk stratification tools to assess both stroke risk and bleeding risk are considered in Chapters 8 and 10 of this guideline.

The balance of benefit against risk applies to all, but an important group are the elderly population, where both risks increase. Observation of current clinical practice shows that aspirin is often prescribed preferentially over warfarin in the elderly.[125,164,271,390,405]

The therapeutic armamentarium has recently been strengthened by the advent of the non-VKA oral anticoagulants. These drugs have been compared with warfarin in recent technology appraisals[324,325,327] (TAs) and the findings of these TAs will be incorporated into this guideline.

This chapter assesses the evidence of benefit and cost-effectiveness of anticoagulation and anti-platelet agents both alone and in combination for stroke prevention.

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

For full details see review protocol in Appendix C.

Table 24: PICO characteristics of review question

Population	People with AF
Intervention/s	Antiplatelets Dual antiplatelets Anticoagulants Anticoagulants and antiplatelets Anticoagulants and dual antiplatelets
Comparison/s	No treatment Control Intervention listed above
Outcomes	Mortality Ischaemic stroke Haemorrhagic stroke Major bleeding Hospitalisation Health related quality of life Thromboembolic complications
Study design	Randomised controlled trials (RCT) Systematic review of RCTs

9.2.1 Clinical evidence

Below is a matrix showing where clinical evidence was identified, and the number of studies found for each comparison for antithrombotic therapy. There were 22 included studies but some trials had multiple arms and were counted twice in matrix below.

AP					
DAP	**2**				
AC	**13**	**1**			
AC + AP	**0**	**0**	**0**		
AC + DAP	**0**	**0**	**0**	**1**	
Control / Placebo	**5**	**0**	**6**	**0**	**0**
	AP	**DAP**	**AC**	**AC + AP**	**AC + DAP**

Key: AP=antiplatelet, DAP=dual antiplatelet and AC=anticoagulant

9.2.1.1 Antiplatelets versus control

A Cochrane review[8,8] and 2 RCT studies[391,442] were included in the review. Three RCT studies were included in the Cochrane review.[355,364,423] Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 25**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

The Cochrane review, Aguilar,[8] was on primary stroke prevention and two studies[355,423] included participants with prior stroke or TIA (secondary prevention) or both (about 6%). The Cochrane review removed this secondary prevention data from its systematic review.

9.2.1.2 Anticoagulants versus control

Two Cochrane reviews were included in this review.[9,393] The first Cochrane review,Aguilar,[9] included 5 RCTs[8,101,140,355,406,423] with AF and no previous stroke or transient ischaemic attack (TIA). The other Cochrane review, Saxena,[393] included 2 RCTs[140,442] with AF and a history of stroke or transient ischaemic attack. One paper reported primary and secondary prevention results separately so for the purposes of GRADE it was counted as two RCTs.[423]

Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 26**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

The Cochrane review, Aguilar,[9] reports that a few (3-8%) participants with prior stroke or TIA were included in each of the trials. Ezekowitz 1992 (SPINAF study)[140] reported the results separately and was included in both Cochrane reviews. To ensure that the analyses in the Cochrane by Aguilar[9] were restricted to primary prevention, they obtained unpublished data from the Atrial Fibrillation Investigators database, and were able to exclude the results of the participants with prior stroke or TIA.

9.2.1.3 Anticoagulants versus antiplatelets

A Cochrane review on the primary prevention of stroke was identified.[10] One paper was removed from the Cochrane review because the comparison was dual antiplatelet versus anticoagulant. In total, there were 6 papers from the Cochrane review.[180,190,195,354,355,447] One paper from the Cochrane included two RCTs of patients older and younger than 75 years of age, so it was counted as two RCTs in GRADE.[190] In addition, three RCTs and a subgroup analysis from a large clinical trial of patients, who had a stroke in the past were added to the review.[85,127,302,368]

A Cochrane review on secondary prevention by Saxena 2004[392] and one RCT[127] was identified that reported the results of another RCT[103] separately for primary and secondary prevention. They were counted as two RCTs in GRADE. The Cochrane review included two RCTs but only one[442] was included as the other one did not match our protocol.

Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 27**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

9.2.1.4 Dual antiplatelets versus antiplatelet

Two RCTs were identified.[5,192] Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 28**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

9.2.1.5 Anticoagulants versus dual antiplatelet

One RCT was identified.[6] Evidence from this study is summarised in the clinical GRADE evidence profile below **Table 29**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J. Anticoagulant and dual antiplatelet versus anticoagulant and antiplatelet.

One RCT was identified.[125] Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 30**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Summary of included studies

Study	Intervention/comparison	Population	Outcomes	Comments
Antiplatelet versus control				
Cochrane review: Aguilar 2005[8,8]. The Cochrane included 3 RCTs[355,364,423] N=2622 Treatment=Range 1.2-1.5 years follow-up	Intervention: Aspirin (75-325 mg/day) Comparison: No treatment/placebo	Patients with AF (93-100% primary prevention) Mean age: 70 years	All-cause mortality Ischaemic stroke Intracranial haemorrhage Systemic emboli Major extracranial bleeds	Cochrane removed the patients who had a previous stroke from the analysis Major bleeds defined as extracranial bleeds
Sato 2006[391] N=871 Stopped early	Intervention: Aspirin (150-200 mg/day) Comparison: No treatment	Chronic or intermittent AF (non-valvular) from 13 centres and 76 affiliated hospitals in Japan. Patients described as low risk Mean age: 65 years	All-cause mortality All stroke intracranial bleeding Major bleeding	Ischaemic stroke calculated by deducting intracranial bleeding from all strokes
Vanlatum 1993 (EAFT study)[442] N=782 Treatment=2.3 years	Intervention: Aspirin (300 mg/day) Comparison: Placebo	Patients with AF who had a TIA or minor ischaemic stroke in previous 3 months Mean age (SD): 73 (8) years	All-cause mortality Non-fatal systemic embolism Major and fatal bleeding complications	Major bleeding includes fatal and cerebral bleeds Strokes included undefined strokes so could not

Study	Intervention/comparison	Population	Outcomes	Comments
				report type of stroke
Anticoagulant versus control				
Cochrane review, Aguilar 2005[9] included 5 RCTs[101,140,355,406,423] N=2367 Treatment =From 1.2-2.2 years follow-up	Intervention: Anticoagulant - warfarin Comparison: Placebo/control	AF documented by electrocardiogram either intermittent or sustained. Patients with prior stroke or TIA at any time before study entry were not included in primary analysis Mean age: 67-68 years in 4 studies and 74 in other	All-cause mortality Ischaemic stroke Intracranial haemorrhage Systemic emboli Major extracranial bleeds	Cochrane removed the patients who had a previous stroke from the analysis
Cochrane review: Saxena 2004[393] – only included 1 RCT Vanlatum 1993 (EAFT study)[140,442] N=964 Treatment=From 1.7-2.3 years follow-up	Intervention: Anticoagulant – warfarin/physician choice Comparison: Placebo	Non-rheumatic AF and previous ischaemic stroke or TIA Mean age (SD) Intervention: 71 (7) Mean age (SD) Control: 70 (8)	Intracranial bleed Major bleeding	Vanlatum study: Major bleeding includes fatal and cerebral bleeds Strokes included undefined strokes so could not report type of stroke
Anticoagulant versus antiplatelet				
Aguilar 2007[10] 6RCTs were included [180,190,195,354,355,447] **COCHRANE**	Intervention: warfarin INR>1.5 or other coumarins (such as acenocumarol) Comparison: Aspirin or other platelet antiaggregants	Inclusion Participants with AF with no history of stroke or transient ischemic attacks Exclusion: patients with concomitant mitral stenosis Mean age: AFASAK II: median 74 ATHENS: over 75 years NASPEAF: 69 years PATAF: 75 years SPAF IIa: 6 years SPAF IIb: over 60 years	All strokes Ischaemic strokes Systemic (non-CNS) emboli All intracranial haemorrhage Major extracranial haemorrhage All-cause mortality Non-CNS bleeding	Two papers excluded: one because it belongs in another section. The other used an intervention not listed in protocol. PATAF (HELLEMONS1999) 0% prior stroke SPAFIIa+b(HALPERIN1994 0% prior stroke in <2yrs) ATHENS(VEMMOS2006) 0% prior stroke

Study	Intervention/comparison	Population	Outcomes	Comments
				AFASAKII (GULLOV1998) unclear AFASAK(PETERSON1989) 5% Major bleeding defined as extracranial bleeds
Rash [368] **WASPO** N=75 Treatment = 1 year	Intervention Warfarin INR 2-3 Comparison: Aspirin 300 mg/d	Inclusion >80 and <90 years of age, were ambulant and had permanent AF. Exclusion: Had one of the following: one more falls or syncopal episode; epileptiform seizures; alcoholic liver disease or excess alcohol intake history of thromboembolism; gastrointestinal or genitourinary bleeding; previous intracranial haemorrhage; BP>180/100; abnormal prothrombin; Folstein mental state score <26; intolerance/allergy warfarin or aspirin; already taking warfarin. Mean age (SD): 83 (80-90)	All-cause mortality Ischaemic stroke Haemorrhagic stroke Serious bleeding	0% had prior stroke Serious bleeding defined as intracranial haemorrhage, fall in haemoglobin (>2g/dl, need for blood transfusion
Mant[302] **BAFTA** N=973 Treatment =2.7 years	Intervention Warfarin INR2-3 Comparison Aspirin 75mg/d	Inclusion: > 75 years or over and had AF or AF flutter. Exclusion: Rheumatic HD, a major haemorrhage; peptic ulcer disease; oesophageal varices; allergic hypersensitivity to either drug; a terminal illness; surgery <3 months; BP> 180/100 mmHg. Should not be on warfarin	All-cause mortality Ischaemic stroke Haemorrhagic stroke All major haemorrhage (including intracranial) Systemic embolism	13% prior stroke
Chen 2012[85] N=786	Intervention Warfarin INR 2.1-	Inclusion > 60 years of age,	All- cause mortality	12.5% prior stroke

Study	Intervention/comparison	Population	Outcomes	Comments
	2.5 Comparison: Aspirin 200 mg/d	ischaemic stroke or systemic embolism after 6 months Exclusion receiving warfarin or aspirin for any reason Mean age: 67 years	Ischaemic stroke Haemorrhagic stroke Major bleeding Systemic emboli	Also had another arm of low dose warfarin
Chen 2013[86] N=1162	Intervention Warfarin INR 1.7-3.0 Comparison Aspirin 200mg/d	Inclusion: aged ≥65 years; paroxysmal AF at a middle or high‑risk of a stroke. Mean age: 72 years	All-cause mortality Ischaemic stroke Haemorrhagic stroke Major bleeding Systemic emboli	Some patients had prior stroke/ TIA Also had another arm of low dose warfarin
Cochrane: Saxena 2004[392]. Included one RCT[442] N=455 Treatment=mean follow-up 2.3 years	Intervention Anticoagulant Comparison: Aspirin 300 mg/d	AF patients who had a TIA or minor ischaemic stroke in the previous 3 months Mean age (SD): Intervention: 71 (7) years Control: 73 (8)	Intracranial bleed All stoke (removed number of intracranial bleeds to calculate ischaemic stroke) Major extracranial bleed	Excluded second study as the intervention did not match the protocol
Diener 2012[127] N=764 Treatment = 1.1 years	Intervention Apixaban 5mg twice daily Comparison Aspirin 81-324 mg day	AF patients who had a previous stroke or TIA Mean age: 70.9 years	Ischaemic stroke Haemorrhagic stroke All-cause mortality Systemic embolism Major bleeding	100% prior stroke or TIA Major bleeding defied as clinically overt bleeding that is accompanied by one of more of the following: decrease in haemoglobin of 2g/dL or more over 24h, transfusion of 2 units or more, bleeding that occurs in a critical site (including

Study	Intervention/comparison	Population	Outcomes	Comments
				intracranial, intraspinal etc.) or bleeding that is fatal
Diener [127] **AVERROES – subgroup analysis** N=4427 Treatment =1.1 years	Intervention Apixaban 2x 5mg/d Comparison Aspirin 81 to 324 mg/d	Inclusion > 50 years of age, AF <6 and no prior stroke. Exclusion receiving vitamin K antagonist therapy, other than atrial fibrillation required long-term anticoagulation Mean age: 70.9 years	All-cause mortality Ischaemic stroke Haemorrhagic stroke All major haemorrhage (including intracranial) Systemic embolism Hospitalisation	0% prior stroke
Dual antiplatelet versus antiplatelet therapy				
ACTIVE A[5] N=7554 Treatment = 3.6 years	Intervention Clopidogrel (75mg/d) and aspirin (75 to 100 mg/d) Comparison Aspirin (75 to 100 mg/d)	Inclusion AF at enrolment or had had at least two episodes of intermittent atrial fibrillation in the previous 6 months. In the ACTIVE studies, patients who were considered to be candidates for VKA enrolled in ACTIVE W and those for whom such therapy was considered to be unsuitable were enrolled in ACTIVE A. Exclusion: required a vitamin K antagonist or clopidogrel or had a risk factor for haemorrhage. Mean age (SD): Intervention: 70.9 (10.2) Control: 71.1 (10.2)	Ischaemic stroke Haemorrhagic stroke All-cause mortality Systemic embolism Major bleeding	13% prior stroke Major haemorrhage defined as any overt bleeding requiring transfusion of at least two units of blood or any overt bleeding meeting the criteria for severe haemorrhage.
Hart[192] N=593 Treatment = 2.3 years This was a subgroup analysis of AF patients from a larger clinical trial	Intervention Clopidogrel (75mg/d) and low dose aspirin (75-162 mg/d) Comparison: Low dose aspirin (75-162 mg/d)	Inclusion: 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 Receiving oral anticoagulants Mean age: 70 years	Ischaemic stroke Haemorrhagic stroke All-cause mortality (HR) Hospitalisation Major bleeding	15% prior stroke Major bleeding includes severe/fatal extra cranial haemorrhage and intracranial bleeds

Study	Intervention/comparison	Population	Outcomes	Comments
Anticoagulant versus dual antiplatelet				
ACTIVE W[6] N=6706 Treatment = 1.28 years	Intervention: 75-100 mg/d aspirin and 75 mg/d clopidogrel Comparison: Vitamin K antagonist INR-23	Inclusion ECG evidence of AF and 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. In the ACTIVE studies, patients who were considered to be candidates for VKA enrolled in ACTIVE W and those for whom such therapy was considered to be unsuitable were enrolled in ACTIVE A. Exclusion: 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. Mean age: 70.2 years	All-cause mortality Ischaemic stroke Haemorrhage stroke	15% prior stroke Major bleeding defined as any bleeding requiring transfusion of a least two units of red blood cells or equivalent of whole bold, or which was severe. Severe bleeding was bleeding associated with any of the following: death, drop in haemoglobin of at least 50g/L, substantial hypotension with the need for inotropic agents, intraocular bleeding leading to substantial loss of vision, bleeding requiring surgical intervention, symptomatic intracranial haemorrhage or requirement of a transfusion

Study	Intervention/comparison	Population	Outcomes	Comments
				of a least four units of blood.
Anticoagulant plus dual antiplatelet versus anticoagulant plus antiplatelet				
DEWILDE[125] WOEST N=563 Treatment = 1.1 years	Intervention Warfarin plus clopidogrel (75mg/d) plus ASA (80mg/d) Comparison: Warfarin plus Clopidogrel (75mg/d)	Inclusion Only patients scheduled for Percutaneous Coronary Intervention (PCI) can be included tough this intervention would also take place without this study. Patients are on oral anticoagulation therapy and this will be continued throughout the period of 1 year-and deployment of at least 1 coronary stent (bare metal stent (BMS) or drug eluting stent (DES)). – age of more than 18 years Exclusion cardiogenic shock, previous intracerebral haemorrhage or significant thrombocytopenia, major bleeding according to time criteria within the past 12 months, age > 80 years Mean age (SD): 70 (7) years	All-cause mortality Ischaemic stroke Haemorrhagic stroke Major bleeding	18% had prior stroke Major bleeding defined using TIMI bleeding (Thrombolysis in Myocardial Infarction criteria).

Table 25: Clinical evidence profile: antiplatelet versus control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiplatelet	Control	Relative (95% CI)	Absolute		
All-cause mortality[355,364,391,423,442]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	None	184/1912 (9.6%)	195/1818 (10.7%)	RR 0.89 (0.74 to 1.06)	12 fewer per 1000 (from 28 fewer to 6 more)	MODERATE	CRITICAL
All-cause mortality - HAZARD RATIO – All-cause mortality [442]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	None	102/404 (25.2%)	99/378 (26.2%)	HR 0.91 (0.69 to 1.2)	20 fewer per 1000 (from 73 fewer to 44 more)	MODERATE	CRITICAL
All ischaemic stroke (fatal and non-fatal) [355,364,391,423]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	None	52/1458 (3.6%)	68/1378 (4.9%)	RR 0.74 (0.52 to 1.06)	13 fewer per 1000 (from 24 fewer to 3 more)	MODERATE	CRITICAL
All intracranial haemorrhage[355,364,391,423]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	7/1458 (0.48%)	4/1378 (0.29%)	RR 1.68 (0.51 to 5.52)	2 more per 1000 (from 1 fewer to 13 more)	LOW	CRITICAL
All systemic emboli[355,364,423,442]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	10/1436 (0.7%)	15/1311 (1.1%)	RR 0.64 (0.29 to 1.42)	4 fewer per 1000 (from 8 fewer to 5 more)	LOW	IMPORTANT
Major bleeding[355,391,423,442]												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	18/1668 (1.1%)	12/1665 (0.72%)	RR 1.45 (0.72 to 2.92)	3 more per 1000 (from 2 fewer to 14 more)	LOW	IMPORTANT

a. Confidence intervals crossed one MID (0.75)
b. Confidence interval crossed both MIDs (0.75 and 1.25)

Table 26: Clinical evidence profile: Anticoagulation versus control

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anticoagulation	Control	Relative (95% CI)	Absolute		
All ischaemic stroke (fatal and non-fatal)[101,140,355,406,423]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/1175 (2%)	73/1184 (5.5%)	RR 0.33 (0.21 to 0.53)	37 fewer per 1000 (from 26 fewer to 43 fewer)	HIGH	CRITICAL
All systemic emboli[101,140,355,406,423,442]												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	4/1379 (0.29%)	11/1373 (0.8%)	RR 0.39 (0.14 to 1.07)	5 fewer per 1000 (from 7 fewer to 1 more)	MODERATE	IMPORTANT
All intracranial haemorrhage[101,140,355,406,423]												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	5/1175 (0.43%)	2/1159 (0.2%)	RR 1.87 (0.51 to 6.82)	1 more per 1000 (from 1 fewer to 10 more)	LOW	CRITICAL
Major bleeding[101,140,355,406,423,442]												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[c]	none	30/1400 (2.1%)	19/1398 (1.4%)	RR 1.56 (0.88 to 2.75)	8 more per 1000 (from 2 fewer to 24 more)	MODERATE	IMPORTANT
All-cause mortality[101,140,355,406,423,442]												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[c]	none	115/1471 (7.8%)	147/1475 (10%)	RR 0.78 (0.62 to 0.98)	22 fewer per 1000 (from 2 fewer to 38 fewer)	MODERATE	CRITICAL
Mortality - Hazard Ratio[442]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness very serious[b]	very serious[a]	none	44/214 (20.6%)	44/214(20.56%)	HR 0.82 (0.53 to 1.26)	34 fewer per 1000 (from 91 fewer to 46 more)	LOW	CRITICAL

a. Confidence interval crossed both MIDs (0.75 and 1.25)
b. Confidence interval crossed one MID (1.25)
c. Confidence interval crossed one MID (0.75)

Table 27: Clinical evidence profile: Anticoagulant versus antiplatelet

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral anticoagulant	Antiplatelet	Relative (95% CI)	Absolute		
Haemorrhagic stroke (fatal and non-fatal)[85, 86,103,127,181,190,195,264,303,355,368,442,447]												
13	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	47/5274 (0.89%)	25/5653	RR 1.6 (1 to 2.56)	3 more per 1000 (from 0 more to 7	LOW	CRITICAL

								(0.43%)		more)		
Ischaemic strokes (fatal and non-fatal)[85, 86,103,127,181,190,195,264,303,355,368,442,447]												
13	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	131/5889 (2.2%)	281/5591 (5.0%)	RR 0.45 (0.37 to 0.55)	28 fewer per 1000 (from 22 fewer to 32 fewer)	MODERATE	CRITICAL
All-cause mortality[103,127,181,190,195,264,303,368,447 86]												
11	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	345/5329 (6.5%)	377/4987 (7.9%)	RR 0.89 (0.78- 1.03)	9 fewer per 1000 (from 17 fewer to 2 more)	MODERATE	CRITICAL
All-cause mortality - Hazard ratio[127,195]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	123/2938 (4.2%)	157/2930 (7.2%)	HR 0.77 (0.61 to 0.98)	16 fewer per 1000 (from 1 fewer to 27 fewer)	LOW	CRITICAL
Major bleeding[103,127,181,190,195,264,303,354,355,368,442,447 86]												
12	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	122/5884 (2.1%)	86/5546 (1.6%)	RR 1.35 (1.03 to 1.76)	6 more per 1000 (from 0 more to 12 more)	LOW	IMPORTANT
Systemic (non-CNS) emboli[86,103,127,181,190,195,264,303,354,355,447]												
11	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	15/5628 (0.27%)	25/5284 (0.39%)	RR 0.54 (0.29 to 0.99)	2 fewer per 1000 (from 0 fewer to 3 fewer)	LOW	IMPORTANT

a. Majority of the evidence, the studies were randomised and allocation concealment was performed. In most of the evidence patients were not blinded, however it is difficult to blind warfarin treatment and the outcome is unbiased.
b. Confidence interval crossed one MID (1.25)
c. Confidence interval crossed one MID (0.75)

Table 28: Clinical evidence profile: Dual antiplatelet versus antiplatelet

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dual antiplatelet**	**Antiplatelet**	**Relative (95% CI)**	**Absolute**		
Ischaemic stroke [5,192]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	249/4070 (6.1%)	357/4067 (8.8%)	RR 0.7 (0.6 to 0.82)	26 fewer per 1000 (from 16 fewer to 35 fewer)	LOW	CRITICAL
Haemorrhagic stroke[5,192]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	31/4070 (0.76%)	22/4067 (0.54%)	RR 1.4 (0.82 to 2.4)	2 more per 1000 (from 1 fewer to 8 more)	LOW	CRITICAL

All-cause mortality[5,192]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	854/4070 (21%)	866/4067 (21.3%)	RR 0.99 (0.91 to 1.07)	2 fewer per 1000 (from 19 fewer to 15 more)	MODERATE	CRITICAL
All-cause mortality – Hazard ratio [192]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	29/298 (9.7%)	25/285 (8.8%)	HR 1.12 (0.65 to 1.90)	10 more per 1000 (from 30 fewer to 72 more)	VERY LOW	CRITICAL
Systemic emboli[5]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	54/3772 (1.4%)	56/3782 (1.5%)	RR 0.97 (0.67 to 1.4)	0 fewer per 1000 (from 5 fewer to 6 more)	MODERATE	IMPORTANT
Hospitalisation [192]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[e]	none	41/298 (13.8%)	43/285 (15.1%)	RR 0.91 (0.61 to 1.35)	13 fewer per 1000 (from 56 fewer to 47 more)	VERY LOW	IMPORTANT
Major bleeding[5,192]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	260/4070 (6.4%)	166/4067 (4.1%)	RR 1.57 (1.3 to 1.9)	23 more per 1000 (from 12 more to 37 more)	MODERATE	IMPORTANT

a. One paper was a subgroup analysis of AF patients from a larger clinical trial that were not pre-specified prior to randomisation. Both trials were adequately randomised and performed allocation concealment.

b. Confidence interval crossed 1 MID (0.75)

c. Confidence interval crossed 1 MID (1.25)

d. Paper was a subgroup analysis of AF patients from a larger clinical trial that were not pre-specified prior to randomisation. Original trial was adequately randomised and performed allocation concealment.

e. Confidence interval crossed 2 MIDs (0.75 and 1.25)

Table 29: Clinical evidence profile: Dual antiplatelet versus anticoagulant

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dual antiplatelet	OAC	Relative (95% CI)	Absolute		
Ischaemic stroke[6]												
1	randomised trials	no serious risk of bias[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	90/3335 (2.7%)	42/3371 (1.2%)	RR 2.17 (1.51 to 3.11)	15 more per 1000 (from 6 more to 26 more)	HIGH	CRITICAL
Haemorrhagic stroke[6]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	5/3335 (0.15%)	15/3371 (0.44%)	RR 0.34 (0.12 to 0.93)	3 fewer per 1000 (from 0 fewer to 4 fewer)	MODERATE	CRITICAL
All-cause mortality[6]												
1	randomised trials	no serious risk of bias[a]	no serious inconsistency	no serious indirectness	serious[c]	none	159/3335 (4.8%)	158/3371 (4.7%)	RR 1.02 (0.82 to 1.26)	1 more per 1000 (from 8 fewer to 12 more)	MODERATE	CRITICAL
Systemic emboli[6]												
1	randomised trials	no serious risk of bias[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/3335 (0.54%)	4/3371 (0.12%)	RR 4.55 (1.54 to 13.43)	4 more per 1000 (from 1 more to 15 more)[4]	HIGH	IMPORTANT
Major bleeding[6]												
1	randomised trials	no serious risk of bias[a]	no serious inconsistency	no serious indirectness	serious[c]	none	101/3335 (3%)	93/3371 (2.8%)	RR 1.10 (0.83 to 1.45)	3 more per 1000 (from 5 fewer to 12 more)	MODERATE	IMPORTANT

a. Open label study but difficult to blind with anticoagulation. All outcomes were adjuncted by a blinded committee.
b. Confidence interval crossed one MID (0.75)
c. Confidence interval crossed one MID (1.25)

Table 30: Clinical evidence profile: oral anticoagulant and dual antiplatelet versus oral anticoagulant and antiplatelet

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OAC+Dual AP	OAC+AP	Relative (95% CI)	Absolute		
All-cause mortality HR [125]												

1	randomised trials	no serious risk of bias[e]	no serious inconsistency	serious[a]	serious[b]	none	18/284 (6.3%)	7/279 (2.5%)	HR 0.39 (0.16 to 0.93)	15 fewer per 1000 (from 2 fewer to 21 fewer)[6]	LOW	CRITICAL
Ischaemic stroke[125]												
1	randomised trials	no serious risk of bias[e]	no serious inconsistency	serious[a]	serious[c]	none	8/284 (2.8%)	2/297 (0.67%)	RR 4.18 (0.90 to 19.53)	21 more per 1000 (from 1 fewer to 125 more)	LOW	CRITICAL
Haemorrhagic stroke[125]												
1	randomised trials	no serious risk of bias[e]	no serious inconsistency	serious[a]	very serious[d]	none	0/284 (0%)	1/297 (0.34%)	RR 0.35 (0.01 to 8.52)	2 fewer per 1000 (from 3 fewer to 25 more)	VERY LOW	CRITICAL
Major bleeding[125]												
1	randomised trials	no serious risk of bias[e]	no serious inconsistency	serious[a]	serious[c]	none	16/284 (5.6%)	9/279 (3.2%)	RR 1.75 (0.78 to 3.89)	24 more per 1000 (from 7 fewer to 93 more)	LOW	IMPORTANT

a. 69% of patients had AF at baseline

b. Confidence interval crossed one MID (0.75)

c. Confidence interval crossed one MID (1.25)

d. Confidence interval crossed two MIDs (0.75 and 1.25)

e. Open label study but outcome is objective

f. The absolute effect is comparing OAC plus AP versus OAC plus DAPT. This is based on the hazard ratio that used OAC plus DAPT as the comparator arm, whilst all other outcomes we used OAC plus AP. The result shows there are 15 fewer deaths in the OAC plus AP group than the OAC plus DAPT.

9.2.2 Economic evidence

Published literature

Four studies were included with the relevant comparisons. [217 224 99,401] These are summarised in the economic evidence profile below (**Table 31**) and study evidence tables in Appendix H.

Thirty three studies that potentially met the inclusion criteria were excluded. Of these fifteen studies [3,21,79,115,124,139,160,189,259,276,333,367,430,436] were selectively excluded due to the availability of more applicable evidence with fewer methodological limitations, and eighteen studies [51,150,171,172,221,270,312,358,413,414 107,116,149,174,185,268,415,432,466] were excluded directly as not applicable to the review question. Excluded studies are summarised in Appendix K, with reasons for exclusion given. See also the study selection flow chart in Appendix E.

New cost-effectiveness analysis

No published economic evaluations were identified that found the optimal strategy to manage stroke risk with antithrombotic therapy with risk scoring systems currently used in the UK. All people with AF could be affected by recommendations informing the stroke prevention pathway, and the health and cost impact or both ischaemic and haemorrhagic stroke is large. Therefore, the GDG prioritised an economic model to find the optimal decision rule of when to anticoagulate a patient based on their risk factors, as well as to determine which stroke prevention therapy, if any, was appropriate for patients at low risk of thromboembolic events.

A discrete event simulation 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 Brunel University as part of the MAPGuide Health Technology Appraisal project.[293] 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.

Due to availability of this robust and validated model, the GDG opted to update and simplify the complete care pathway model to allow a focus specifically on the stroke prevention pathway. The base case analysis considers incremental differences in 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 pathway. The model was updated using a network meta-analysis of the data found in the clinical review. The network meta-analysis is summarised below, and a full technical report of this, and the model methods and parameters can be found in appendix L and M.

A summary of results from the model can be found in the economic evidence profile below (**Table 31**) and reported in full in the technical appendix L.

Network Meta-Analysis on antithrombotic treatment.

As part of the economic model, a network meta-analysis was conducted to synthesize the results of the papers retrieved from the systematic review for parameterisation in the model. The results are summarised in the below table, and a full account can be found in the technical appendix M.

Table 31: 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

Summary statements from the NCGC Network Meta-Analysis

For the following outcomes, a strategy of:

All cause mortality

- Anticoagulation was highly likely to be the optimal strategy (73% likelihood), and a do nothing strategy is likely to be least optimal. There is a great deal of certainty that anticoagulation is effective in comparison to a do nothing strategy, however the relative effects between the other comparisons are less clear.

Ischaemic stroke

- Anticoagulation was 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 to do nothing is the least optimal strategy, ranking fourth.

Haemorrhagic stroke

- A do nothing strategy was highly likely to 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

- Anticoagulation is extremely probable to be the optimal strategy (95% likelihood). A do nothing strategy 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 32: Economic evidence profile: Antithrombotic therapy

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects	Cost effectiveness	Uncertainty
Jowett 2011[217] UK	Directly applicable (a)	Potentially serious limitations (b)	Within trial (BAFTA) analysis comparing 1. Warfarin 2. Aspirin In a population older than 75.	- 166 (95% CI:-452 to 89)	0.020 (95% CI:-0.070 to 0.111)	Warfarin dominates aspirin being less costly and more effective	Inspection of results on the cost-effectiveness plane suggests there is a high degree of uncertainty in the results, with Warfarin most likely to be the most cost-effective option (% NR) For age groups 75-79 years old, warfarin is the dominant strategy. In age groups 80-84 years old warfarin has a cost per QALY of £14556. In age groups of 85 years plus warfarin with a cost per QALY of £6917.
Kansal 2012 [224] UK	Directly applicable (c)	Potentially serious limitations (d)	Markov model comparing **Intervention 1:** No antithrombotic therapy ~~**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)	**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)	**QALYs (mean per patient):** Intvn 1: 7.12 ~~Intvn 2: 8.06~~ Intvn 4: 7.59 Intvn 3: 7.82	Warfarin dominates aspirin and no treatment being less costly and more effective	Detailed results of the sensitivity analyses were not given for the comparators for this review question. Incomplete incremental results not reported for subgroup analysis (age over and under 80 years) for comparators of interest.
Shah 2012 [401] USA	Partially applicable (e)	Potentially serious limitations (f)	**Intervention 1:** No antithrombotic	**Total costs (mean per patient):**	**QALYs (mean per patient):**	Warfarin dominates dual antiplatelet	Inspection of graphics for three way sensitivity analysis suggests that for patients with:

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects	Cost effectiveness	Uncertainty
			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 1: na ~~Intvn 2: £30,038~~ ~~Intvn 3: £29,631~~ Intvn 5: £23,054 Intvn 4: £15,595 Intvn 6: £13,561	Intvn 1: nr ~~Intvn 2: 8.54~~ ~~Intvn 3: 8.64~~ Intvn 5: 8.32 Intvn 4: 8.40 Intvn 6: 8.17	therapy being less costly and more effective, and cost effective when compared against aspirin in the base case. ~~**ICER (Intvn 3 vs. Intvn 4):**~~ ~~£58,666~~ ~~per QALY gained~~ **ICER (Intvn 4 vs. Intvn 6):** £8,844 per QALY gained	• $CHADS_2$ score of 0 aspirin is optimal for pts with a $HEMORR_2HAGES$ score of 0-2, and no antithrombotic is preferable for $HEMORR_2HAGES$ score 3+. • $CHADS_2$ score of 1, aspirin is optimal for pts with a $HEMORR_2HAGES$ score of 2+, and warfarin is preferable for pts with a $HEMORR_2HAGES$ score 0-1. If time in therapeutic range is >72.6% • $CHADS_2$ score of 2,warfain is optimal for pts with a $HEMORR_2HAGES$ score of 0-2 and dabigatran is preferable for pts with a $HEMORR_2HAGES$ 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+,.If time spent in INR >72.6% then warfarin is optimal across all $HEMORR_2HAGES$ scores, otherwise dabigatran is optimal for all scores of $HEMORR_2HAGES$ score
Coleman 2012 [99]([US])	Partially applicable (g)	Minor limitations (h)	**Intervention 1:** Aspirin 75-100mg, On-going treatment. **Intervention 2:**	£6588 (h)	0.36 QALYs	£18,299 per QALY gained	Cost effectiveness of dual antiplatelet therapy particularly sensitive to $CHADS_2$ score, major bleeding risk, relative risk decrease for ischaemic

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects	Cost effectiveness	Uncertainty
			Clopidogrel plus aspirin, Clop. 75mg, Aspirin 75-100mg, On-going treatment. Discontinued if major haemorrhage occurs.				stroke and the utility of clopidogrel plus aspirin.
Adapted Brunel MAPGuide model[293], NCGC, UK	Directly applicable (i)	Potentially serious limitations (j)	**Intervention 1:** No antithrombotic therapy **Intervention 2:** single antiplatelet **Intervention 3:** dual antiplatelet **Intervention 4:** Anticoagulation **Extended analysis of using risk scoring tools** to determine a decision rule when anticoagulation was appropriate. This compared several two line strategies which combined interventions listed. These are summarised into groups where the decision rule was to: Not give anticoagulation (strategy group A) or, give single antiplatelets (strategy group B) or, give dual antiplatelets (strategy group C) when below a given stroke risk score and above a given bleeding risk score,	Total cost per patient **Blanket strategies** Intvn 1: 19319 Intvn 2: 20521 Intvn 3: 20573 Intvn 4: 25591	Total QALY gain per patient **Blanket strategies** Intvn 1: 5.24 Intvn 2: 5.03 Intvn 3: 4.80 Intvn 4: 5.15	Intvn 1 was the only non-dominated option, being more effective and less costly than alternatives	Results sensitive to decision of when to anticoagulate according to stroke and bleeding risk score. All sensitivity analyses supported the use of a "do nothing" strategy, rather than an offer of single or dual antiplatelets, as an alternative to anticoagulation. This was consistent for every decision rule assessed. In deterministic analysis, lowering haemorrhagic adverse event risk of anticoagulation changed the overall conclusions of the most cost effective decision rule, with conclusions matching those of the probabilistic analysis. Lowering case fatality rates of bleeding did not change the conclusion on the deterministic analysis. The probabilistic analysis shows increasing uncertainty around the QALY gain (in comparison to a do nothing strategy) with increasing numbers of patients put on anticoagulation with higher bleeding risk thresholds.
				Extended analysis of using risk scoring tools Strategy A (i.e. "do not give anticoagulation" for low stroke risk and high bleeding risk patients) achieved the highest net monetary benefit for any given combination of bleeding and stroke risk scores. Therefore results by stroke risk score are presented below for this group of strategies only. Non dominated options were to "not give antithrombotic therapy" or to "give anticoagulation at CHA_2DS_2-VASc score of 2 or above and a HAS-BLED score of 0, otherwise do nothing" Incremental cost = £1.84 Incremental QALY gain = 0.00125 Cost per QALY gain = £1467.94		

Study	Applicability	Limitations	Other comments	Incremental cost (£)	Incremental effects	Cost effectiveness	Uncertainty
			otherwise anticoagulate.				Small absolute differences between the strategies, in particular in the QALY gain, means small differences in effect could have a large impact on the incremental cost-effectiveness ratio between the optimal strategies. Of all strategies assessed, including those using combinations of bleeding and stroke risk thresholds to determine management, the three highest ranking strategies with highest probability of being optimal were: a) Give anticoagulation at CHA_2DS_2-VASc score of 2 or above and a HAS-BLED score of 0, otherwise do nothing = 16% probability b)Give anticoagulation at $CHADS_2$ score of 1 or above and a HAS-BLED score of 0, otherwise do nothing = 14% probability c)Give anticoagulation at CHA_2DS_2-VASc score of 1 or above and a HAS-BLED score of 0, otherwise do nothing = 14% probability

Probabilistic Results		Value for outcome: QALY (discounted)							
Intervention if under a given stroke risk score		Do not give AC	Give anticoagulation if at, or under, bleeding risk specified by HASBLED score of....						
			0	1	2	3	4	5	NA
Control	NA	5.24	5.24	5.21	5.15	5.08	5.03	5.03	5.15
	CHADSVASC1		5.24	5.21	5.16	5.09	5.04	5.03	5.14
	CHADS1		5.24	5.21	5.17	5.10	5.05	5.03	5.15
	CHADSVASC2		5.25	5.23	5.18	5.12	5.07	5.07	5.16

Probabilistic Results		Value for outcome: Cost (discounted)							
Intervention if under a given stroke risk score		Do not give AC	Give anticoagulation if at, or under, bleeding risk specified by HASBLED score of....						
			0	1	2	3	4	5	NA
Control	NA	19318.56	19429.43	20480.27	23542.50	26399.53	27630.82	27892.94	25590.77
	CHADSVASC1		19392.64	20361.53	23425.38	26339.68	27568.94	27709.90	25777.68
	CHADS1		19324.04	20480.27	23130.05	26015.04	27239.32	27892.94	25590.77
	CHADSVASC2		19320.40	20096.32	22968.27	25858.03	27065.57	27260.27	25444.92

Probabilistic Results		Value for outcome: NB (discounted)							
Strategy			Give anticoagulation if at, or under, bleeding risk specified by HASBLED score of....						
		Do not give AC	0	1	2	3	4	5	NA
Control	NA	85560.78	85371.18	83656.90	79503.35	75288.93	73046.02	72650.60	77385.50
	CHADSVASC1		85487.54	83890.64	79702.80	75461.88	73204.02	72941.99	77014.59
	CHADS1		85556.30	83656.90	80230.95	75965.13	73814.80	72650.60	77385.50
	CHADSVASC2		85584.01	84531.98	80724.20	76618.37	74393.75	74065.16	77803.23

(a) UK NHS perspective. Costs in UK 2007 sterling with 3.5% discount rate. EQ5D used for utility.
(b) One source for treatment effect (BAFTA trial). Limited time horizon: Mean follow up of 2.7 years which was extrapolated over 4 years. Drug costs not included. Bootstrapping to account for uncertainty but results presented graphically. Subgroups stratified by age, not by risk score.
(c) UK NHS perspective. Costs in UK 2010 sterling with 3.5% discount rate. EQ5D used for utility
(d) Primary source for probabilities used in the model was the RE-LY trial with an adaptation of an network meta-analysis (Roskall et al 2010). Potential conflict of interest in funding source (Boehringer-Ingleheim funded the health economists to complete the analysis). Reporting of results of probabilistic and deterministic sensitivity analysis are limited, detailing only the comparators against dabigatran. Did not stratify for risk of stroke.
(e) US healthcare setting and Medicare cost perspective. Discount rate of 3% for both costs and QALYs.

(f) 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. No probabilistic analysis performed and tornado plots focus on the cost per QALY of dabigatran. The comparator of dabigatran has been crossed out as not a comparator of interest in this review.

(g) US healthcare setting and Medicare cost perspective. Discount rate of 3% for both costs and QALYs.

(h) 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

(i) UK dataset used to populate model, with NICE reference case followed.

(j) Probabilistic analysis performed, effectiveness informed by systematic review and network meta-analysis. Exploration of risk scoring on management decisions. Assumptions and parameters validated as reasonable for decision making, with deterministic sensitivity analysis on parameter estimates of concern.

9.2.3 Evidence statements

Clinical

Antiplatelet versus control

Moderate quality evidence showed that antiplatelets compared to placebo may have no effect on:

- All-cause mortality, when expressed as time to event (one study, N= 782).
- All-cause mortality (five studies, N= 3730).

Antiplatelets may decrease the risk of ischaemic stroke compared with placebo (four studies, N= 2836).

Antiplatelets have no effect on the risk of systemic emboli compared with placebo (four studies, N= 2747).

Anticoagulant versus control

Evidence from 6 studies showed that anticoagulants decrease the risk of:

- All-cause mortality (Moderate quality evidence, N= 2946)
- Ischaemic stroke (High quality evidence, N= 2359)

Low quality evidence showed that anticoagulants may reduce the risk of all-cause mortality, when expressed as time to event compared with placebo, but the direction of the estimate of effect could favour either intervention (One study, N= 439).

Moderate quality evidence showed that anticoagulants may decrease the risk of systemic emboli compared with placebo (six studies, N= 2752).

Evidence from 6 studies showed that anticoagulants may increase the risk of:

- Haemorrhagic stroke (low quality evidence, N= 2359)
- Major bleeding (moderate quality evidence, N= 2798)

Anticoagulant versus antiplatelet therapy

Evidence showed that, compared to antiplatelets, anticoagulants reduce:

- All-cause mortality (eleven studies, N= 10316),
- Ischaemic stroke (thirteen studies, N= 11482)

Low quality evidence showed that, compared to antiplatelets, anticoagulants may reduce:

- all-cause mortality, as calculated as time to event (two studies, N=5868)
- haemorrhagic stroke (thirteen studies, N=11542)
- major bleeding (thirteen studies, N= 11430)
- systemic embolic (eleven studies, N= 10912)

Dual antiplatelet therapy versus antiplatelet

Very low quality evidence showed that dual antiplatelet therapy had an unclear effect on the risk of all-cause mortality, as calculated as time- to-event (one study, N= 583)

Low quality evidence showed that dual antiplatelet therapy reduced the risk of ischaemic stroke (two studies, N=8137).

Moderate quality evidence showed that dual antiplatelet therapy increased the risk of major bleeding (two studies, N= 8137).

Evidence showed that dual antiplatelet therapy had no effect on:

- mortality (Moderate quality evidence, two studies, N=8137)
- haemorrhagic stroke (Low quality evidence, two studies, N=8137)
- systemic emboli (Moderate quality evidence, one study, N=7554)
- hospitalisation (Very low quality evidence, one study, N=583)

No evidence on quality of life was identified.

Dual antiplatelets versus anticoagulants

Evidence from one study (N= 6706) showed that dual antiplatelets had:

- no effect on (both moderate quality evidence):

- All-cause mortality
- Major haemorrhage

-increased (both high quality evidence):

- the risk of ischaemic stroke
- the risk of systemic emboli

-decreased the risk of haemorrhagic stroke (Moderate quality evidence).

Anticoagulant plus dual antiplatelet therapy (triple therapy) versus anticoagulant plus antiplatelet therapy

Very low quality evidence from one study of 563 people showed that up to 12 months of warfarin plus dual antiplatelet therapy may have no effect on the risk of haemorrhagic stroke compared with warfarin plus clopidogrel, but the direction of the estimate of effect could favour either intervention.

Low quality evidence from one study (N= 563) showed that up to 12 months of warfarin plus dual antiplatelet therapy increased:

- the risk of all-cause mortality
- the risk of ischaemic stroke
- major bleeding
- the risk of stent thrombosis

Economic

- Three cost–effectiveness analyses found that anticoagulation dominated single antiplatelet therapy for stroke prevention. These analyses were assessed as directly to partially applicable and with minor to potentially serious limitations.

- One cost–effectiveness analysis found that warfarin was cost effective when compared to single antiplatelet therapy for stroke prevention (ICER: £8,844 per QALY gained). This analysis was assessed as partially applicable and with potentially serious limitations.
- Two cost–effectiveness analyses found that warfarin dominated dual antiplatelet therapy for stroke prevention. These analyses were assessed as directly to partially applicable and with minor to potentially serious limitations.
- One cost–effectiveness analysis found that dual antiplatelet therapy was cost effective when compared to single antiplatelet for stroke prevention (ICER: £18,299 per QALY gained). This analysis was assessed as partially applicable and with minor limitations.
- Five cost-effectiveness analyses showed results were sensitive to the stroke risk score of the population, and two cost-effectiveness analyses showed results were sensitive to bleeding risk score.
- One cost-effectiveness sensitivity analysis found that the highest net monetary benefit was achieved when anticoagulation was given when the patient had a CHA_2DS_2-VASc score of 2 or above and at the lowest HAS-BLED score and with a do nothing approach for patients with lower stroke or higher bleeding risk (16% probability of optimality when assessing strategies where anticoagulation initiated at a low stroke risk). A do nothing approach was in comparison to giving single antiplatelet or dual antiplatelet for patients, and comparison of initiation of anticoagulation at alternative stroke or bleeding risk thresholds.

9.2.4 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	The critical outcomes considered for this review were mortality, ischaemic stroke and haemorrhagic stroke. Major bleeding was also an important outcome considered by the GDG when weighing up the benefits of stroke prevention against risk of bleeding.
Trade-off between clinical benefits and harms	**Antiplatelet versus control:** The GDG concluded that the evidence was consistent with no clinical benefit of aspirin in reducing mortality and systemic emboli. The GDG also concluded that although there was a modest benefit in reducing ischaemic stroke it was partially offset by a modest harm in increased bleeding and haemorrhagic stroke. The GDG concluded that there was limited benefit in offering aspirin as the benefit was not outweighed by the associated harms. The GDG additionally noted that the modest benefit in reducing ischaemic stroke was heavily dependent on results from a single study SPAF1 which used a dose of aspirin that would not be used in current clinical practice. The group agreed that it was important that patients at increased stroke risk should not be offered aspirin for stroke prevention. However, the GDG recognised that some patients might still need to take aspirin for indications other than AF. Examples include in the management of acute myocardial infarction or in the first two weeks after acute ischaemic stroke. Please see recommendations 1.3.22 to 1.3.29 in the following NICE clinical guideline: Myocardial infarction: secondary prevention CG172. For patients at low risk of stroke, where anticoagulation was not indicated, the economic model suggested that a higher QALY gain could be achieved by not offering any therapy than by offering single or dual antiplatelet therapy (please see economic considerations for more detail)

Anticoagulant versus control:

The GDG considered that anticoagulation had a clinical benefit over control in reducing mortality and ischaemic stoke with a moderate benefit for preventing systemic emboli. However, anticoagulation may have a modest harm for major bleeding and haemorrhagic stroke compared to control.

The GDG agreed that overall the benefits of anticoagulant therapy in reducing ischaemic stroke risk outweighed the harms of bleeding although they did note that the INR ranges for anticoagulation differed from contemporary practice in two studies (Eezeekowitz 1992 and Singer 1990). The INR was reported as <1.8 and the GDG agreed this indicated a sub therapeutic range and consequently this may have had an impact on both the magnitude of stroke reduction and bleeding risk.

Anticoagulant versus antiplatelet monotherapy:

The GDG agreed that for people at increased risk of stroke, anticoagulants compared to single antiplatelet therapy:

- decreased the risk of all-cause mortality and ischaemic stroke
- moderately decreased the risk of systemic emboli
- however, in contrast, anticoagulants had a moderately harmful effect by increasing the risk of haemorrhagic stroke and major bleeding compared with antiplatelet therapy.

The GDG agreed that anticoagulants were more clinically beneficial than antiplatelets and should be clearly recommended as first line therapy for patients at increased stroke risk.

Dual antiplatelet versus antiplatelet monotherapy

Two RCTs[5,192] in people with AF, of whom 13-15% had a prior stroke, showed that dual antiplatelet therapy had a beneficial effect on reducing the risk of ischaemic stroke compared with single antiplatelet therapy. However, no difference was detected in the risk for all-cause mortality, haemorrhagic stroke, or systemic emboli. Conversely, dual antiplatelet therapy increased the risk of major bleeding.

Dual antiplatelet versus anticoagulant monotherapy

One RCT[6] showed that dual antiplatelet therapy increases the risk of ischaemic stroke and systemic emboli when compared with anticoagulant therapy. Conversely a reduced risk of haemorrhagic stroke was noted. No difference was detected on the risk of mortality or major bleeding.

Overall, the GDG agreed that anticoagulant monotherapy should be recommended over dual antiplatelet therapy in people with AF who are at increased risk of stroke, but that if anticoagulation was contraindicated or all forms of anticoagulation were not tolerated that dual antiplatelet therapy could be considered instead.

Dual antiplatelet and anticoagulant (triple therapy) versus antiplatelet and anticoagulant:

The GDG discussed the potential benefits and risks of triple therapy (dual antiplatelet therapy in combination with warfarin) compared to dual therapy (warfarin plus single antiplatelet treatment) in people with a pre-existing indication for anticoagulation who had undergone percutaneous intervention (PCI) with stent implantation.

Evidence[125] from a moderately indirect population (69% had atrial fibrillation at baseline) suggested that warfarin plus single antiplatelet therapy (warfarin plus

	clopidogrel) was more beneficial than triple therapy (warfarin plus clopidogrel and aspirin). Triple therapy increased the risk of all-cause mortality, ischaemic stroke and major bleeding. Approximately two thirds of the group had received drug eluting stents. Whilst the GDG acknowledged that the study had not assessed the outcomes of dual antiplatelet therapy in the absence of anticoagulation, they considered that the benefits associated with continued anticoagulation were likely to outweigh the benefits of giving dual antiplatelet therapy and discontinuing warfarin. **Discussion** In conclusion, the GDG considered antiplatelet therapy to have limited benefits for AF patients in preventing strokes and made a strong recommendation that aspirin should not be offered to patients at increased risk of stroke. The GDG considered the role of dual antiplatelet therapy with aspirin and clopidogrel. They acknowledged that as the evidence[5,192] demonstrated that dual antiplatelet therapy was more clinically effective than aspirin alone. The GDG considered making a recommendation favouring the use of dual antiplatelet therapy in patients in whom all forms of anticoagulation were contra-indicated or not tolerated. However, concerns were expressed that the main group of patients this would apply to were those at increased bleeding risk. The fact that dual antiplatelet therapy increased risk of major bleeding in comparison with aspirin alone was noted and it was thought inappropriate to recommend the use of dual antiplatelet therapy for those at increased bleeding risk. While there may be some patients in whom all forms of anticoagulation might not be tolerated and amongst whom the use of dual antiplatelet therapy might be reasonable, the GDG considered that the potential number of patients was low and that this indication did not warrant a specific recommendation. The economic model discussed below provided the GDG with the thresholds of risk for people with AF that should be treated. The GDG also emphasised that the recommendations on anticoagulation applied to all patients with AF irrespective of whether they were symptomatic, to all categories of AF (paroxysmal, persistent and permanent), to patients following cardioversion considered at continuing risk of arrhythmia recurrence and to patients with atrial flutter. The GDG did not consider evidence relating to the comparison of specific non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin, which has been the subject of individual single technology appraisals (STAs). However they thought it important to emphasise that following a decision to commence anticoagulation, all of the options for anticoagulation should be considered and discussed with a patient including the advantages and disadvantages of the different treatments available. This has been formulated into a recommendation. The GDG also wished to emphasise that a patient should only be commenced on a particular NOAC if he or she fulfilled the eligibility criteria described in the STA for that particular drug. It was recognized that a small group of patients would fulfil a general recommendation for anticoagulation in the guideline but fail to fulfil criteria for the use of any of the NOACs as described in their individual STAs.
Economic considerations	Four economic evaluations were included in the review, and one original economic evaluation was conducted.

The studies indicated that when risk of stroke was not taken into account, warfarin is cost effective when compared to aspirin. One partially applicable USA study[401]indicated that when stroke and bleeding risk was taken into account, no treatment may be optimal for those with low risk of stroke and high risk of bleeding and aspirin may be cost effective for those with low risk of stroke and bleeding. The sensitivity analysis showed that time in therapeutic range was important when assessing the cost effectiveness of warfarin, which stresses the economic importance of monitoring quality of control for whom warfarin is recommended. Warfarin was cost effective when time spent in INR >72.6%.

One study suggested that dual antiplatelet therapy was more cost effective than mono antiplatelet therapy[98], and another study suggested dual antiplatelet therapy was dominated by warfarin [401]. Overall, using anticoagulation as a stroke preventive therapy is likely to be the most cost effective option. However, the cost effectiveness of the strategy could be further improved by giving treatment to the patients most likely to benefit.

In the absence of economic evidence to indicate the most cost-effective threshold to initiate anticoagulation, the GDG prioritised this antithrombotic decision rules for modelling within the guideline. In particular, the GDG wished to know which stroke prevention strategy (do nothing, single antiplatelet, dual antiplatelet) may be optimal at below the stroke risk threshold where anticoagulation is recommended in existing NICE guidance. An existing model developed by Brunel University was adapted and updated (with kind permission from Brunel University) with results from a network meta-analysis of the systematic review.

The economic analysis found that where anticoagulation was not indicated, a 'do nothing' approach dominated (i.e. was more effective and less costly) than single or dual antiplatelet therapy. In consideration of blanket strategies, where treatment is not tailored to the patient's risk of stroke or bleeding, neither single nor dual antiplatelet therapy was found to be cost effective. On average, a blanket strategy of do nothing appeared more cost effective than that of giving everyone anticoagulation, however it is important to note the cohort assessed is predominantly at low risk of stroke (see discussion on quality of evidence regarding use of an incidence cohort within the model). The optimal strategy is to tailor according to risk, and adopt a "do nothing approach" for patients with a low risk of stroke (i.e. under a CHA_2DS_2-VASc score of 2) or if bleeding risk is high. Otherwise the patient should be offered anticoagulation.

There is a large degree of uncertainty within the model results, especially in consideration of bleeding risk associated with anticoagulation. As more patients with higher bleeding risks are treated with anticoagulation, the QALY and life year gain associated with the strategy becomes less stable with potential higher QALY gains and substantial QALY loss (due to haemorrhagic stroke), alongside increased costs. Overall this leads to a result where there is a low likelihood that anticoagulating patients with a high bleeding risk and low stroke risk is cost effective.

The GDG considered that in view of the uncertainty and data limitations relating to bleeding risk, that they should not specify a bleeding risk threshold in the recommendation. The fact that many of the bleeding risk factors were modifiable reinforced this decision. By the same argument and small absolute differences between the results of many strategies, GDG felt that the stroke risk threshold to anticoagulate may be lower than a CHA_2DS_2-VASc of 2, if there was certainty of a low risk of bleeding or the patient modified their risk factors to achieve a low baseline risk of bleeding.

	In their interpretation of model results and in their consideration when to give anticoagulation at a threshold lower than a CHA2DS2-VASc of 2, the GDG further considered the role of gender in risk stratification of patients with no other risk factors. Their considerations of the evidence also took into account the discussion, evidence, and limitations of the respective risks scores (please see chapter 8 and chapter 9 for further detail). They were of the opinion that any effect of gender in this group was small and that a CHA_2DS_2-VASc score of 1 in women (women under age 65 with no other risk factors) should be regarded as low risk, and should not receive anticoagulation.. Men with a CHA_2DS_2-VASc score of 1 were regarded as at intermediate risk, and a group in whom anticoagulation should be considered. In conclusion, the GDG recommended a first decision step to identify a low stroke risk group (that is CHA_2DS_2-VASc score of 0 for men or 1 for females) who did not require anticoagulation. Subsequent to this step, two groups were defined, an intermediate risk group of men with a CHA_2DS_2-VASc score of 1 amongst whom anticoagulation should be considered and a higher risk group comprising both men and women with a CHA_2DS_2-VASc score of 2 or more who should be offered anticoagulation.
Quality of evidence	**Antiplatelet versus control:** The RCTs included in this review were low to moderate quality. The GDG noted that the studies used different doses of aspirin ranging from 75mg to 325 mg. The SPAFI [423] study used the highest dose of aspirin which would not be used in clinical practice and the GDG interpreted these results with caution. **Anticoagulant versus control:** The RCTs included in this review had low to high quality evidence for this comparison, although the majority of evidence was moderate. The GDG noted that these were all older studies ranging from 1989-1992 and had short follow-up times. **Antiplatelet versus anticoagulant:** The RCTs included in this review had low to moderate quality evidence for this comparison. The GDG noted that the Perez-Gomez[354] study compared the antiplatelet triflusal which is unavailable in the UK. **Dual antiplatelet versus antiplatelet** Two RCTs[5,192] were included in this review with very low to moderate quality evidence for this comparison. One study was a subgroup analysis of AF patients from a larger clinical trial that were not pre-specified prior to randomisation. **Dual antiplatelet versus anticoagulant** One RCT[6] was included in this review with low to high quality evidence for this comparison. **Dual antiplatelet and anticoagulant versus antiplatelet and anticoagulant:** There was one RCT[125] reporting low to very low GRADE quality rating. This study used an indirect population and only 69% had AF. The GDG discussed that INR control is different between these populations. The GDG were concerned on two counts, firstly that the outcomes detected could be from the patients without AF, and secondly that the study was under-powered for detecting stent thrombosis. As a consequence, the results need to be interpreted with caution. No evidence was identified for prasugrel or ticagrelor in combination with anticoagulation.

Economic

Overall, none of the included economic studies from the published literature could provide a firm conclusion as to which drug was optimal for a patient with AF for a given stroke or bleeding risk. Two [217,224] were directly applicable but did not stratify specifically by risk of stroke, and therefore both were considered to have potentially serious limitations.

The other, [401] which did stratify by risk of stroke using the $CHADS_2$ score, was only partially applicable due to the USA perspective used and the risk scores used. For example, the $HEMORR_2HAGES$ score which requires genetic testing is unlikely to be used in the UK for bleeding risk stratification purposes. Furthermore the study did not explore CHA_2DS_2-VASc, a potentially more refined score for lower risk patients, as a means of stratification and this may have led to different thresholds for whom aspirin or no treatment was optimal.

Although the effectiveness parameters of the USA study had similar values to those found in the clinical review, there was a concern that the high costs in the study may have led to different conclusions to one taking the current UK perspective. Further, the GDG noted that only moderate harm or benefit could be ascertained from the clinical review, meaning that probabilistic sensitivity analysis would be useful in determining the likelihood that a given drug would be cost effective given the uncertainty intervals around the mean estimate. As the USA study did not undertake probabilistic sensitivity analysis, this uncertainty was not explored.

In comparison, the economic model adapted from the Brunel MAPGuide model was felt to be directly applicable but with potential limitations which were taken into account when interpreting the evidence.

There were the limitations of the data informing the parameterisation of effect. In particular, the trials assessing warfarin may lead to overestimation of bleeding risk in context of improved anticoagulation monitoring. Furthermore, case fatality for major bleeding in particular may be overestimated, as a range was found in the published literature. Nonetheless sensitivity analysis demonstrated that even when using the lowest risks thought credible by the GDG, conclusions on cost effectiveness remained robust, although lower bleeding and case fatality rates meant higher bleeding risk thresholds became optimal from purely a clinical viewpoint.

The approach to costing class comparisons differed from the typical approach of weighting intervention costs according to estimated use (typically by using prescription data). 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 pooled evidence regarding warfarin and the new agents (such as apixaban) for class comparisons and the use of warfarin intervention as a proxy cost for this class was noted as a potential limitation. However, direct evidence regarding a 'do nothing strategy' versus anticoagulation predated the new agents and mainly specified warfarin as the comparator. Evidence from the new agents therefore have an indirect rather than a direct impact on the effect size between a do nothing approach and anticoagulation estimated through the NMA. That is to say the impact of the new agents in determining the recommended threshold to give anticoagulation following a do nothing approach is likely to be minimal given the data sources used. As such, 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 use of using the cost of warfarin as a proxy for this class to assist decision making was felt appropriate. The model used an incidence cohort, which is typical of discrete event simulation models. Where strategies involved treatment decisions on the basis of risk of stroke and bleeding, the conclusions takes into account age and risk factors dynamically. However it should be noted that the starting age of an incident cohort is typically younger and healthier than a prevalent cohort, and as such cost effectiveness of a blanket anticoagulation strategy may appear reduced in comparison to doing nothing due to a higher proportion of time spent by the cohort in low risk states. The GDG noted that although absolute risks changed over time as the simulated patient's accrued risk factors, the model did not allow for these risk factors to be modifiable by the clinician. Furthermore, predictive ability of the scoring systems used could not be assessed and none had been validated within the same cohort of UK patients. There is therefore some uncertainty regarding the accuracy of the prediction of risk when using these scores which is not captured within the model.
Other considerations	The recommendation came from the evidence and experience and opinion of the GDG. The GDG did not think that there were any equality issues that required further consideration other than age, which was integrated within the stroke risk factor score. This chapter is linked to the chapter on stroke risk tools (Chapter 8) where CHA_2DS_2-VASc is recommended. The GDG incorporated three NICE technology appraisal recommendations[324,325,327] that are included below. The GDG noted that patients with AF might be taking aspirin for a variety of other conditions and that the recommendations applying to these conditions would apply to the need for aspirin in combination with anticoagulants. The GDG felt that it was important that if a patient opted to not take anticoagulation that this decision and reason was documented. The GDG excluded studies that looked at fixed doses of warfarin as warfarin is not used in this manner and they thought it would be in appropriate to include these as it is poor clinical practice.
Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196

10 Bleeding risk tools

This section was partially updated in 2021. See http://www.nice.org.uk/guidance/ng196/evidence for the 2021 evidence reviews.

10.1 Introduction

Effective stroke prevention in atrial fibrillation (AF) requires anticoagulation therapy. A common clinical dilemma is balancing stroke reduction against the potential for serious bleeding (especially intracranial haemorrhage) with the use of oral anticoagulation.

Many risk factors for bleeding are also risk factors for stroke, but whilst bleeding risk correlates with stroke risk scores (e.g. $CHADS_2$, CHA_2DS_2-VASc), specific bleeding risk scores may perform better than stroke risk scores for predicting bleeding.

In considering the value of any score, a balance is also needed between its predictive value and its practicality for everyday clinical use, for example, in busy outpatient clinics or ward rounds.

The objective of this chapter is to review the clinical utility and cost-effectiveness of various bleeding risk scores in AF. Three scores were considered: HAS-BLED, $HAEMORR_2HAGES$ and ATRIA (Table 1)

10.2 Review question: What is the clinical and cost effectiveness of HAS-BLED compared to other tools in assessing bleeding risk in people with AF?

For full details see review protocol in Appendix C.

Table 33: PICO characteristics of review question

Population	People with AF
Intervention/s	HAS-BLED $CHADS_2$ ATRIA $HEMORR_2HAGES$
Outcomes	**Statistical outcomes:** Hazard ratio Area Under Curve (AUC) / C indices Calibration Reclassification index Sensitivity Specificity **Patient outcomes:** Final outcomes of bleeds Major bleeds (including fatal and intracranial bleeding) Mortality from bleeding Quality of life
Study design	Cohort studies

10.2.1 Clinical evidence

Seventeen studies were included in the review.[24,27,143,154,162,166,183,286,288,318,336,337,360,382-384,396] Evidence from these is summarised in the included studies table below. See also the study selection flow chart

in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.
The primary outcomes for this review were hazard ratios for major bleeding and each bleeding tool reported different categorical ratios for their tool. We reported the median hazard ratios and range from the studies reporting over one hundred bleeding events to minimise risk of bias.
The area under the ROC curve (AUC) data for each study was reported as the c-statistic. The AUC describes the overall prognostic accuracy in regards to the tests discriminatory power across the full range of thresholds. The GDG agreed on the following criteria for AUC:

- ≤0.50: worse than chance
- 0.50–0.60: fail
- 0.61–0.70: poor
- 0.71–0.80: fair
- 0.81–0.92: good
- 0.91–1.00: excellent or perfect test.

For further information please see the adapted GRADE table below (**Table 35**).

Table 34: Summary of studies included in the review

Study	Bleeding risk score	Population	Outcomes	Comments
Apostolakis 2012A27 Retrospective cohort (n=2292)	HAS-BLED HEMORR2HAGES	AF, anticoagulation: all on warfarin. External validation study; Non-warfarin anticoagulation validation	Major bleeding (39 events) Hazard Ratio (HR)- Cox AUC Calibration Net Reclassification Index (NRI)	History of bleeding excluded; no genetic data
Apostolakis 201324 Post hoc from trial AMADEUS	HAS-BLED CHADS2	AF undergoing anticoagulation	AUC NRI	History of bleeding and alcohol abuse excluded; these are criteria of the HAS-BLED score
Fang 2011143 Internal validation for ATRIA Retorpsective cohort	Atria	Non valvular, non-transient AF	Major bleeding (307 events) Time varying covariates: AUC, NRI,	Duration of follow up not reported. Some baseline details not reported (age and sex)
Friberg 2012B154 Retrospective cohort (registry data); external validation (n=68,307	HAS-BLED HEMORR2HAGES	AF (according to ICD-10, code 1489); warfarin and non-warfarin separately	Major bleeding (defined as all intracranial bleeds, gastro-intestinal bleeds and anaemia) 5810 events (195 in those not on OAC) AUC	Labile INR data not available so ignored in HAS-BLED; genetic factors not available so ignored in HEMORR2HAGES

Study	Bleeding risk score	Population	Outcomes	Comments
on warfarin at baseline)				
Gage 2006162 Retrospective registry data (Medicare) (n=1604 on warfarin)	HEMORR2HAGES	Patients with AF on warfarin (subset)	Major bleeding (defined by hospitalisation)30 events (aspirin), 67 (warfarin), AUC Rates	
Gallego 2012A166 Prospective cohort (n=965)	HAS-BLED ≥3 versus <3 (assumed lower group)	Consecutive patients with permanent/paroxysmal non-valvular AF, all on anticoagulants, but with INR between 2.0 and 3.0 during previous 6 months. Patients from outpatient clinic	Major bleeding (ISTH criteria, decrease of 20g/l) 75 events HR(Cox) AUC	Risk in lowest group not stated
Guo 2012183	HAS-BLED	Patients with AF	AUC	Reported AUC for CHADS2 and CHA2DS2-VASc for stroke risk
Lip 2012C286 Retrospective cohort (n=7156)	HAS-BLED ≥3 versus 1-2 versus <1 Atria HEMORR2HAGES	Non-valvular AF or atrial flutter. With and without Vitamin K Antagonist (VKA) (reported separately for AUC)	Major bleeding with ≥20g/l decrease (n=550; unclear for VKA HR AUC Lowest risk group: 49/1282 (3.8%)	Genetic information not available
Lip 2011E288 Retrospective cohort study from2 RCTs (n=7329; 3665 on warfarin)	HAS-BLED ≥3 versus 1-2 versus <1 (assumed) HEMORR2HAGES	Permanent/paroxysmal non-valvular AF, with at least 1 risk factor for stroke; randomised to ximelagatran versus warfarin. Reported separately for warfarin, warfarin plus aspirin and VKA naïve at baseline	Major bleeding (fatal/clinically overt bleeding, with ≥20g/l decrease) (217 events; warfarin only 136) HR (warfarin only)	Genetic information not available
Naganuma 2012318 Retrospectiv	HAS-BLED (≥3 versus 1-2) Validation	Non-valvular AF; patients >75 years; all on	Major bleeding (intracranial, intraocular, GI, hospital admission, blood transfusion)	No details on imputation. Risk for 1-2 points: 7/346

Study	Bleeding risk score	Population	Outcomes	Comments
e cohort (n=845)		warfarin, with INR	36 events HR (Cox, possibly MV)	(2.0%)
Oldgren 2011336 Retrospective cohort	CHADS2	AF with one documented risk factor for stroke.	None reported	Not a bleeding risk tool validation paper
Olesen 2011A339 Retrospective cohort (N=118584, n=44771 on anticoagulation)	HAS-BLED HEMORR2HAGES	Non-valvular AF with or without OAC	C-statistic HR for major bleeding (unadjusted cox proportional hazard analyses) 2051 bleeding events. Outcome was hospitalisation or death from major bleeding, including gastrointestinal bleeding, intracranial bleeding, bleeding from the urinary tract or airway bleeding.	Genetic and labile INR information not available
Pisters 2010360 Retrospective analysis (database)	HAS-BLED HEMORR2HAGES Appears to be derivation study for HAS-BLED; external validation HEMORR2HAGES	AF; results reported separately for anticoagulants alone, antiplatelet therapy alone, both and none	Major bleeding – hospitalisation and/or Hb decrease of >2g/l and/or blood transfusion 48 events only AUC only	Genetic data not available
Roldan 2011384 Prospective cohort; but baseline from outpatient database N=829	HAS-BLED	Permanent AF who were stabilised on oral anticoagulation therapy	HR (multivariate analysis) 68 bleeds	
Roldan 2013383 Prospective cohort; but baseline from outpatient database	HAS-BLED ≥3 versus <3 Atria ≥5 versus <5	Consecutive patients with permanent/paroxysmal non-valvular AF, all on acenocoumarol, but with INR between 2.0 and 3.0 during previous 6 months	79 haemorrhagic events HR (unadjusted) AUC NRI	Only stable warfarin and experienced patients included. Prognostic factors all available in database => collected retrospectively
Roldan	HAS-BLED	AF patients on	AUC	Only patients with

Study	Bleeding risk score	Population	Outcomes	Comments
2013b382	CHADS2	anticoagulation	HR (univariable)	stable oral anticoagulation were included.
Seet 2013396 Prospective cohort; but baseline from retrospective outpatient database N=100	HAS-BLED HEMORR2HAGES	Ischaemic stroke patients with AF	41 major bleeding events C statistic (continuous outcome, no CIs) 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.	Genetic information not available.

Table 35: Clinical evidence profile: Bleeding risk scores

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
Hazard ratio for major bleeding (categorical variables) – HAS-BLED score[286,288,337]										
HAS-BLED ≥3vs<3										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	High: 158/1254 (12.6%) Moderate and low: 392/5902 (6.6%)	53 more per 1000 (from 37 more to 70 more)	HR[95% CI]: 1.85 [1.60-2.14]	HIGH
HAS-BLED 1-2 versus <1										
3	Cohort studies	serious limitations [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Moderate (score 2): 721/14933 (4.8%) Low (score 0-1): 377/15570 (2.4%)	25 more per 1000 (from 19 more to 31 more)	Median HR[95% CI]: 2.07 [1.83-2.34] Range of HR: 2.00-4.31	MODERATE
HAS-BLED ≥3vs<1										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
3	Cohort studies	serious limitations [a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	≥3: 158/1254 (12.6%) <1: 49/1282 (3.8%)	91 more per 1000 (from 57 more to 136 more)	Median HR[95% CI]: 3.57 [2.59-4.92] Range of HR: 3.00-8.56	MODERATE
Hazard ratio for major bleeding (categorical variables) – HEMORR$_2$HAGES score[286,288,337]										
HEM ≥2 versus <2										
1	Cohort studies	serious limitations [b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR[95% CI]: 1.80 [1.49-2.17]	MODERATE
HEM mod versus low										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
3	Cohort studies	serious limitations [b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Low: 592/21185 (2.8%) Moderate: 1006/18713 (5.4%) High: 453/4873 (9.3%)	28 more per 1000 (from 23 more to 34 more)	Median HR[95% CI]: 2.04 [1.85-2.26] Range: 1.85-2.19	MODERATE
HEM high versus low										
3	Cohort studies	serious limitations [b]	no serious inconsistency	no serious indirectness	Serious imprecision [c]	none	MEDIAN - LIP 2012: NR Olesen 2011: Low: 592/21185 (2.8%) High: 453/4873 (9.3%) Lip 2011*: High: 2/99 (2%) Low: 81/2694 (3.0%)	*55 more per 1000 (from 15 more to 127 more)	Median HR[95% CI]: 2.90 [1.5-5.61] Range: 0.75-3.87	LOW
Hazard ratio for major bleeding (categorical variables) – HEMORR$_2$HAGES score[286]										
ARIA ≥4 versus <4										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR[95% CI]: 1.61 [1.41-1.84]	HIGH
ATRIA mod versus low										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR[95% CI]: 2.09 [1.46-2.99]	HIGH
ATRIA high versus low										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	HR[95% CI]: 2.48 [1.88-3.27]	HIGH
C-statistics[24,154,286,288,337,382]										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
HAS-BLED										
6	Cohort studies	serious limitations [a, d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Lip 2012: High: 158/1254 (12.6%) Moderate: 343/4620 (7.4%) Low: 49/1282 (3.8%)	NR	Median c-statistic [95% CI]: 0.61 [0.59-0.62] 0.61 [0.58-0.65] Range of HR: 0.60-0.795	MODERATE
ATRIA										
1	Cohort studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	NR	NR	c-statistic [95% CI]: 0.60 [0.56-0.63]	HIGH
HEMORR$_2$HAGES										

Quality assessment							No of patients/events		Effect	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of events/people (%) with and without risk factor MEDIAN VALUE	Median risk for no bleed and/or absolute risk difference	Hazard ratios Median [95% CI] Range	Quality
4	Cohort studies	serious limitations [b]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Lip 2011: High: 2/99 (2%) Moderate: 53/872 (6.1%) Low: 81/2694 (3.0%) Friberg 2012: NR	NR	Median statistic [95% CI]: 0.61 [0.56-0.65] 0.63 [0.61-0.64] Range of HR: 0.59-0.782	MODERATE
$CHADS_2$										
2	Cohort	no serious limitations	no serious inconsistency	no serious indirectness	No serious imprecision	none	Apostolakis 2013: Low: 7/54 (13%) Moderate: 165/1540 (10.7%) High: 79/699 (11.3%)	NR	C-statistic [95% CI]: 0.51 (0.47-0.55) 0.59 (0.56-0.62)	HIGH

a. Studies have a serious risk of bias as one or more of the studies has missing information on the score (labile INR)
b. Studies have a serious risk of bias as one or more of the studies have missing information on the score (genetic information)
c. Confidence interval crossed two MIDs (0.75 and 1.25) in one of the three studies
d. Studies have a serious risk of bias as one of the studies used population without alcohol abuse or previous major bleeding which are components of the score

10.2.2 Economic evidence

Published literature

No relevant published economic evaluations were identified.

One economic evaluations relating to this review question was identified but excluded due to not looking at the specific tools in the protocol. [430] This is summarised in Appendix K, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

10.2.3 Evidence statements

Clinical

Moderate quality evidence from six studies reported c-statistics for HAS-BLED score ranging from 0.60 to 0.795 which is considered to cross from poor to fair discrimination between the risk groups.

High quality evidence from one study reported a c-statistic for ATRIA score at 0.6 which is considered poor at discriminating between the risk groups.

Moderate quality evidence from four studies reported c-statistics for HEMORR$_2$HAGES score ranging from 0.59-0.782 which crosses the category of fail to fair discrimination between the risk groups.

High quality evidence from two studies reported c-statistics for CHADS$_2$ of 0.51 and 0.59 which is considered to fail to discriminate between risk groups.

The median hazard ratio for bleeding for comparing high to low risk scores was 3.57 for HAS-BLED (Moderate quality evidence), 2.90 for HEMORR$_2$HAGES score (Low quality evidence) and 2.48 for ATRIA score (High quality evidence). These comparisons were across one cohort of patients and found that HAS-BLED was better at discriminating between risk groups than the other two scores.

Economic

No relevant economic evaluations were identified.

10.2.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	The GDG considered the critical patient outcome to be major bleeding. Where possible hazard ratios were reported for major bleeding. The c statistic (area under

	the curve) was also considered of relevance by the GDG because it determines the scores ability to discriminate between risk groups. The GDG also considered the use of risk stratification for bleeding against that for stroke, and agreed that the avoidance of a stroke was of greater importance than avoidance of a bleed (this was confirmed by the GDG patient members). Therefore the bleeding risk tool should have high specificity, in order to ensure a low number of false positives. Thus, the tool should avoid predictions that would incorrectly encourage stopping anticoagulation (which in turn increases the risk of stroke).
Trade-off between clinical benefits and harms	The primary outcome for this review was hazard ratios for major bleeding and each bleeding tool reported different categorical ratios for their tool. We reported the median hazard ratio and range from the studies reporting over one hundred bleeding events to minimise risk of bias. The HAS-BLED hazard ratio for high versus low and moderate risk was 1.85 [1.60-2.14], 2.07 [1.83-2.34] for moderate versus low and 3.57 [2.59-4.92] for high versus low risk. The HEMORR$_2$HAGES score had a hazard ratio of 1.8 [1.49-2.17] comparing high and intermediate risk compared to low risk groups. Moderate compared to low risk had a median hazard ration of 2.04 [1.85-2.26] and high versus low risk had a median hazard ratio of 2.9 [1.5-5.61]. The ATRIA score had a hazard ratio of 1.6 [1.41-1.84] for intermediate and high versus low risk groups. One study[286] reported moderate versus low hazard ratio of 2.09 [1.46-2.99] and high versus low risk groups as 2.48 [1.88-3.27]. The GDG compared hazard ratios for the different scores reporting high versus low risk groups across one common cohort from the Lip 2012 study[286]. HAS-BLED score had a hazard ratio of 3.57, HEMORR$_2$HAGES was 2.90 and ATRIA score was 2.48. This demonstrated that the HAS-BLED score was better at discriminating between groups than the other two scores within this same cohort of AF patients. Six studies[24,154,286,288,337,382] reported c-statistics (area under the curve) using the HAS-BLED score and found a median score of 0.61 [0.58-0.65] with a range of 0.60-0.795. One study[286,286] reported a c-statistic of 0.60 [0.56-0.63] for the ATRIA score. Four studies reported c-statistics for the HEMORR$_2$HAGES score and the two median scores were 0.63 [0.61-0.64] and 0.61 [0.56-0.65] with a range of 0.59-0.782. The CHADS$_2$ scores had median scores of 0.59 [0.56-0.62] and 0.51 [0.47-0.55]. The review found that the bleeding risk scores were generally poor at discriminating between risk groups, with HAS-BLED and HEMORR$_2$HAGES score having a c-statistic of more than 0.7 in only 2 studies[339,383], whilst all reported studies using the ATRIA score had a c-statistic of less than 0.7. The GDG considered that other factors such as applicability should be considered when making recommendations. The GDG agreed that if a bleeding risk score was used then it should be the HAS-BLED score as the other scores are more complex, miss important risk factors or include risk factors that are impractical (for example genetic information). The GDG felt that the benefit of reducing stroke in general outweighed the disadvantage of increasing the risk of a bleed. However, it was also recognized that amongst relatively low risk patients (CHA$_2$DS$_2$-VASc =2) that the economic analysis indicated that anticoagulation became less cost effective at higher HAS-BLED scores. They GDG agreed that the main use of the score should be to identify patients at high risk of bleeding who could benefit from increased vigilance and a specific focus on correction of modifiable risk factors. Therefore, the GDG recommended that the modifiable risk factors should be highlighted and if possible corrected to reduce the

	bleeding risk. The modifiable risk factors are uncontrolled hypertension, poor control of INR ('labile INRs'), concurrent medication / concomitant use of aspirin and NSAIDs and excessive alcohol consumption. The GDG were of the opinion that the decision to withhold anticoagulation because of concerns over bleeding risk meant depriving a patient of a treatment which, were it not for the bleeding risk, might have been of benefit in stroke prevention. As a number of factors contributing to bleeding risk are dynamic and also potentially correctable, the GDG considered that the decision to withhold anticoagulation should not be made in perpetuity but should be subject to regular review and reconsideration as appropriate. They also thought it important that both the review and the outcome of the review should be documented. Patient views were important when considering the trade-off between the benefits and harms and the groups agreed that most patients are more concerned about reducing stroke risk then bleeding risk (indeed this was confirmed by the GDG patient members). The group agreed that it was important to ensure that information and education was provided to ensure the benefits and harms fully understood (see the NICE patient experience guideline). In addition the group felt that provision of information and re-education about the importance of treatment might help to change the perception of some patient, who for various reasons, do not want to take warfarin. The GDG agreed that there was no link between falls and bleeding risk. They were concerned that excessive emphasis was often place on falls as a risk factor and wanted to ensure that patients were not denied anticoagulation treatment for this reason.
Economic considerations	There was no economic evidence to inform this question. The GDG discussed the resource implications of undertaking a scoring system, noting that the HEMORR$_2$HAGES was most complicated and resource intensive as it required genetic testing, and least likely to be used in current practice . As there was no evidence to suggest superiority of the HEMORR$_2$HAGES score, the GDG felt this scoring system should not be actively encouraged. For the other scores, the GDG noted that much of the information could be retrieved by clinical history and through tests which were likely to have already been undertaken in the care pathway, and therefore minimal additional resource use would be involved. The economic implications of the question posed relate to the optimal treatment strategy given a particular risk score, and the number of patients which would not benefit from the optimal strategy given the inaccuracies of the scoring system used. Clinical evidence on the accuracy of bleeding risk scores suggested that HAS-BLED was marginally more accurate in its discriminatory power; however no evidence was retrieved to inform any conclusion regarding the scoring system's predictive capabilities to inform treatment management. The GDG noted that the most likely health benefit, and therefore economic benefit, would arise from the use of the tool to mitigate risk by encouraging a reduction in modifiable bleeding risk factors. For this reason, the GDG lent in favour of using the HAS-BLED risk score which identifies more of these factors and is currently the most widely used in current practice. The economic model undertaken to assess stroke prevention strategies also assessed decision rules whereby the decision to anticoagulate was determined by stroke and

	bleeding risk, as measured by the HAS-BLED score. The model offers supportive evidence that bleeding risk should be taken into account alongside ischaemic stroke risk when determining the optimal score to initiate anticoagulation. Further detail regarding the model results and interpretation is provided in Appendix L and Chapter 9).
Quality of evidence	The majority of the studies were retrospective. Some studies did not have the data needed to complete the scores and modified scores were used. Half of the included studies had less than one hundred events which is a major study limitation. However, the outcomes reported in the clinical evidence reported a sensitivity analysis only using the studies with over one hundred events. There was also variability between studies on definition of major bleeding. These limitations were taken into consideration when formulating recommendations.
Other considerations	The GDG highlighted that international guidelines recommend the use of the HAS-BLED score as a simple and practical way to assess bleeding risk in anticoagulated patients with AF.[66] Risk scores need to be pragmatic. The GDG noted the following for harmful alcohol consumption, renal function, liver function and uncontrolled blood pressure: Harmful alcohol consumption: The GDG agreed to align with the definition used in the 2012 ESC guidelines i.e. alcohol excess or abuse, which is essentially an intake where the clinician assesses there would be an impact on health or bleeding risk. In addition the GDG noted the NICE guideline on 'Alcohol: diagnosis, assessment and management of harmful drinking and alcohol dependence (CG115) published in Feb 2011 http://www.nice.org.uk/nicemedia/live/13337/53191/53191.pdf Abnormal renal function: This could be defined as serum creatinine >200, or creatinine clearance <30mls/min, or need for dialysis). Also please see the draft consultation CKD guideline http://www.nice.org.uk/nicemedia/live/13712/66658/66658.pdf (page 54) - due for publication 23rd July 2014. Abnormal liver function: this could be defined as rise of liver enzymes >2x ULN (Upper Limit of Normal) , or known liver cirrhosis. Uncontrolled hypertension: Please see the NICE guideline (CG127) on hypertension published in August 2011, page 10/36 provides definitions. http://www.nice.org.uk/nicemedia/live/13561/56008/56008.pdf They also noted the ESC[66] guideline states that the HAS-BLED score should not be used as a means to withhold oral anticoagulation, but to 'flag up' patients potentially at risk of bleeding for careful review and follow-up, and to correct the potentially reversible bleeding risk factors evident within the HAS-BLED score.[66] Of note, the HAS-BLED score is the only score predictive of intracranial haemorrhage[27] and has also been validated in non-caucasian cohorts[183,318,383] and with non-warfarin anticoagulated patients who have AF.[25,25,292,383] The recommendations were drafted from the evidence and on the experience and opinion of the GDG.

11 Monitoring

11.1 Introduction

Atrial Fibrillation (AF) is a chronic disease which has an impact on important health outcomes, particularly heart failure, stroke, and indeed mortality. Many patients are elderly and have multiple comorbidities, which can change over time. Regular assessment of a patient's symptoms and the risk of stroke, bleeding, and other cardiovascular events is needed.

For this reason it is important that patients identified with atrial fibrillation, of whatever aetiology or whatever classification, are regularly monitored in terms of their underlying condition, the atrial fibrillation itself, in terms of their therapy, the need for a symptoms directed approach to management and appropriate stroke prevention. For example, if patients are taking warfarin for stroke prevention, regular monitoring is an essential part of anticoagulant control to achieve a high proportion of time spent within the therapeutic range (INR 2-3), which is associated with best outcomes[163,454]. This is referred to as time in therapeutic range, expressed as a percentage and calculated assuming a linear change between INR results as originally described by Rosendaal. Some clinical factors are associated with a high time in therapeutic range but comorbidities and interacting drugs may influence the quality of INR control.[26,183]

The following section aims to consider the evidence to ascertain the most clinical and cost-effective means of monitoring these parameters for patients with atrial fibrillation. The aim has not been to compare different strategies of delivering anticoagulant services, which is outside the scope of this review, but to assess whether additional systematic monitoring of patients with atrial fibrillation is cost-effective. One question prior to undertaking the review was whether a recommendation for a regular review of patients with atrial fibrillation would be cost-effective. A second question was whether a regular overview of the risk and benefits of anticoagulation, together with assessment of quality of anticoagulant control, would be merited.

11.2 Review question: What is the clinical and cost effectiveness of systematic monitoring of patients with AF?

For full details see review protocol in Appendix C.

Table 36: PICO characteristics of review question

Population	People with AF
Intervention/s	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/s	No regular monitoring or monitoring of any time point
Outcomes	Mortality Stroke or thromboembolic complications Health related quality of life Time in therapeutic range (INR) - for monitoring of anticoagulation question 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

Study design	• RCTs • Systematic reviews • Non-randomised studies (if no RCTS or systematic reviews)

11.2.1 Clinical evidence

No relevant clinical studies were identified.

11.2.2 Economic evidence

Published literature

No relevant economic evaluations comparing monitoring strategies for people with atrial fibrillation were included.

One study[220] which considered monitoring (non-anticoagulation) was excluded due to the intervention not meeting the protocol. Seven papers [170,218,269 311 20,350,374] regarding optimal monitoring strategies for specific strategies of anticoagulation control were identified; however these were excluded as they did not assess time or frequency of monitoring anticoagulation control. These are summarised in Appendix K, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

11.2.3 Evidence statements

Clinical

No clinical evidence was identified.

Economic

No relevant economic evaluations were identified.

11.2.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	The GDG considered the critical outcomes to be mortality; stroke or thromboembolic complications and health related quality of life. The time in INR range was also considered an important outcome for the evidence on anticoagulation monitoring.
Trade-off between clinical benefits and harms	There was no clinical or cost-effectiveness evidence. The GDG agreed that it was important to monitor patients on anticoagulants to ensure that they were maintaining an INR between 2 and 3. It is important to achieve these acceptable INR levels as if it is lower there is risk of stroke and if it is higher then there is a risk of a major bleed. The best way to measure this is time in therapeutic range (TTR) and studies have linked an increase in TTR to improved outcomes. The GDG agreed that the recommended TTR should be over 65% and this is reported using at least 6 months maintenance period and excluding the first 6 weeks during the initiation period when the dose is slowly increased to reach optimal levels. The NICE topic advisory group from the NICE anticoagulation commissioning guide agreed that after the initial stabilisation of dose, a minimum of 60% of people under the care of the anticoagulation service should be within therapeutic range at a given point in time. Although, they stated that over 65% would be desirable. Further information can be found at the following link: http://publications.nice.org.uk/support-for-commissioning-anticoagulation-therapy-cmg49/3-monitoring-the-safety-and-quality-of-anticoagulation-therapy The NICE topic advisory group consensus was that for all people taking

	anticoagulation therapy should be reviewed at least once a year, including: • Reassessment of stroke or venous thromboembolism risk • Reassessment of bleeding risk • Assessment of renal function • Incidence of adverse events relating to anticoagulation therapy since last review • Assessment of compliance • Choice of alternative anticoagulant The review of people taking anticoagulants should also be in line with NICE clinical guideline 76 on medicines adherence. Link to NICE guidance: http://publications.nice.org.uk/support-for-commissioning-anticoagulation-therapy-cmg49/54-specifying-anticoagulation-therapy-for-all-people-receiving-anticoagulation-therapy#543-monitoring-by-healthcare-professionals Monitoring by healthcare professionals It was agreed that the TTR should be monitored annually and if patients have poor control then they should be re-evaluated to try to improve quality of anticoagulation control. If poor control is not improved then alternative treatments should be considered, for example, with novel oral anticoagulants. Anticoagulation clinics often assess patients who are not reaching the recommended TTR and these patients need more frequent monitoring. It is therefore difficult to recommend a frequency for regular monitoring as all patients are different and optimal frequency for an individual will depend on that individual's level of control.
Economic considerations	There was no economic evidence to inform this question. Appropriate monitoring for INR control was considered to have economic implications due to the potential to improve the cost effectiveness of warfarin (i.e. via reduction of bleeding and improved stroke prevention). A sensitivity analysis undertaken for the economic model on appropriate stroke prevention treatment showed that should bleeding rates on warfarin be reduced to levels expected with aspirin (which GDG felt to be a proxy for those on warfarin with good control) then a greater QALY and life year gain could be achieved at low stroke risk thresholds, even for patients with medium to high absolute risk of bleeding. None the less when costs were considered in this analysis, the net monetary benefit was highest for strategies which took bleeding risk into account. Bleeding risk and effective INR control remains an important determinant of cost effectiveness of stroke prevention using anticoagulation.
Quality of evidence	There was no clinical or cost-effectiveness evidence for this review.
Other considerations	As a result of the absence of evidence the recommendation was based on GDG consensus with expert advisor input. No evidence was looked for regarding this but the GDG acknowledged that at least 20 INR results would be optimal to determine a patient's TTR but this could take up to a year to accumulate. Therefore, the GDG recommended at least 6 months maintenance period before calculating TTR as it was more manageable and patients should not wait for a year before testing. The GDG noted the importance of monitoring renal function particularly for the non-Vitamin K antagonists oral anticoagulants. **Self – monitoring and self-management of anticoagulation:** NICE is developing diagnostics guidance on 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).

Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	The GDG considered the critical outcomes to be mortality; stroke or thromboembolic complications and health related quality of life. The time in INR range was also considered an important outcome for the evidence on anticoagulation monitoring.
Trade-off between clinical benefits and harms	There was no clinical evidence for this review. The GDG thought that if patients with AF were seen by virtue of other opportunistic appointments on an annual basis then the points mentioned in the commissioning guide 'annual review' could be picked up (NICE Commissioning Guide 49) and a routine scheduled annual review in addition to this would not be warranted (the benefits of an annual review in addition to the opportunistic review in relation to cost and time could not be warranted by the GDG). If there is no 'opportunistic' annual review then all AF patients (regardless of whether taking AC or not) should be reviewed annually. The GDG debated that the majority of patients would be reviewed due to processes already in place within the health services, including annual review of patients on medication and patients over 65 years old. It was noted that 85% of patients diagnosed with AF in England are aged 65 and over.[106] The GDG discussed specific groups that would require monitoring and these patients should be reviewed. These include patients that are not on anticoagulant and who develop an additional risk factor for stroke and should thus be considered for antithrombotics. Overall the GDG felt that opportunistic review was important so that when patients seek medical attention for other comorbidities they should have their stroke and bleeding risk assessed at the same time. The GDG considered two separate review questions. The first was the value of systematic review in AF and it was decided that there was not an advantage in systematic review but to cover it with opportunistic review and review for intercurrent events. At a later stage we looked at reviewing quality of anticoagulation and that produced the two recommendations requiring annual review.
Economic considerations	There was no economic evidence to inform this question. The GDG discussed the economic implications of a systematic monitoring strategy, versus a strategy where the patients presented with self-identified symptoms and seeking care. A routine review may involve a consultant, or additional health professionals such as a cardiac technician, but this will be dependent on the patient's needs. The monitoring strategy was a means of determining: • A patient's current clinical status, and • A patient's prognosis given current treatment, or • A patient's prognosis given an alternative treatment. The cost effectiveness of the monitoring strategy would depend on the incremental health gain and cost between the two alternative treatment options which may

	follow using the information given by the patient review. Given that much of recommended management of AF is governed according to the patient's symptoms, it was felt that a strategy based on self-presentation according to noticeable change in symptoms could result in optimal timely changes in management (as opposed to the patient waiting for the next scheduled appointment). Further, scheduled follow up appointments could incur greater resource use in terms of outpatient visits than a system whereby patients present by their own accord, especially when considering a lifetime perspective. However systematic monitoring could be offset if prognostic factors which are silent to the patient, for example high blood pressure, can be detected and appropriately managed. But given existing review processes (i.e. for patients above 65 and on medication) it is likely these factors would be taken into account within existing care. Therefore the GDG came to a consensus that certain subgroups of AF patients should be reviewed at particular points when a change in management could be indicated, and in particular ensure those who entered a higher stroke risk category or had comorbidities which could complicate AF management are catered for appropriately. Some indicators of increased risk, such as age, could be monitored without the patient returning to clinic. Other indicators would prompt a healthcare contact for other reasons, i.e. diagnosis of diabetes or coronary heart disease. At these points, the AF patient should be invited to a review at timely intervals when their risk factors indicated that a change in management may be optimal. For patients, where the clinician feels there is a need for systematic annual review due to increased risk, this should be undertaken.
Quality of evidence	There was no clinical or cost-effectiveness evidence for this review.
Other considerations	These recommendations were based on the experience and opinion of the GDG. The GDG acknowledged that a system which is semi-reliant on patient self-presentation requires that the patient is well informed and confident in contacting the health services. The GDG highlighted the importance of a specialist service which was dedicated to people with AF.

12 Left atrial appendage occlusion

12.1 Introduction

The left atrial appendage is believed to be the major source of thrombus causing stroke and peripheral thromboembolism in patients with atrial fibrillation (AF). The loss of contraction in the appendage in the presence of AF leads to stasis of blood and possible thrombus formation. For some years, removal or obliteration of the left atrial appendage has been considered to be a potential adjunct to surgery in patients with AF undergoing cardiac surgery for other indications.

The advent of catheter-based techniques for closure or obliteration of the left atrial appendage therefore provides another approach to stroke prevention. This would potentially be a means of reducing stroke risk in patients with significant contra-indications to anticoagulation. It might also be considered as a first-line alternative to anticoagulation in patients without anticoagulant contraindications.

This chapter considers the role of catheter- based left atrial appendage occlusion in stroke prevention in people with AF.

12.2 Review question: What is the clinical and cost effectiveness of left atrial appendage occlusion (LAAO) compared to anti-thrombotic therapy in the prevention of stroke in people with AF?

For full details see review protocol in Appendix C.

Table 37: PICO characteristics of review question

Population	People with AF and indication for anticoagulation Sub-groups: patients who cannot take anticoagulants and people who can take anticoagulants
Intervention/s	Left atrial appendage occlusion
Comparison/s	Anti-thrombotic therapy, antiplatelets or placebo
Outcomes	Mortality Ischaemic stroke Haemorrhagic stroke Major bleeding Hospitalisation Procedural complications Health-related quality of life Thromboembolic complications
Study design	Randomised controlled trials (RCT) Systematic reviews of RCTs

12.2.1 Clinical evidence

One randomised controlled trial (RCT), Holmes 2009[204] (PROTECT AF trial), was included in the review and is summarised in **Table 38** below. An additional study by Reddy 2013[372] reported 2.3 year follow-up data from the PROTECT AF trial. This study reported event outcomes but clarified that one person can only count once towards an outcome measure. The GDG noted that although this study compared LAAO with warfarin, participants in the intervention arm (LAAO) were also given warfarin for 45 days after the device had been implanted. Evidence from this is summarised in the clinical GRADE evidence profile below (**Table 39**).See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 38: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Holmes 2009a[204] N=707 Patients followed up for an aggregate of 1065 patient-years. Mean follow-up per patient was 18 months. Reddy 2013[372] reported 2.3 year follow-up data.	Intervention: Left atrial appendage occlusion n=463 Comparison: warfarin, n=244 (2:1 randomisation)	People with non-valvular AF with at least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes, hypertension, or were 75 years or older. Patients excluded if they had a contraindication to warfarin.	Mortality Ischaemic stroke Haemorrhagic stroke Systemic embolism Primary safety (excessive bleeding or procedure related complications)	Both arms received warfarin. Patients in the intervention arm received warfarin after the device was implanted for 45 days to facilitate device endothelialisation.

Table 39: Clinical evidence profile: LAAO (and warfarin versus warfarin alone)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAAO and warfarin	Warfarin	Relative (95% CI)	Absolute		
Mortality (follow-up median 2.3 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/463 (7.3%)	10.7%	RR 0.69 (0.42 to 1.12)	33 fewer per 1000 (from 62 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
Ischaemic stroke (follow-up median 2.3 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/463 (4.1%)	3.3%	RR 1.25 (0.56 to 2.82)	8 more per 1000 (from 15 fewer to 60 more)	⊕OOO VERY LOW	CRITICAL
Haemorrhagic stroke												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/463 (0.65%)	2.9%	RR 0.23 (0.06 to 0.87)	22 fewer per 1000 (from 4 fewer to 27 fewer)	⊕⊕OO LOW	CRITICAL
Systemic embolism												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/463 (0.65%)	0%	OR 4.62 (0.43 to 50.15)	-	⊕OOO VERY LOW	IMPORTANT
Primary safety												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54/463 (11.7%)	8.2%	RR 1.42 (0.87 to 2.32)	34 more per 1000 (from 11 fewer to 108 more)	⊕⊕OO LOW	IMPORTANT

1. Study limitations - both study arms received warfarin
2. Confidence interval crossed one MID (0.75 or 1.25)
3. Confidence interval crossed both MIDs (0.75 and 1.25)

12.2.2 Economic evidence

Published literature

One economic evaluation was identified with the relevant comparison and has been included in this review.[412] This is summarised in the economic evidence profile below and the economic evidence tables in Appendix H. No studies were selectively excluded.

See also the economic article selection flow chart in Appendix E.

Table 40: Economic evidence profile: LAAO and warfarin versus warfarin alone

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Singh 2013[412] (Canada)	Partially applicable (a)	Minor limitations (b)	Markov patient level simulation model	£3002	0.13 QALYS	£16,595 per QALY gained	The ICER ranged from £16,595 to £22,385 per QALY gained with a respective discount of 0% and 5%. The probability intervention LAAO cost effective is 43% or 47% using a Canadian dollar threshold of $50,000 or $100,000 respectively Authors report LAAO not being cost effective if the odds ratio for stroke with LAAO versus warfarin was>1.56 (found by deterministic analysis) Inspection of the scatter plot of the cost-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.

(a) Cost Utility Analysis from a Canadian healthcare system with a 5% discount rate applied
(b) Probabilistic analysis undertaken, key parameters considered, based on RCT trials.

12.2.3 Evidence statements

Clinical

Evidence from one study (N= 707) comparing LAAO plus warfarin to warfarin alone showed that LAAO (as an adjunct to warfarin) was associated with:

- no clinical benefit in reducing mortality, ischaemic stroke, systemic embolism or primary safety (low to very low quality evidence).
- a decrease in number of haemorrhagic strokes (Low quality evidence).

Economic

One cost–utility analysis found that LAAO and warfarin could be equally as cost effective as warfarin in patients with AF (ICER: £16,595 to £22,385 per QALY gained (Discounting rate 0% to 5%). This analysis was assessed as partially applicable and with minor limitations.

12.2.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	Mortality, ischaemic stroke and haemorrhagic stroke were considered the critical outcomes for this review. The GDG also considered the safety aspects important when making recommendations including systemic embolism as well as procedural complications.
Trade-off between clinical benefits and harms	The GDG noted that warfarin was given in both warms of this trial, hence LAAO and warfarin compared to warfarin. There was no difference found between LAAO with warfarin and outcomes for mortality, ischaemic stroke, systemic embolism or primary safety when compared to a warfarin alone. The study[204,372] did find a reduction in the number of haemorrhagic strokes with LAAO and warfarin compared to warfarin alone, which in absolute terms equated to 22 fewer per 1000 (4 fewer to 27 fewer). The short term risks for this procedure included cardiac tamponade, thromboembolism and device embolisation. Relating to this, the GDG was interested in the long term benefits of the procedure to make an informed judgement on the risk versus the benefit of the procedure. However, the one study included in this review only reported short term follow-up (of approximately 2.3 years). The GDG acknowledged that this study had 4 year data that was awaiting publication. Therefore, the GDG agreed that there was insufficient evidence to recommend LAAO as an alternative to anticoagulation in patients without a contraindication to anticoagulation. However, LAAO was thought to offer a major advance in patients at risk of stroke and who are unable to take any form of anticoagulation. Although there was no RCT evidence relating to patients with a contra-indication to anticoagulation, the GDG noted that there was non-randomised clinical trial[371] evidence relating to this group and that there was no reason to believe that the RCT evidence could not be extrapolated to this group. The GDG agreed that it was appropriate to make a recommendation that LAAO should be considered in this population of patients unable to take any form of anticoagulation. The GDG agreed that it was important

	when LAAO was being considered that the benefits and risks of the procedure were clearly discussed with the patient to make an informed decision. The GDG also noted that patients in trials of LAAO were maintained on anti-platelet agents in the long term. This applied both to patients capable of taking anticoagulation, who were maintained on aspirin and clopidogrel after discontinuation of anticoagulation until 6 months after device implantation and thereafter maintained on aspirin[372] and to patients with an anticoagulant contra-indication, who were maintained on aspirin and clopidogrel for 6 months and thereafter on aspirin.[372] Patients considering LAAO should therefore be informed of the continuing need for anti-platelet therapy.
Economic considerations	One economic evaluation [412] was found to inform this question. The analysis was well conducted. However the results had limited applicability to the UK context. The probabilistic analysis suggested there was a high degree of uncertainty surrounding the conclusion of the results, with inspection of the graph indicating approximately an equal number of incremental point estimates in each quadrant of the cost-effectiveness plane. The conclusion of the analysis was sensitive to the discount rate employed; suggesting that long term effectiveness of LAAO would be an important consideration. However there was little reporting of how this aspect was considered in the analysis. Overall, this analysis indicates that LAAO or warfarin could be cost-effective and further research may be warranted. An accurate costing of the LAAO device and procedure was not obtained for this question. Percutaneous occlusion of the left atrial appendage has the OPCS code of 4.5 K22.8, being described as other operations on wall of atrium. At the time of writing, the procedure was included under the SSNDS Definition No 13. Specialised Cardiology & Cardiac Surgery Services (adult). This indicates that the procedure is specialised and not undertaken frequently. It was agreed that it was highly unlikely that NHS reference cost given for health resource groups containing the OPCS code 4.5K22.8 will be reflective of this procedure, as the cost presented will be aggregated with non-similar procedures. The Watchman™ device has been estimated to have a cost of approximately £4,000 plus £400 for the insertion of the catheter. Thus the total cost including VAT at 20% is £5,280. This will not be inclusive of staff time, hospital admission and overheads. The NHS North East Treatment Advisory Group estimated the cost of the LAAO procedure without complications to be £ £7,610.[330] The breakdown of this estimation is not given, although the group do state it is not inclusive of additional pre- or post-operative follow-up appointments that are specific to implantation of the device or imaging techniques such as echocardiograms which are required before, during and after implantation. The importance of considering the economic implications over a lifetime was emphasised. The GDG noted that alongside the high upfront cost, the need and resources used in for follow up was also important. However, there was insufficient clinical evidence of appropriate follow up time to make an informed estimate to what the long term resource implications may be. In comparison to anticoagulation, the GDG did not believe that that the upfront costs of the device would be less than that spent on anticoagulation over a patient's lifetime. Given the uncertain, and potentially equivocal effect, between the comparators and the likelihood that anticoagulation is less costly, the GDG recommended anticoagulation in preference to LAAO as a first line strategy.

	In regards to LAAO's potential as a strategy for those contraindicated to anticoagulation, the comparator is a "do nothing approach" with no intervention cost. The GDG believed that the cost of stroke would outweigh the cost of the device, and therefore cost effectiveness would be influenced by the prior risk of stroke. Therefore it was felt in patients who could not take anticoagulants, but had a high risk of stroke; LAAO should be considered as a potentially cost-effective intervention.
Quality of evidence	There was one small study[204,372] with low to very low outcome quality ratings. The GDG noted that the intervention arm was given warfarin as well as the comparison arm and did not report long-term outcomes. The economic study[412] was judged to have partial applicability (due to discounting rate and Canadian perspective applied) and minor limitations.
Other considerations	The GDG noted that this is not a new procedure and has been around for some time but previous devices have not been subjected to of randomised controlled trials. The left atrial appendage can also be removed during other cardiac procedures. The GDG agreed that patients will need to be informed of the risks of this procedure for decision making. Risk of bleeding and stroke will need to be considered alongside scans to look at the shape of the LAA to determine whether suitable for this device. The recommendations were based on the evidence and the experience and opinion of the GDG. There is a NICE Patient experience guideline (CG138) (http://www.nice.org.uk/nicemedia/live/13668/58283/58283.pdf) that should be referred to. There is a NICE Interventional Procedure (349) on percutaneous occlusion of the left atrial appendage – http://publications.nice.org.uk/percutaneous-occlusion-of-the-left-atrial-appendage-in-non-valvular-atrial-fibrillation-for-the-ipg349 The GDG discussed the importance of clinicians having the relevant training and experience to carry out this procedure and refer to the IPG where this is recommended.

13 Rate versus rhythm control

This section was partially updated in 2021. See http://www.nice.org.uk/guidance/ng196/evidence for the 2021 evidence reviews.

13.1 Introduction

A number of factors contribute to symptoms in patients with atrial fibrillation (AF). One factor is the loss of atrial contraction and the synchronisation of atrial contraction between the atria and ventricles, and the consequent reduction of atrial contribution to the cardiac output. A second is the rapidity of ventricular rate and the irregularity of ventricular rhythm in AF.

Treatments for these respective aspects represent the two main strategies in the management of patients with AF. A rate control strategy accepts the presence or occurrence of AF and aims to control ventricular rate and degree of irregularity despite continuing fibrillation within the atria. The alternative strategy of rhythm control attempts to restore and maintain sinus rhythm.

In some patients with AF, ventricular rate control is adequate without the need to resort to drug therapy for rate control. For others, rate control is achieved through the use of drugs which slow the maximum rate of conduction through the AV node.

In a rhythm control strategy, the objective of drug therapy is the maintenance of sinus rhythm. In patients with persistent AF, sinus rhythm must first be restored, which is achieved either by electrical cardioversion or by using drugs.

Although there is a prima facie case that the rhythm control approach and maintenance of sinus rhythm should be superior to rate control, this is not necessarily the case. Drugs used for the maintenance of sinus rhythm have side effects. Moreover, the restoration of sinus rhythm may lead to a false sense of security regarding stroke risk and to the discontinuation of anticoagulant therapy. The risk of stroke is still present should AF recur, and often happens asymptomatically.

Trials have therefore been undertaken to assess the relative merits of the two approaches and the results of these studies are considered in this chapter. The role of pulmonary vein isolation in pursuing a rhythm control strategy is considered separately in chapter 17.

13.2 Review question: 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?

For full details see review protocol in Appendix C.

Table 41: PICO characteristics of review question

Population	People with paroxysmal, permanent and persistent AF
Intervention/s	Patients under aggressive rhythm strategies
Comparison/s	Patients under aggressive rate strategies **Sub group analysis:** • Heart failure (impaired LV function) • Reversible causes (see full list Appendix C)
Outcomes	Mortality Heath related quality of life Stroke or thromboembolic complications Major bleeding - all Re-hospitalisation with a primary diagnosis of AF Patients developing heart failure Restoration of sinus rhythm

	Recurrence of AF
Study design	Systematic reviews and randomised controlled trials

13.2.1 Clinical evidence

We searched for systematic reviews and RCTs comparing rhythm control versus rate control for atrial fibrillation. Eight trials, including 15 papers[78,134,153,176,186,188,203,334,342,385,389,403,441,462,463] were identified, for this review. Evidence from these trials are summarised in the clinical GRADE evidence profile below (**Table 43**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 42: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes
STAF trial[78]	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 versus rate control using beta-blockers, digitalis, calcium channel blockers or atrioventricular node ablation/ modification.	Patients 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.	Death Cardiopulmonary resuscitation Cerebrovascular event Systemic embolism
PIAF trial[203 177]	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 versus rate control diltiazem 90 mg two or three times a day.	Patients 18-75 years presenting with symptomatic persistent AF of between 7 days and 360 days duration.	Symptom improvement, including elimination of palpitations, reduction in frequency of episodes of dyspnoea, reduction of dizzy spells.
J-Rhythm trial[334, 463]	Rhythm control with antiarrhythmic drugs selected according to "The Japanese Guideline for Atrial Fibrillation Management" versus rate control using beta-blockers, calcium channel blockers and digitalis.	Patients with paroxysmal AF (PAF) treated by either rate or rhythm control.	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 scores on Japanese Society of Electrocardiology's AF QoL Questionnaire and

Study	Intervention/comparison	Population	Outcomes
			the efficacy and safety of drugs required in AF treatment.
Hot Café trial[342]	Rhythm control by cardioversion prior to drug treatment with propafenone, disopyrmide, or sotalol. Beta blockers were given if clinically indicated versus rate control using beta-blockers, digitalis, calcium channel blockers or a combination of these drugs. Cardioversion and atrioventricular ablation with pacemaker placement were alternative non-pharmaco-logic strategies.	Patients 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.	Primary composite endpoint; all-cause mortality; thrombo-embolic events and major bleeding complications
CTAF trial[134, 385]	Aggressive rhythm control: amiodarone and either sotalol or dofetilide if required; 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 was recommended if bradycardia prevented the use of antiarrhythmic drugs versus adjusted doses of beta blockers with digitalis to achieve the targeted heart rate of less 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.	Left ventricular ejection fraction (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 $\geq$ 6 hours or requiring cardioversion within the previous 6 months; and, eligibility for long term therapy in either study group.	The primary outcome was death from cardiovascular causes. Secondary outcomes were death 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
Café II trial[403]	Rhythm control with oral amiodarone; if AF persisted after 2 months, cardioversion was performed versus rate control using beta-blockers and	Patients 18 years or older with Persistent AF and chronic symptomatic heart	The primary outcome was QoL using SF-36vII at 1 year. Secondary outcome of interest was sinus rhythm.

Study	Intervention/comparison	Population	Outcomes
	digoxin.	failure (NYHA ≥ Class II symptoms) with evidence of systolic dysfunction on ECG.	
RACE trial[186, 188,441]	Rhythm control consisted of serial electrical cardioversion with institution of antiarrhythmic drugs (sotalol, class IC drugs including flecainide or propafenone or amiodarone) versus rate control was achieved using negative chronotropic drugs including digitalis, beta blocker and nondihydro-pyridine calcium channel blocker.	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.	Composite of cardiovascular death, hospitalisation for CHF, thrombo-embolic complication, bleeding, pacemaker implantation or severe adverse effects of antiarrhythmic drugs. Quality of life was also reported.
AFFIRM trial[153, 389, 462]	Rhythm control Drugs chosen by the treating physician and may include cardioversion. Drugs could include amiodarone, disopyramide, dofetilide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol and combinations of these drugs versus rate control using beta-blockers, digoxin, calcium channel blockers 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.	Patients 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.	Overall mortality; a composite endpoint comprised death, disabling stroke, disabling anoxic encephalopathy, major bleeding and cardiac arrest.

Table 43: Rhythm control versus rate control for atrial fibrillation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rhythm control	Rate control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up maximum 6 years; assessed with: death)[78,203,334,342,385,403,462]												
7	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	587/3495 (16.8%)	553/3482 (15.9%)	RR 1.07 (0.96 to 1.18)	11 more per 1000 (from 6 fewer to 29 more)	MODERATE	CRITICAL
Cardiovascular mortality in heart failure patients (follow-up maximum 6 years; assessed with: death)[188,385,403,462]												
4	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	250/1051 (23.8%)	243/1041 (23.3%)	RR 1.01 (0.87 to 1.18)	2 more per 1000 (from 30 fewer to 42 more)	MODERATE	CRITICAL
Stroke or thromboembolic complications (follow-up maximum 6 years; assessed with: symptoms; scan)[78,334,342,385,441,462]												
6	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	152/3604 (4.2%)	143/3582 (4%)	RR 1.06 (0.84 to 1.32)	2 more per 1000 (from 6 fewer to 13 more)	LOW	CRITICAL
Stroke or thromboembolic complications in heart failure patients (follow-up maximum 6 years; assessed with: symptoms; scan)[188,385]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	28/813 (3.4%)	34/824 (4.1%)	RR 0.83 (0.51 to 1.36)	7 fewer per 1000 (from 20 fewer to 15 more)	VERY LOW	CRITICAL
Bleeding (follow-up maximum 6 years; assessed with: symptoms)[78,334,342,441,462]												
5	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	167/2922 (5.7%)	164/2888 (5.7%)	RR 1.01 (0.82 to 1.24)	1 more per 1000 (from 10 fewer to 14 more)	MODERATE	IMPORTANT
Bleeding in patients with heart failure (follow-up maximum 6 years; assessed with: symptoms)[188]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[d]	none	3/131 (2.3%)	9/130 (6.9%)	RR 0.33 (0.09 to 1.19)	46 fewer per 1000 (from 63 fewer to 13 more)	LOW	IMPORTANT
Hospitalisation; random effect (follow-up maximum 6 years; assessed with: Patient records)[78,188,203,342,385,462]												
5	randomised trials	serious[a]	serious[e]	no serious indirectness	serious[b]	none	1964/3046 (64.5%)	1690/3047 (55.5%)	RR 1.52 (1.21 to 1.90)	288 more per 1000 (from 116 more to 499 more)	VERY LOW	IMPORTANT
Hospitalisation in patients with heart failure (follow-up maximum 6 years; assessed with: Patient records)[385]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	436/682 (63.9%)	409/694 (58.9%)	RR 1.08 (1 to 1.18)	47 more per 1000 (from 0 more to 106 more)	MODERATE	IMPORTANT
Heart failure: Patients developing heart failure (follow-up maximum 6 years; assessed with: Clinical signs and symptoms)[334,385,441,462]												
4	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	247/3400 (7.3%)	267/3381 (7.9%)	RR 0.94 (0.8 to 1.09)	5 fewer per 1000 (from 16 fewer to 7 more)	MODERATE	IMPORTANT

Sinus rhythm at last follow-up; random effect (follow-up maximum 3 years; assessed with: ECG)[78,203,334]												
3	randomised trials	serious[a]	serious[e]	no serious indirectness	no serious imprecision	none	414/646 (64.1%)	198/629 (31.5%)	RR 3.37 (1.29 to 8.84)	746 more per 1000 (from 91 more to 1000 more)	LOW	IMPORTANT
AF at last follow-up (follow-up maximum 2.5 years; assessed with: ECG)[342]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/101 (37.6%)	101/101 (100%)	RR 0.38 (0.3 to 0.49)	620 fewer per 1000 (from 510 fewer to 700 fewer)	MODERATE	IMPORTANT
General health QoL SF-36 (follow-up maximum 3 years; measured with: SF-36 questionnaire; Better indicated by higher values)[78,188,203]												
3	randomised trials	serious[a]	serious[e]	no serious indirectness	no serious imprecision	none	358	359	-	MD 1.49 higher (3.01 lower to 5.99 higher)	LOW	CRITICAL
Physical function QoL SF-36 (follow-up maximum 3 years; measured with: SF-36; Better indicated by higher values)[78,188,203]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	359	-	MD 6.04 higher (3.16 to 8.92 higher)	MODERATE	CRITICAL
Physical role function QoL Sf-36 (follow-up maximum 3 years; measured with: SF-36; Better indicated by higher values)[78,188,203]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	359	-	MD 5.71 higher (1.13 to 10.29 higher)	MODERATE	CRITICAL
Bodily pain QoL SF-36 (measured with: Sf-36; Better indicated by higher values)[78,188,203]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	359	-	MD 1.39 higher (1.69 lower to 4.47 higher)	MODERATE	CRITICAL
Mental health QoL SF-36 (measured with: SF-36; Better indicated by higher values)[78,188,203]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	359	-	MD 2.05 higher (0.01 lower to 4.11 higher)	MODERATE	CRITICAL
Social functioning QoL SF-36 (follow-up maximum 3 years; measured with: SF-36; Better indicated by higher values)[78,188,203]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	359	-	MD 2.28 higher (0.42 lower to 4.98 higher)	MODERATE	CRITICAL
Role emotional QoL SF-36 (follow-up maximum 3 years; measured with: Sf-36; Better indicated by higher values)[78,188,203]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	359	-	MD 2.69 lower (6.69 lower to 1.31 higher)	MODERATE	CRITICAL
Vitality QoL SF-36 MA (follow-up maximum 3 years; measured with: SF-36; Better indicated by higher values)[78,188,203]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	358	359	-	MD 3.43 higher (1.11 to 5.75 higher)	MODERATE	CRITICAL

[a] Blinding not possible due to variations in treatment. Randomisation and allocation concealment not consistently reported.
[b] Confidence interval crossed one MID (1.25)
[c] Confidence interval crossed both MIDs (0.75 and 1.25)
[d] Confidence interval crossed one MID (0.75).
[e] Unexplained heterogeneity I-squared >50% fixed and random effects models

13.2.2 Economic evidence

Published literature

Three studies were included that compared the cost effectiveness of rhythm control versus rate control in patients with AF.[186,304 353] These are summarised in the economic evidence profile below and the economic evidence tables in Appendix H.

Three studies that met the inclusion criteria were selectively excluded due to having less applicability or more limitations than the included studies.[357 81,357 365] These studies are summarised in Appendix H, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Table 44: Economic evidence profile: rhythm control versus rate control

Study	Applicability	Limitations	Other comments	Incremental costs	Incremental effects	Cost effectiveness	Uncertainty
Hagens 2004, Netherlands [186]	Partially applicable (a)	Potentially serious limitations (b)	Patients with persistent AF. Primary endpoint from RACE study =composite of morbidity and mortality (c) Intvn 1 = Rate control=digitalis, CCC, BB or a combination. Intvn 2 = Rhythm control= serial electrical CV plus AAD	Rhythm control cost £694 more than rate control (d)	3.7% more patients reached primary endpoint with rhythm control	Rate control dominated rhythm control (being less costly and more effective)	Analysis of uncertainty: Varying costs on the different cost categories by -20% and plus 20% did not affect the cost-effectiveness conclusions.
Marshall 2004, USA. [304]	Partially applicable (e)	Potentially serious limitations (f)	A retrospective cost-effectiveness analysis using resource-use data and survival data for patients with mostly persistent AF (64.5 %.) from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. [304] Outcomes measured in cost per life year gained.	Rhythm control cost £3187 more than rate control (g)	Mean survival was reduced by 0.07 years greater with rhythm control	Rate control dominated rhythm control (being less costly and more effective)	Rhythm control strategy was dominated for all three cost scenarios (base case, low and high estimate). Rhythm control was associated with lower survival at an additional cost relative to rate control in 95% of samples.
Perez 2011, USA. [353]	Partially applicable (h)	Minor limitations (i)	Markov model with 3 month cycles over patient lifetime. Population had persistent or paroxysmal AF with heart failure.	Rhythm control cost £5819 more than rate control (j)	0.198 QALYs were lost with rhythm control (95% CI 0.129 fewer to 0.369 fewer)	Rate control dominated rhythm control (being less costly and more effective)	One-way sensitivity analyses showed that rate control was less costly and more effective than rhythm control. PSA results support the base case conclusion. The

Study	Applicability	Limitations	Other comments	Incremental costs	Incremental effects	Cost effectiveness	Uncertainty
							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).

Abbreviations: AAD= antiarrhythmic, AF = Atrial fibrillation; Ami = Amiodarone, ASA = aspirin; CE= cost effectiveness; CV=cardioversion; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs = quality-adjusted life years; PSA= probabilistic sensitivity analysis ; Quin = Quinidine: Ref = Reference; Sot = Sotalol; W = Warfarin

(a) Netherlands setting. 4% discount rate. Health outcome morbidity and mortality composite rather than QALYs. Societal perspective with costs disaggregated to allow a provider perspective.

(b) 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. There was no rationale for this approach, and the reported treatment differences were not subject to sensitivity analysis.

(c) Primary endpoint was the composite of cardiovascular mortality, heart failure, thrombo-embolic complications, bleeding, pacemaker implantation, or severe adverse effects of antiarrhythmic drugs .Effects given for percentage of patients reaching primary endpoint (i.e. the lower the percentage, the more beneficial the intervention).

(d) Only costs associated with study endpoint (c) were included. 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. Costs reported here are direct medical costs only. Converted using 2000 purchasing power parities[344] Reported totals and tabulated disaggregated costs has a 3 euro discrepancy – which was assumed to have occurred by rounding.

(e) USA setting. 3% discount rate. CEA analysis using survival as endpoint rather than CUA with QALYs as study endpoint.

(f) Costs and effects data measured for a mean follow-up period 3.5 years.

(g) USA setting. Perspective third party payer.

(h) Converted using 2002 purchasing power parities[344]

(i) Data taken from a variety of published studies including post hoc analysis of AFFIRM.

(j) Converted using 2009 purchasing power parities[344]

13.2.3 Evidence statements

Clinical

AF

Moderate quality evidence showed no difference between rate and rhythm control in:

- mortality (7 studies, N=6977)
- bleeding (9 studies, N=12591)

Low quality evidence from six studies (N=7186) showed that there *may* be no difference between rhythm and rate control in:

- stroke
- thromboembolic complications

Very low quality evidence from five studies (N= 6093) showed that rate control may reduce hospitalisations, but the direction of the estimate of effect could favour either intervention.
Low quality evidence from eight studies (N=1275) showed more in sinus rhythm at last follow-up in the rhythm control group.
Moderate quality evidence from one study (N= 202) showed more in AF at last follow-up in the rhythm control group.
No evidence was found for health-related quality of life for an AF population.

AF and heart failure (HF)

Low to moderate quality evidence showed no difference between rhythm and rate control in:

- Hospitalisations (Moderate quality evidence, one study, N=1376)
- Quality of life SF-36 outcomes for general health, bodily pain, mental health, social functioning and role emotional. (Low to moderate quality evidence, three studies, N=100s).

Very low quality evidence from two studies (N=1637) showed that there may be no difference between rhythm and rate control in reducing stroke or thromboembolic complications, but the direction of the estimate of effect could favour either intervention.
Moderate quality evidence from three studies (N=100) showed that a rhythm control strategy is more clinically effective at improving quality of life outcomes for physical function, physical role function and vitality.
Low quality evidence from one study (N=261) showed that rhythm control treatment may decrease bleeding in patients with AF and HF, but the direction of the estimate of effect could favour either intervention.
No evidence was found for mortality for an AF and HF population.

Economic

Two cost–effectiveness analyses and one cost utility analysis found that rate control was dominant (more effective and less costly) when compared to rhythm control. These analyses were assessed as partially applicable with minor to potentially serious limitations.

13.2.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	Mortality, health related quality of life, and stroke or thromboembolic complications were considered the critical outcomes for this question. The GDG were interested in a comparing a strategy approach and therefore did not specify which drugs were used and whether used in monotherapy or combination therapy.
Trade-off between clinical benefits and harms	No clinical difference was found between rhythm and rate control strategies in reducing mortality, stroke or thromboembolic complications, bleeding or developing heart failure, quality of life SF-36 outcomes for general health, bodily pain, mental health, social functioning and emotional status. A rhythm control strategy was found to be more clinically effective at increasing sinus rhythm and reducing AF recurrence at last follow-up. This was expected as the rate control strategy was not attempting to regain sinus rhythm. The rhythm control strategy was found to be more clinically effective at improving quality of life outcomes for physical function, physical role function and vitality. The rate control strategy was found to be more clinically effective at reducing hospitalisations than rhythm control strategies. The GDG considered this not only to be due to more hospitalisations for cardioversion but also due to more healthcare contact due to return of symptoms. In patients with AF and heart failure, low to moderate quality evidence showed that there may be no clinical difference between rhythm and rate control strategies in reducing mortality, stroke or thromboembolic complications or number of hospitalisations. The GDG discussed and agreed that the evidence shows no advantage of rhythm control over rate control. Rate control is the simpler strategy clinically. The health economic studies also favoured rate control over rhythm control (see below). In view of these considerations, the GDG agreed that rate control should be offered as first line treatment, while also taking in to consideration the patient's symptoms and preferences, as well as associated comorbidities and AF subtypes. Rhythm control should be offered as second line therapy if rate control does not control symptoms. In this situation many patients would prefer rhythm control in order to improve their quality of life. There is no evidence to determine whether there is a health economic benefit in offering rhythm control for this particular group of patients. There are some exceptions to when rhythm control should be considered before rate. Examples of patients who might be primarily treated with a rhythm control strategy include patients with acute onset AF, patients with a treatable or reversible cause for their AF and patients in whom AF was thought to precede the development of heart failure and to be the primary cause of the heart failure and patients with atrial flutter who are considered suitable for an ablation strategy to restore sinus rhythm. The GDG wished to make it clear that these are examples of exceptions and do not represent an exhaustive list of clinical situations in which a rhythm control strategy might be considered preferable to rate control. The GDG considered the roles of rate and rhythm management as applied to different clinical sub-types of AF. It was recognised that for patients with paroxysmal AF and already capable of achieving sinus rhythm, this might lead to a lower threshold for a rhythm control strategy. However, it was also noted that the studies

	considered comprised a mixed population of paroxysmal and persistent AF. For example in the AFFIRM study, 34.6% of the rate control group were in sinus rhythm at 5 years and by definition were paroxysmal. For this reason rate control was still thought to be the treatment of first choice for patients with paroxysmal AF. The GDG considered the fact that rate and rhythm strategies are not mutually exclusive alternative strategies and that a rhythm strategy might at various times also necessitate drug therapy for rate control during periods of relapse into atrial fibrillation. This is illustrated by the AFFIRM study[7] where at the study outset 21.8% of patients in the rhythm control group were receiving a beta-blocker. When treatment at any time during the study was considered 49.6% of patients in the rhythm control group received a beta-blocker. A rhythm control strategy does not therefore preclude the inclusion of drugs for rate control and these may be variably needed at different times. Rate versus rhythm control might therefore be more correctly considered as rate versus rhythm and rate control. However the GDG thought that expressing the choice of strategy in this way, would not help clarify the fundamental objective which is rate or rhythm control.
Economic considerations	All three economic studies found that rate-control strategies were preferable to rhythm-control strategies because they were less costly and more effective. The economic analysis of AFFIRM in a USA setting,[304]showed that rhythm control is consistently more expensive than rate control in such patients and consequently rate control is the preferred alternative (rhythm control was dominated by rate control) on the basis of cost. Patients in the rate-control group used fewer resources (hospital days, pacemaker procedures, cardioversions and short-stay and emergency department visits). Similarly, in the economic analysis of the RACE trial set in the Netherlands,[186] costs of therapy were higher for rhythm control compared to rate control due to higher costs for electrical cardioversions, hospital admissions, and costs for medication. As the incidence of primary endpoints under rhythm control was comparable to rate control, rate control was considered to be the most cost-effective treatment option for patients with persistent AF. Resource use was limited to the time horizon in two studies (mean of 2.3 years in the RACE trial and 3.5 years in the AFFIRM trial). However, in a decision analytic study (Perez et al) that considered lifetime costs and benefits came to the same conclusion: that is, that rate control is less costly and more effective than rhythm control. Overall the economic evidence suggests that rhythm control is likely to be dominated by rate control, primarily because rhythm control involves more healthcare contacts to administer the intervention (and also subsequently in follow up) whilst not offering a clear clinical advantage. These findings were consistent with the clinical evidence. The GDG concluded rate control should be offered as first line therapy. However, if symptoms are present whilst on rate control giving rise to greater incremental benefit, or a clear clinical advantage could be gained for a given population by using rhythm control, the GDG felt rhythm control should also be considered. This was due to the suspicion that the increased contact with healthcare providers whilst on rhythm control strategies was in part driven due to recurrent symptoms (i.e. not just to administer the intervention), which in turn increased the overall cost of the strategy. Therefore, if rate control has been unsuccessful in controlling patient symptoms and there is strong clinical suspicion that the patient's symptoms are likely to be controlled by a rhythm control strategy, rhythm control could be cost effective in these groups.
Quality of evidence	Very low to moderate quality evidence was found for this question. The GDG considered the difficulties with analysing quality of life data due to its

	subjective nature and what may be a benefit to one patient may not be seen as a benefit to another. The economic evidence was considered to have minor to potentially serious limitations. However, conclusions remained robust across settings, perspective, time horizon and methods used. None of the studies reported reversible causes of AF as a separate sub-group that could be analysed.
Other considerations	The recommendation for rate control strategies to be offered as first line treatment was based on the evidence whereas the recommendation on circumstances when electrical and pharmacological rhythm control would be appropriate was based on the experience and opinion of the GDG. Patient choice would be important for patients with acute onset of AF (within 48 hours). These patients were usually seen within the emergency department although it was noted that this was not always the case. The GDG considered that although there was no randomised clinical trial evidence applying to this group, that these patients often experienced new and frightening symptoms and that a rhythm management strategy could be an appropriate option. It is recognised that high ventricular rates associated with AF can result in ventricular dysfunction. Therefore, if ventricular dysfunction persists after adequate rate control and if there is clinical suspicion that ventricular dysfunction is the result of AF (AF precedes heart failure, with no other causal factor identified) rhythm control should be considered regardless of the patient symptoms. It has been a consistent view from patients both within the GDG and the guideline scoping meetings that the time taken for patients to have their care adjusted and when appropriate, to be referred for specialist care is unacceptable. Furthermore, there is evidence that paroxysmal AF is more likely to be amenable to rhythm control strategies and in some patients paroxysmal AF may progress to persistent AF over time. Therefore it was the opinion of the GDG that when first line therapy (rate control) has failed to improve symptoms, patients should be reassessed in a timely manner and, where appropriate, rhythm control offered and initiated as quickly as possible.

14 Rate control strategies

This section was partially updated in 2021. See http://www.nice.org.uk/guidance/ng196/evidence for the 2021 evidence reviews.

14.1 Introduction

In a rate control strategy, the main goal of arrhythmia management becomes control of the ventricular rate. In patients with persistent and permanent atrial fibrillation (AF), rate control applies continuously. In patients with paroxysmal AF, the objective of rate control is to limit ventricular response during an AF episode.

Poor control of the ventricular rate can be a major factor contributing to disability and symptom limitation in many patients with atrial fibrillation. Conduction through the atrio-ventricular (AV) node is under autonomic control and increases markedly with activity levels, so the goal of rate control is to avoid excessive rate increase with activity. The degree of rate control required is therefore likely to vary considerably between individuals, according to their activity levels.

In some patients, who have relatively slow AV nodal conduction or low activity levels, ventricular rate both at rest and with exercise may be sufficiently controlled without rate-limiting drug therapy. More commonly, one or more drugs may be required to slow AV conduction and limit ventricular rate response.

Categories of drug used to limit ventricular rate response include beta blockers, rate limiting calcium channel blockers, and digoxin. These drugs may be used as monotherapy, but frequently drug combinations are required. Even with the use of drug combinations, some patients may continue to experience excessive ventricular rates. Drug therapy may be limited by drug side effects, and paradoxically some individuals may also experience excessive ventricular slowing at rest.

This chapter considers the role of drugs for the long-term management of rate control.

14.2 Review question: What is the clinical and cost effectiveness of using different rate control drug strategies in the pharmacological management of atrial fibrillation?

For full details see review protocol in Appendix C

Table 45: PICO characteristics of review question

Population	People with AF Report the following sub-groups separately: • Paroxysmal • Persistent/permanent • Unstable with acute AF • Heart failure (impaired LV function) This will include papers with a mixed population including atrial flutter but should not include paper with all atrial flutter patients.
Intervention/s	Rate limiting calcium channel blockers Digoxin Beta-blockers Amiodarone Dronedarone (non-permanent AF only) Combinations
Comparison/s	No treatment Other intervention

Outcomes	Mortality (long-term) Health-related quality of life Rate control – heart rate (time or amount of people) Stroke or thromboembolic complications Rate of discontinuation of drug due to side effects Rehospitalisation with a primary diagnosis of AF or heat failure Time to response Left ventricular function – number of people / ejection fraction as %
Exclusions	Population – atrial flutter only.
Study design	Randomised controlled trial (RCT) Systematic reviews of RCTs

14.2.1 Clinical evidence

Three studies were identified and included in the review: Khand 2003[232], Mulder 2012[317] and Tse 2001B.[435] Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 52**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

We searched for systematic reviews and randomised trials comparing the effectiveness of different classes of rate control drugs with each other and against placebo in the pharmacological management of heart rate in atrial fibrillation. Crossover studies were excluded.

Table 46: Summary of studies included in the review- chronic AF

Study	Intervention/comparison	Population	Outcomes	Comments
Khand 2003[232]	Digoxin versus beta-blocker	Persistent AF and heart failure	Rate control Left ventricular ejection function (LVEF%)	All patients received open label digoxin in phase 1
Mulder 2012[317]	Beta-blocker versus placebo	AF and heart failure	All-cause mortality Rehospitalisation with heart failure	All patients were >70 years old
Tse 2001B[435]	Digoxin versus amiodarone	Chronic AF	Rate control	Small study numbers

Table 47: Clinical evidence profile: digoxin versus amiodarone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digoxin	Amiodarone	Relative (95% CI)	Absolute		
% reduction in VR during ambulatory exercise[435]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	7	8	-	MD 2 higher (10.72 lower to 14.72 higher)	VERY LOW	CRITICAL
% reduction in ventricular rate (VR) from baseline during peak exercise[435]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	7	8	-	MD 1 higher (10.27 lower to 12.27 higher)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	–	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	–	CRITICAL

a Randomisation method unclear, blinding unclear; differences in SF-36 scores between groups at baseline
b CI crosses both MIDs

Table 48: Clinical evidence profile: B-blocker versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blocker	Control	Relative (95% CI)	Absolute		
Mortality[317]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	67/361 (18.6%)	72/377 (19.1%)	RR 0.97 (0.72 to 1.31)	6 fewer per 1000 (from 53 fewer to 59 more)	VERY LOW	CRITICAL
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Rate control												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Rehospitalisation with heart failure[317]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	72/361 (19.9%)	58/377 (15.4%)	RR 1.3 (0.95 to 1.78)	46 more per 1000 (from 8 fewer to 120 more)	LOW	IMPORTANT

a. Randomisation and allocation concealment unclear
b. Confidence interval crossed 2 MIDs
c. Confidence interval crossed 1 MID

Table 49: Clinical evidence profile: Beta-blocker versus digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta blocker	digoxin	Relative (95% CI)	Absolute		
Mortality												
0	-	-	-	-	-	-	-	-	-	-	–	CRITICAL
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	–	CRITICAL
24-h mean HR at 6 months (Better indicated by lower values) [232]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	16	20	-	MD 13.1 higher (2.83 to 23.37 higher)	VERY LOW	CRITICAL
LVEF (%) (Better indicated by lower values) [232]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	16	20	-	MD 5.6 lower (13.04 lower to 1.84 higher)	LOW	IMPORTANT

a. Unclear blinding and allocation concealment

b. Confidence interval crossed 2 MIDs

c. Confidence interval crossed one MID

14.2.2 Economic evidence

Published literature

No relevant economic evaluations comparing different pharmacological rate strategies were identified. No studies were selectively excluded.

See also the economic article selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant list prices of the drugs are provided in appendix N.

14.2.3 Evidence statements

Clinical

Persistent and permanent AF

Beta-blocker versus placebo in AF and heart failure patients:

- Very low quality evidence from one study (N=738)showed that there is no difference in mortality rates at 21 months
- Low quality evidence from one study (N=100) showed that more taking beta blockers were rehospitalised with heart failure at 21 months

Very low quality evidence from one study (N= 46) showed that digoxin is clinically more effective than a beta-blocker in reducing 24 hour mean heart rate at 6 months in AF and heart failure.

Low quality evidence from one study (N= 100) showed that there is no clinical difference between digoxin and beta-blocker in improving LVEF at 6 months.

Very low quality evidence from one study (N= 15) showed that there was no clinical difference between digoxin and amiodarone in ventricular rate during exercise.

Economic

No relevant economic evaluations were identified.

14.2.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	The GDG considered the critical outcomes to be mortality, health related quality of life and heart rate to assess rate control.
Trade-off between clinical benefits and harms	**Persistent and permanent AF:** There was no clinical difference between digoxin and amiodarone for the percentage reduction in ventricular rate.[435] The GDG agreed that there was very limited evidence in this area. They felt that beta-blockers or rate limiting calcium channel blockers should be offered as the preferred initial monotherapy. Digoxin should only be considered as monotherapy in sedentary patients, as it is less effective for rate control during exercise or in conditions of high sympathetic drive (for example: infection or decompensated heart failure). The GDG thought it unlikely that sotalol would be used over other beta blockers for purposes of rate control as its class III antiarrhythmic action would not apply. They were also concerned about possible adverse effects of this drug (see information in section 15.2.4). <u>Paroxysmal AF</u> The GDG agreed that a different drug selection would be appropriate for people with paroxysmal AF. Digoxin was thought to have an even smaller role in the management of patients with paroxysmal AF. It was also thought likely that there was a limited role for combination drug therapy in paroxysmal AF and that clinicians would have a lower threshold for resorting to a rhythm control strategy in response to persistent symptoms despite the use of a beta blocker or calcium channel blocker. <u>Heart failure sub-group:</u> Beta-blockers versus placebo: One paper (Mulder 2012) in patients with AF and heart failure found no difference between a beta-blocker and placebo in mortality and rehospitalisation. The rehospitalisation was not statistically significant but favoured placebo which raised concerns that giving this drug to AF patients with heart failure could be harmful. However, the GDG were cautious in interpreting the results of this paper as it is a subgroup analysis (of the SENIORS study) and these were not pre-defined primary outcome of the randomised study. In addition there is only one paper with no consistency of evidence. Beta-blocker versus digoxin: One small study[232] found a clinical benefit for digoxin compared to beta-blocker in 24 hour mean heart rate for patients with AF and heart failure. There was no difference in LVEF % between the two groups. The GDG expressed caution about the use of verapamil and diltiazem in patients with heart failure. Apart from this, there was thought to be no evidence to manage patients with heart failure differently from AF patients as a whole. The GDG also expressed caution about the use of verapamil and beta blockers in combination because of adverse effects on left ventricular function. They noted that

	the BNF regarded the combination as potentially hazardous and that it should only be contemplated if myocardial function was well preserved. The GDG took the view that other drug options were generally available and that this combination is best avoided. The GDG noted that care is also necessary in the use of beta blockers with diltiazem in patients with left ventricular impairment or impaired A-V node conduction. It was the view of the GDG that choice of drug for rate control would in many patients be dictated by co-morbidities **Amiodarone:** One study compared digoxin with amiodarone and found no difference between the groups for percentage reduction in ventricular rate.[435] Considering in addition the potentially serious side effect associated with long term use, it was strongly agreed amongst the GDG that amiodarone should not be offered for management of rate control of chronic AF. The GDG discussed a definition of what constituted adequate rate control. The results of the RACE II study[440] comparing strict and lenient rate control were considered. As lenient rate control as found to be as effective in this study as strict control, the definition of lenient control from the study was considered to be representative of adequate rate control, that is a mean resting ventricular response rate (measured by ECG in the supine position after a few minutes of rest) of less than 110 beats per minute.
Economic considerations	No economic evaluations were included that compared different pharmacological rate control strategies in patients with AF. The GDG noted that the immediate costs of acute rate control drugs were higher than for chronic control (as they involved IV infusion and hospital admission). However, as drugs for chronic rate control would be taken over a life time rather than administered as a one off event, the economic implications of recommendations for chronic rate control was higher than that for acute rate control. As a first line strategy, the number of patients affected by recommendations regarding drugs for chronic rate control will be large. However, the GDG considered the unit acquisition cost of the rate control drugs to be very low in comparison to alternative interventions within the guideline. In discussion, the GDG also noted that the drugs considered are already in widespread use in current practice, and as such the cost impact of the recommendation is likely to be low. The GDG considered other factors which may influence the resource use associated with any of the drugs. Amiodarone has monitoring requirements to reduce the likelihood of adverse side effects and events. For example, dronedarone which is initiated in hospital with specialist input, requires regular monitoring of liver function tests (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) and ECG every 6 months. Amiodarone can cause serious adverse 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 require on-going supervision. Digoxin was considered to have the least monitoring requirement out of these three drugs. Digoxin levels may be requested if digoxin toxicity is suspected and regular U&E monitoring may be required (with particular attention to renal function). Digoxin also had a lower acquisition cost than amiodarone, calcium channel blockers and the majority of beta blockers (with the exception of atenolol).

	Rate limiting calcium channel blockers, which are mainly prescribed as modified release formulations to improve compliance, have relatively few monitoring requirements in comparison with other drugs listed on the protocol, and their healthcare resource use is therefore expected to be lower. It was also noted that Verapamil had a lower acquisition cost than Diltiazem (more than double the cost of Verapamil). It was also observed that different brands of slow release diltiazem are not interchangeable and should be specified. The GDG did not wish to comment on specific drugs as the cost-effectiveness evidence was not available to inform the recommendation, but on the basis of unit cost wished to highlight that Verapamil is likely to be cheaper, and if Ditliazem is considered, the prescriber should consider the cheapest brand of this drug where appropriate in line with patient choice and previous experience. Beta blockers, also have less intensive monitoring requirements. Sotalol needs to be initiated and doses increased in a facility capable of monitoring and assessing cardiac rhythm and ECG due to the possibility of pro-arrhythmic events. Sotalol at low doses (commonly used in UK practice) essentially has Class II antiarrhythmic (beta-blocker) activity, but once higher doses are used (e.g. >240mg/day) then Class III antiarrhythmic activity is manifest, renal function and electrolyte balance also need to be assessed at initiation. Given the low unit cost of rate limiting calcium channel blockers, the GDG thought it was likely their use was cost effective compared to a "do nothing" approach. However, their relative cost effectiveness to beta blockers and digoxin remains unclear. As such the GDG felt that any of these drugs could be cost effective, especially in comparison to alternatives with a greater side effect profile. There was no economic evidence to inform the recommendation on amiodarone. Amiodarone had an average acquisition cost in comparison to the other rate control drugs reviewed. However, it can cause serious adverse 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, with monitoring including checks of thyroid and liver function and a regular ECG. On account of the risks and costs of the adverse side effects, despite monitoring, the GDG considered amiodarone was unlikely to be a cost-effective option for chronic rate control in relation to other rate control drugs available.
Quality of evidence	There were a small number of RCTs identified; each compared different drug strategies so were unable to be meta-analysed. All the studies were of low or very low quality and had small studies with low participant numbers. The unit cost and potential resource use of different pharmacological rate control drugs was validated by clinical members of the GDG at the time of writing.
Other considerations	The recommendations were based on the evidence and the experience and opinion of the GDG. It was noted that dronedarone is not licensed for rate control and there is technology appraisal guidance for dronedarone for maintenance of sinus rhythm (see Chapter 16). Extra vigilance for hypotension and bradycardia was advised for combination therapy.

	These recommendations were made for all patients with AF and would include the sub-group of AF patients with heart failure as their treatment would be the same. The GDG observed that rate and rhythm control were not necessarily alternatives. While rate control was considered first line, it would not necessarily be discontinued if progressing to a rhythm control strategy. In practice a rate control agent (e.g. a beta blocker) would often be maintained in combination with rhythm control therapy. This question included people with acute AF but this sub-group was reported separately in another chapter on acute AF. (see Chapter 19).

15 Restoration of sinus rhythm

15.1 Introduction

The approach to atrial fibrillation (AF) management includes consideration of rate control or rhythm control strategies, which are now very much patient centred and symptom directed,[284] as discussed in Chapter 13.

Where a rhythm control strategy is being considered, such a strategy may include cardioversion of AF to sinus rhythm (and long term maintenance of the latter) or the reduction of paroxysms of AF (and the maintenance of sinus rhythm[284]). In general terms, antiarrhythmic drugs can be used for cardioversion, reduction of paroxysms and long-term maintenance of sinus rhythm. The most commonly used antiarrhythmic drugs are Class 1c (for example flecainide and propafenone) and Class III (amiodarone, sotalol, dronedarone) agents.

This chapter focuses on cardioversion of persistent AF, which can be performed electrically or pharmacologically using antiarrhythmic drugs. It should be noted that pharmacological management of atrial flutter and AF are very different, as atrial flutter responds better to electrical cardioversion, and antiarrhythmic drugs are only modestly effective.[260]

The recommendations presented in the current chapter relate to the management of AF persisting for longer than 48 hours. The management of AF in the majority of patients considered in this chapter would conform to patients conventionally classified as having persistent AF: that is those with AF persisting for more than 7 days.

15.2 Review question: 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?

For full details see review protocol in Appendix C.

Table 50: PICO characteristics of review question

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
Intervention/s	Flecainide Propafenone Amiodarone Sotalol Beta-blockers Dronedarone (for comparative purposes only) Calcium channel blockers Digoxin Vernakalent (for comparative purposes only) Magnesium Alone or in combination Electrical cardioversion alone or in combination with antiarrhythmic drug therapy
Comparison/s	No treatment

	Any intervention listed above
Outcomes	Mortality (30 days and longest endpoint) Health-related quality of life Restoration of sinus rhythm/time to restoration for acute Stroke or thromboembolic events Rehospitalisation with a primary diagnosis of AF Patients developing heart failure Maintenance of sinus rhythm/Recurrence of AF
Study design	Randomised controlled trials (RCT) Systematic reviews of RCTs

15.2.1 Clinical evidence

We searched for systematic reviews and randomised trials comparing the effectiveness of rhythm control drugs versus a rhythm control drug of another class or placebo for the pharmacological restoration of sinus rhythm.

For the electrical restoration of sinus rhythm part of the review question we searched for randomised controlled trials comparing electrical cardioversion (ECV) compared with pharmacological treatment or electrical cardioversion combined with drugs to restore sinus rhythm.

Five studies were included in the section of the review for pharmacological restoration of sinus rhythm: Galperin 2001[167], Kingma 1992[237], Kochiadakis 1999[243], Kochiadakis 1999A[245], Singh 2005[408].

Thirteen studies were included in the section of the review for electrical restoration of sinus rhythm:, Bertaglia 2001[44], Bianconi 1993[47], Bianconi 1996[46], Capucci 2000[75], Climent 2004[96], Channer 2004[83], Desimone 1999 [120], Hemels 2006[196], Kanoupakis 2004[223], Leheuzey 2010[265], Manios 2003[301], Nergardh 2007[329], Villani 2000[448].

Evidence from these are summarised in the clinical GRADE evidence profile below. See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 51: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes
Bertaglia 2001[44]	ECV plus amiodarone versus ECV plus amiodarone plus verapamil	Persistent AF	Recurrence of AF
Bianconi 1993[47]	ECV plus propafenone versus ECV plus placebo	Chronic AF	Restoration of sinus rhythm
Bianconi 1996[46]	ECV plus propafenone versus ECV plus placebo	Chronic AF	Restoration of sinus rhythm
Capucci 2000[75]	ECV plus amiodarone versus ECV plus diltiazem	Chronic persistent AF	Restoration of sinus rhythm Recurrence of AF
Channer 2004[83]	ECV plus amiodarone versus ECV plus placebo	Persistent AF	Restoration of sinus rhythm Maintenance of sinus rhythm
Climent 2004[96]	ECV plus flecainide versus ECV plus placebo	Persistent AF	Restoration of sinus rhythm Relapse of AF
Desimone 1999[120]	ECV plus propafenone plus verapamil versus ECV plus propafenone	Persistent or chronic	Restoration of sinus rhythm Recurrence of AF
Galperin 2001[167]	Amiodarone versus placebo	Chronic AF	Restoration of sinus rhythm
Hemels 2006[196]	ECV plus verapamil versus ECV plus digoxin	Persistent AF	Recurrence of AF

Study	Intervention/comparison	Population	Outcomes
Kanoupakis 2004[223]	ECV plus amiodarone versus ECV alone ECV plus beta-blocker versus ECV alone	Persistent AF	Restoration of sinus rhythm Relapse of AF
Kingma 1992[237]	Flecainide versus verapamil Flecainide versus propafenone Verapamil versus propafenone	Paroxysmal AF	Restoration of sinus rhythm
Kochiadakis 1999A[245]	Amiodarone versus placebo	Persistent AF	Restoration of sinus rhythm
Kochiadakis 1999[243]	Amiodarone versus propafenone Amiodarone versus placebo Propafenone versus placebo	Chronic AF	Restoration of sinus rhythm
Leheuzey 2010[265]	ECV plus amiodarone versus ECV plus dronedarone	Persistent AF	Restoration of sinus rhythm Recurrence of AF Heart failure Mortality
Manios 2003[301]	ECV plus amiodarone versus ECV alone ECV plus diltiazem versus ECV alone ECV plus amiodarone versus ECV plus diltiazem	Persistent AF	Restoration of sinus rhythm Recurrence of AF
Nergardh 2007[329]	ECV plus beta-blocker versus ECV plus placebo ECV plus diltiazem versus ECV alone	Persistent AF	Restoration of sinus rhythm Relapse of AF Maintenance of sinus rhythm Stroke
Singh 2005[408]	Amiodarone versus sotalol Amiodarone versus placebo Sotalol versus placebo	Persistent AF	Restoration of sinus rhythm
Villani 2000[448]	ECV plus amiodarone versus ECV plus digoxin plus diltiazem	Chronic persistent AF	Restoration of sinus rhythm Recurrence of AF

15.2.1.1 Pharmacological restoration of sinus rhythm

Table 52: Clinical evidence profile: propafenone versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propafenone	Placebo	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- chronic AF [243]												
1	randomised trials	very serious[a]	N/A	no serious indirectness	no serious imprecision	none	16/64 (25%)	0/70 (0%)	RR 18.55 (2.54 to 135.53)	Could not be calculated	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias; all patients also received digoxin

Table 53: Clinical evidence profile: flecainide versus propafenone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flecainide	Propafenone	Relative (95% CI)	Absolute		
Restoration of sinus rhythm -Persistent AF [237]												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	32/37 (86.5%)	11/20 (55%)	RR 1.57 (1.04 to 2.38)	314 more per 1000 (from 22 more to 759 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Stroke or thromboembolic events												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

a. Reporting bias; selection bias; concomitant therapy with other protocol drugs
b. Confidence interval crosses 1 MID

Table 54: Clinical evidence profile: amiodarone versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amiodarone	Placebo	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- persistent AF [167,243,245,408]												
4	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	118/372 (31.7%)	1/249(0 %)	RR 34.79 (9.89 to 122.34)	278 more per 1000 (from 32 more to 1000 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias in four studies; small numbers in one study; all patients received digoxin in two studies; performance bias, reporting bias and attrition bias in one study

Table 55: Clinical evidence profile: propafenone versus amiodarone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propafenone	Amiodarone	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- chronic AF [243]												
1	Randomised trials	very serious[a]	N/A	no serious indirectness	very serious[b]	none	16/64 (25%)	16/68 (23.5%)	RR 1.06 (0.62 to 1.81)	14 more per 1000 (from 89 fewer to 190 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a Selection bias; all patients received digoxin
b Confidence intervals crosses 2 MIDs

Table 56: Clinical evidence profile: amiodarone versus sotalol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amiodarone	Sotalol	Relative (95% CI)	Absolute		
Restoration of sinus rhythm - at 28 days-Persistent AF [408]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	70/258 (27.1%)	59/244 (24.2%)	RR 1.12 (0.83 to 1.51)	29 more per 1000 (from 41 fewer to 123 more)	MODERATE	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a Confidence interval crossed 1 MID

Table 57: Clinical evidence profile: sotalol versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sotalol	Placebo	Relative (95% CI)	Absolute		
Restoration of sinus rhythm at 28 days-Persistent AF [408]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/244 (24.2%)	1/132 (0.8%)	RR 31.92 (4.47 to 227.76)	247 more per 1000 (from 28 more to 1000 more)	HIGH	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

Table 58: Clinical evidence profile: flecainide versus verapamil (calcium channel blocker)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flecainide	Verapamil	Relative (95% CI)	Absolute		
Restoration of sinus rhythm at 1 hour -Persistent AF [237]												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/37 (86.5%)	1/20 (5%)	RR 17.3 (2.55 to 117.35)	815 more per 1000 (from 78 more to 1000 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Reporting bias; selection bias; concomitant therapy with other protocol drugs

15.2.1.2 Electrical Restoration of sinus rhythm

Table 59: Clinical evidence profile: ECV plus amiodarone versus ECV alone/placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECV + amiodarone	ECV + placebo	Relative (95% CI)	Absolute		

Restoration of sinus rhythm - Immediately after electrical cardioversion [83,223,301]												
3	randomised trials	serious[a]	serious[b]	no serious indirectness	serious[c]	none	142/172 (82.6%)	92/118(79%)	RR 1.12 (0.93 to 1.36)	95 more per 1000 (from 55 fewer to 284 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Maintenance of sinus rhythm - 1 year [83]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/96 (52.1%)	2/30 (6.7%)	RR 7.81 (2.02 to 30.21)	456 more per 1000 (from 68 more to 1000 more)	MODERATE	IMPORTANT
Relapse of AF - 4-6 weeks [223,301]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	16/76 (21.1%)	28/63 (44.7%)	RR 0.48 (0.29 to 0.8)	232 fewer per 1000 (from 89 fewer to 317 fewer)	LOW	IMPORTANT

a. Selection bias detected

b. Heterogeneity detected

c. Confidence interval crossed one MID

15.2.1.3 Electrical and pharmacological restoration of sinus rhythm

Table 60: Clinical evidence profile: ECV plus flecainide versus ECV plus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Electrical cardioversion + flecainide**	**ECV + placebo**	**Relative (95% CI)**	**Absolute**		
Restoration of sinus rhythm – Immediate[96]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	19/26 (73.1%)	23/28 (82.1%)	RR 0.89 (0.67 to 1.19)	90 fewer per 1000 (from 271 fewer to 156 more)	LOW	CRITICAL
Mortality												
0	No evidence available					none	-	0%	-	-		CRITICAL

Relapse of AF - 1 month[96]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	10/19 (52.6%)	12/23 (52.2%)	RR 1.01 (0.57 to 1.8)	5 more per 1000 (from 224 fewer to 418 more)	VERY LOW	IMPORTANT
Quality of life												
0	No evidence available					none	-	0%	-	-		CRITICAL

a. Selection bias detected
b. Confidence interval crossed one MID (0.75 or 1.25)
c. Confidence interval crossed both MIDs (0.75 and 1.25)

Table 61: Clinical evidence profile: ECV plus propafenone versus ECV alone/placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electrical cardioversion + propafenone	electrical cardioversion + placebo	Relative (95% CI)	Absolute		
Reversion to sinus rhythm [47]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	47/64 (73.4%)	41/70 (73.7%)	RR 1.26 (0.98 to 1.62)	192 more per 1000 (from 15 fewer to 457 more)	LOW	CRITICAL
Mortality												
0	No evidence available					none	-	0%	-	-		CRITICAL
Quality of life												
0	No evidence available					none	-	0%	-	-		CRITICAL

a. Selection bias detected
b. Confidence interval crossed one MID

Table 62: Clinical evidence profile: ECV plus beta-blocker versus ECV alone/placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electrical cardioversion + beta-blocker	electrical cardioversion + placebo	Relative (95% CI)	Absolute		
Restoration of sinus rhythm - Immediately after cardioversion[223,329]												
2	randomised trials	serious[a]	serious[b]	no serious indirectness	serious[c]	none	118/126 (93.7%)	108/126 (92.6%)	RR 1.11 (0.90 to 1.38)	102 more per 1000 (from 93 fewer to 352 more)	VERY LOW	CRITICAL
Relapse of AF - 6 weeks[223,329]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	41/75 (54.7%)	40/75 (53.3%)	RR 1.02 (0.76 to 1.38)	11 more per 1000 (from 128 fewer to 203 more)	LOW	IMPORTANT
Mortality												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Maintenance of sinus rhythm - 24 weeks[329]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	none	38/83 (45.8%)	22/85 (25.9%)	RR 1.77 (1.15 to 2.72)	199 more per 1000 (from 39 more to 445 more)	LOW	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Stroke - 6 weeks[329]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none	1/83 (1.2%)	0/85 (0%)	RR 3.07 (0.13 to 74.34)	-	VERY LOW	IMPORTANT

a. Selection bias detected
b. Heterogeneity was detected - random effects used
c. Confidence interval crossed one IDs (0.75 or 1.25)
d. Confidence interval crossed both MIDs (0.75 and 1.25)

Table 63: Clinical evidence profile: ECV plus diltiazem versus ECV alone/placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electrical cardioversion + diltiazem	electrical cardioversion alone	Relative (95% CI)	Absolute		
Restoration of sinus rhythm - Immediately after electrical cardioversion[301]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	28/33 (84.8%)	29/35 (82.9%)	RR 1.02 (0.83 to 1.26)	17 more per 1000 (from 141 fewer to 216 more)	LOW	CRITICAL
Mortality												
0	No evidence available					none	-	-	-	-		CRITICAL
Relapse of AF - 6 weeks after electrical cardioversion[301]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	none	16/30 (53.3%)	15/30 (50%)	RR 1.07 (0.65 to 1.74)	35 more per 1000 (from 175 fewer to 370 more)	VERY LOW	IMPORTANT
Quality of life												
0	No evidence available					none	-	0%	-	-		CRITICAL

a. Selection bias detected

b. Confidence interval crossed one MID (0.75 or 1.25)

c. Confidence interval crossed two MIDs (0.75 and 1.25)

Table 64: Clinical evidence profile: ECV plus amiodarone versus ECV plus digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electrical cardioversion + amiodarone	electrical cardioversion + digoxin	Relative (95% CI)	Absolute		
Restoration of sinus rhythm – Immediate[448]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	30/33 (90.9%)	19/29 (65.5%)	RR 1.39 (1.04 to 1.85)	255 more per 1000 (from 26 more to 557 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Recurrence of AF - 1 month[448]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/29 (27.6%)	12/16 (75%)	RR 0.37 (0.19 to 0.71)	472 fewer per 1000 (from 218 fewer to 608 fewer)	MODERATE	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL

a. Selection bias

b. Confidence interval crossed one MID

Table 65: Clinical evidence profile: ECV plus amiodarone versus ECV plus diltiazem

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electrical cardioversion + amiodarone	electrical cardioversion + diltiazem	Relative (95% CI)	Absolute		
Restoration of sinus rhythm – Immediate[75,301,448]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	80/86 (93%)	80/105 (76.7%)	RR 1.21 (1.08 to 1.37)	161 more per 1000 (from 61 more to 284 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Recurrence of AF - 6 weeks - 2 months Immediate[75,301,448]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	23/83 (27.7%)	43/80 (53.3%)	RR 0.52 (0.34 to 0.77)	256 fewer per 1000 (from 123 fewer to 352 fewer)	LOW	IMPORTANT

a. Selection bias

b. Confidence interval crossed one MID

Table 66: Clinical evidence profile: ECV plus amiodarone versus ECV plus dronedarone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electrical cardioversion + amiodarone	electrical cardioversion + dronedarone	Relative (95% CI)	Absolute		
Restoration of sinus rhythm - Immediately after electrical cardioversion[265]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	131/153 (85.6%)	166/200 (83%)	RR 1.03 (0.94 to 1.13)	25 more per 1000 (from 50 fewer to 108 more)	HIGH	CRITICAL
Recurrence of AF - 12 months[265]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	62/214 (29%)	91/195 (46.7%)	RR 0.62 (0.48 to 0.8)	177 fewer per 1000 (from 93 fewer to 243 fewer)	MODERATE	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	none	-	-	-	-	-	CRITICAL
Heart failure - 12 months[265]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[a]	none	19/255 (7.5%)	16/249 (6.4%)	RR 1.16 (0.61 to 2.2)	10 more per 1000 (from 25 fewer to 77 more)	MODERATE	IMPORTANT
Mortality - 12 months[265]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	5/255 (2%)	2249 (0.8%)	RR 2.44 (0.48 to 12.47)	12 more per 1000 (from 4 fewer to 92 more)	LOW	CRITICAL

a. Confidence interval crossed one MID (0.75 or 1.25)
b. Confidence interval crossed both MIDs (0.75 and 1.25)

Table 67: Clinical evidence profile: ECV plus amiodarone plus verapamil versus ECV plus amiodarone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electrical cardioversion + amiodarone + verapamil	Electrical cardioversion + amiodarone	Relative (95% CI)	Absolute		
AF relapse - 30 days[44]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	21/39 (53.8%)	18/42 (42.9%)	RR 1.26 (0.8 to 1.98)	112 more per 1000 (from 86 fewer to 420 more)	LOW	IMPORTANT
Mortality												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Restoration of sinus rhythm												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL

a. Selection bias detected
b. Confidence interval crossed one MID (0.75 or 1.25)

Table 68: Clinical evidence profile: ECV plus propafenone plus verapamil versus ECV plus propafenone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Electrical cardioversion + propafenone + verapamil	electrical cardioversion + propafenone	Relative (95% CI)	Absolute		
Restoration of sinus rhythm - Immediately after electrical cardioversion[120]												

1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/64 (100%)	33/33 (100%)	RR 1 (0.95 to 1.05)	0 fewer per 1000 (from 50 fewer to 50 more)	MODERATE	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Recurrence of AF - 3 months[120]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	10/64 (15.6%)	13/33 (39.4%)	RR 0.4 (0.2 to 0.81)	236 fewer per 1000 (from 75 fewer to 315 fewer)	LOW	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL

a. Selection bias
b. Confidence interval crossed one MID (0.75 or 1.25)

Table 69: Clinical evidence profile: ECV plus verapamil versus ECV plus digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Electrical cardioversion + verapamil**	**electrical cardioversion + digoxin**	**Relative (95% CI)**	**Absolute**		
Recurrence of AF - 18 months[196]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	21/74 (28.4%)	25/70 (35.7%)	RR 0.79 (0.49 to 1.28)	75 fewer per 1000 (from 182 fewer to 100 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	none	-	0%	-	-	-	CRITICAL

a. Selection bias detected

b. Confidence interval crossed both MIDs (0.75 and 1.25)

15.2.2 Economic evidence

Published literature

No published literature was included to inform this question.

Four economic evaluations relating to this review question were identified but were excluded due to a combination of limited applicability and methodological limitations.[138],[81],[119], [388] These are summarised in Appendix K with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs of the interventions were considered. Direct current cardioversion (X501) and external cardioversion electrical cardioversion (X502) are not coded separately as a HRG, and therefore the day case unit cost for Arrhythmia or Conduction Disorders (EB07) is the closest proxy, which has a weighted cost of £835 taking comorbidities and or complications into account. The list prices for the drugs used for pharmacological cardio version can be found in appendix N.

Table 70: Day case NHS reference costs for Arrhythmia or Conduction Disorders.[123]

Reference cost HRG	National average unit cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
Arrhythmia or Conduction Disorders, with complications and/or comorbidities(EB07H); as recorded for day case patients (a)	£842	£405	£1,096
Arrhythmia or Conduction Disorders, without with complications and/or comorbidities (EB07I); as recorded for day case patients (b)	£834	£437	£1,059

a) The number of data submissions for this code was 147, with 2391 units of activity.

b) The number of data submissions for this code was 152, with 15146 units of activity.

15.2.3 Evidence statements

Pharmacological restoration of rhythm- Antiarrhythmic versus placebo:

Evidence showed that amiodarone (Low quality evidence, four studies, N=621) and sotalol (High quality evidence, one study, N=376) are both clinically effective compared to placebo.

Pharmacological restoration of rhythm- Antiarrhythmic versus another antiarrhythmic:

Very low quality evidence showed that flecainide may be clinically effective compared to propafenone (one study, N=57).

Very low quality evidence showed that there may be no clinical difference between amiodarone and propafenone but the direction of the estimate of effect could favour either intervention (one study, N=66)

Moderate quality evidence showed that there may be no clinical difference between amiodarone and sotalol (one study, N=502).

Very low quality evidence showed that flecainide is more clinically effective than verapamil (calcium channel blocker) in restoring sinus rhythm in people with persistent AF (one study, N=57).

Electrical versus electrical with adjunctive pharmacological

Mortality

Low quality evidence showed that ECV plus dronedarone may be more clinically effective compared with ECV plus amiodarone, but the direction of the estimate of effect could favour either intervention (one study, N=504).

Restoring sinus rhythm

Moderate quality evidence from one study (N= 97) showed no clinical difference between ECV plus propafenone plus verapamil and ECV plus propafenone.

Evidence showed that there may be no clinical difference between:

- ECV plus amiodarone compared with ECV alone or placebo (Very low quality evidence, three studies, N=209), but the direction of the estimate of effect favoured ECV plus amiodarone.
- ECV plus flecainide compared with ECV plus placebo (Low quality evidence, one study, N=54), but the direction of the estimate of effect favoured ECV alone or placebo.
- ECV plus beta-blocker compared with ECV alone or with placebo (Low quality evidence, two studies, N=252), but the direction of the estimate of effect favoured ECV +beta-blocker.
- ECV plus diltiazem and ECV alone (Low quality evidence, one study, N=68)
- ECV plus amiodarone and ECV plus dronedarone (High quality evidence one study, N=353)
- Evidence showed the following may be more clinically effective:
- ECV plus propafenone compared to ECV plus placebo (Low quality evidence, two studies, N=134)
- ECV plus amiodarone compared to ECV plus digoxin (Low quality evidence, one study, N=62)
- ECV plus amiodarone compared to than ECV plus diltiazem (Low quality evidence, three studies, N=191).

Health-related quality of life

No evidence was found.

Maintenance of sinus rhythm/Recurrence of AF

Moderate quality evidence from one study (N= 126) showed that ECV plus amiodarone is more clinically effective than ECV alone or placebo in maintaining sinus rhythm at 1 year.

Evidence showed the following may be more clinically effective:

- ECV plus amiodarone compared with ECV alone or placebo (Low quality evidence, one study, N= 126).
- ECV plus Amiodarone compared with ECV plus digoxin (Moderate quality evidence, one study, N= 45)
- ECV plus Amiodarone compared with ECV plus diltiazem (Low quality evidence, three studies, N=163)
- ECV plus Amiodarone compared with ECV plus dronedarone (Moderate quality evidence, one study, N=409)
- ECV plus amiodarone compared with ECV plus amiodarone plus verapamil (Low quality evidence, one study, N=81)
- ECV plus beta-blocker compared with EVC plus placebo (Low quality evidence, one study, N= 168)
- ECV plus Propafenone plus verapamil compared with ECV plus propafenone (Low quality evidence, one study, N=97)

  Evidence showed there may be no clinical difference:

- ECV plus flecainide compared with ECV plus placebo (Very low quality evidence, one study, N= 42), but there direction of the estimate of effect could favour either intervention.
- ECV plus beta-blocker compared with ECV plus placebo (Low quality evidence, two studies, N=226), but the direction of the estimate of effect favoured ECV plus beta-blocker.
- ECV plus diltiazem and ECV alone (Low quality evidence, one study, N=68), but the direction of the estimate of effect could favour either intervention
- ECV plus verapamil and ECV plus digoxin (Very low quality evidence, one study, N=144), but the direction of the estimate of effect could favour either intervention.

Patients developing heart failure
Moderate quality evidence showed that there may be no clinical difference between ECV plus amiodarone and ECV plus dronedarone (one study, N=409), but the direction of the estimate of effect could favour either intervention.

Stroke or thromboembolic events
Very low quality evidence showed that EVC plus placebo is more clinically effective than ECV+ beta-blocker, but the direction of the estimate of effect could favour either intervention (one study N= 168).

Economic
No relevant economic evaluations were identified.

15.2.4 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	The GDG considered the following outcomes to be critical for decision making: mortality, health related quality of life and restoration of sinus rhythm. The only critical outcome reported for these studies was restoration of sinus rhythm.
Trade-off between clinical benefits and harms	The GDG were of the opinion that although there was limited randomised clinical trial evidence that clinical experience and comparison of reversion rates between trials suggested a benefit of ECV over pharmacological cardioversion for patients with AF of duration longer than 48 hours. There was little evidence favouring an adjunctive role for drugs in association with ECV in the immediate restoration of sinus rhythm. However, there was some evidence to support an adjunctive role for drugs in maintaining sinus rhythm following cardioversion and the GDG were of the opinion that the evidence was strongest in relation to amiodarone. The decision whether to offer adjunctive amiodarone would depend on consideration of the likelihood of maintaining sinus rhythm following ECV. Clinical factors which might suggest increased likelihood of relapse or a previous early relapse following ECV would favour adjunctive therapy. If patients are undergoing cardioversion the GDG decided that they should have ECV or ECV with amiodarone. The GDG recommended that patients should have

	amiodarone for up to one year in line with the evidence supporting this recommendation. There was no difference for ECV and amiodarone versus ECV in initial restoration of sinus rhythm. However, ECV combined with amiodarone showed a clinical benefit in reducing relapse of AF compared to ECV alone after 1-2 months. The GDG then went on to discuss the known potential harms associated with the long-term use of amiodarone which include corneal deposits, liver impairment and thyroid problems. Due to the nature of the long-term side effects it is important that the decision is made with the patient and these potential harms are discussed before the decision is made. In recommending therapy for up to one year, the GDG considered the trade-off between the evidence cited above and the wish to discontinue a potentially toxic drug as soon as possible. The GDG wanted to clarify that depending on clinical circumstances amiodarone might be discontinued earlier.
Economic considerations	There was no economic evidence of sufficient applicability or quality to inform this question. There is widespread variation in clinical practice over when electrical cardioversion is appropriate (or not) for a patients who are refractory to other rhythm control strategies. The cost of electrical cardioversion is not reported for the current UK context in various studies, and it is possible that cardioversion is often miscoded leading NHS reference costs to not be reflective of the actual cost (or indeed HES activity to be reflective of the population affected). None the less clinical members estimated costs for electrical cardioversion that fell within the range quoted for a day case (£437 to £1,059). The majority of elective DC cardioversions are performed using warfarin (4 x weekly INR results within a therapeutic window are required pre procedure to ensure there are no clots inside the heart), however a transoesophageal echocardiogram (TOE) can be used to look for clots, therefore negating the need for warfarin full work up. This in turn would impact on the overall cost of the cardioversion strategy. Further the patient is likely to require an ECG prior to the cardioversion. In terms of the cardioversion itself, it requires anaesthetics, defibrillation pads (estimated at £20 per patient) and equipment (which would normally be available). In terms of staffing an anaesthetist and assistant, with a qualified healthcare professional to undertake the cardioversion (nurse or doctor) would need to be available for the short duration of the cardioversion (approximately 30 minutes), with recovery care staff available for the patient subsequently (with estimated recovery taking 2 hours). Electrical cardioversion is likely to be a more costly strategy than pharmacological cardioversion to restore rhythm in the first instance, and therefore using electrical cardioversion repeatedly was unlikely to be a cost-effective strategy. However, the GDG recognised that restoration of rhythm was only one aspect of a rhythm control strategy and the resulting net benefit would also depend on the maintenance of sinus rhythm. This in turn was likely to be the greatest influencing factor in determining overall quality of life improvement. Equally, the majority of the resource use and cost of the overall strategy was likely to be associated with the maintenance of sinus rhythm, rather than its restoration. In the absence of economic evidence, the GDG considered the clinical evidence, and as electrical cardioversion with or without amiodarone for up to 12 months was found to have a longer term effect on rhythm control, this strategy on balance was thought to be the most cost-effective option to restore rhythm in the context of a rhythm control strategy.
Quality of evidence	The studies identified reported almost exclusively on the restoration of rhythm

	outcome and long-term maintenance of sinus rhythm. The only other outcome reported was 'time to restoration of rhythm' which represents a lower quality of evidence. The use of amiodarone as a conjunctive drug to electrical cardioversion is supported by the findings of three studies which found 21.1% (16/76) fewer patients relapsed into AF at 4-6 weeks (low quality evidence [223,301]), and 52.1% (50/96) more patients had their sinus rhythm maintained at 1 year (moderate quality evidence[83]). The GDG did not feel that there was sufficient quality evidence to make a strong recommendation in favour of using amiodarone as an adjunct in all patients given the severe side effects. However, felt that the evidence was sufficient that amiodarone should at least be considered as a means of sustaining effect from electrical cardioversion.
Other considerations	The recommendation was based on the evidence and the experience and opinion of the GDG. None of the studies reported separate outcomes for people with AF due to reversible causes. Acute AF was reported in this review question but the evidence can be found in a separate chapter (see Chapter 19).

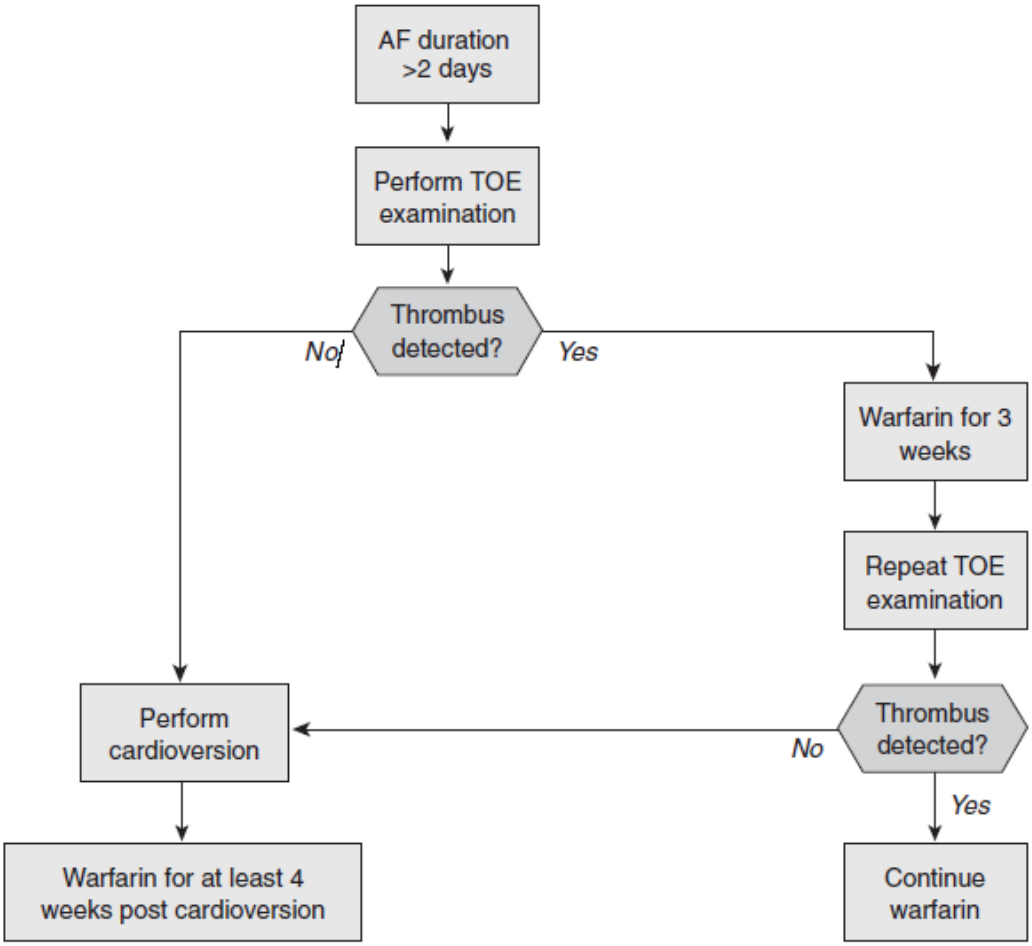
15.3 Transoesophageal echocardiography-guided cardioversion

Cardioversion of AF is associated with an increased risk of stroke and thromboembolism. In order to minimise this risk, anticoagulation is conventionally recommended for a minimum of 3 weeks before and during cardioversion, and for a minimum of 4 weeks after cardioversion. Even when pre-cardioversion transoesphageal echocardiography (TOE) fails to demonstrate left atrial thrombus, some patients have a thromboembolism post cardioversion (especially if no anticoagulation has been administered).[182,279]

As it may take some time to achieve therapeutic international normalised ratio for 3 consecutive weeks, some patients may wait months before cardioversion is attempted. As it is perceived that patients are more likely to successfully cardiovert the shorter the time they have been in AF, strategies to facilitate early cardioversion have been explored.

One strategy is TOE-guided cardioversion, where a patient with AF of more than 48 hours duration has a TOE to assess for intra-cardiac thrombus. In the absence of thrombus, heparin is usually given and cardioversion is performed. Anticoagulation with warfarin is subsequently continued for a minimum of 4 weeks. Patients in whom a thrombus is identified by TOE are considered at high risk of post-cardioversion thromboembolism and are usually treated with conventional therapeutic anticoagulation for at least 3 to 4 weeks before the TOE is repeated (see **Figure 3**). This strategy requires an experienced TOE operator, especially since visualisation of thrombus may be operator-dependent.

Figure 3: Cardioversion with TOE-guided strategy



15.3.1 Methodological introduction

Only studies where a comparison was made between a strategy of TOE-guided cardioversion and cardioversion without a prior TOE were included.

The primary clinical outcome of these studies w9as that the incidence of post-cardioversion thromboembolic events and other outcomes reported included the restoration and maintenance of sinus rhythm.

Of the two studies considering clinical outcomes included, one was a RCT,[239] and the other a cohort study.[397] In the former, in addition to the use of TOE examination, both the duration of anticoagulation and treatment were different between the two groups; in the later study, only the use of TOE examination was different between the two groups. Neither of the studies were adequately powered.

Of the two studies considering health economic outcomes,[240,399] one[399] estimated the cost per quality-adjusted life-year (QALY) of three strategies:

1. conventional therapy transthoracic echocardiography (TTE) and warfarin therapy for one month before cardioversion)
2. initial transthoracic echocardiography followed by transoesophageal echocardiographic- guided cardioversion and early cardioversion if no thrombus is detected (TTE/TOE)
3. initial TOE-guided cardioversion with early cardioversion if no thrombus is detected.

The other study[240] estimated the costs and incremental cost per QALY of TOE-guided anticoagulation versus conventional anticoagulation based on the Assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE) trial.[239]

15.3.2 Evidence statements

One study[239] did not find any significant difference between TOE-guided cardioversion and a conventional strategy in terms of the incidence of thromboembolic events, stroke, successful initial cardioversion or maintenance of sinus rhythm at 8 weeks (1+). The difference in terms of mortality was of borderline significance (p=0.06) in favour of the conventional strategy. (1+)

A second study also failed to find any significant effect on the incidence of all embolic events between the two strategies.[397] (2+)

One study[239] found a lower incidence of bleeding events with a TOE-guided strategy compared with a conventional strategy (2.9% versus 5.5%, respectively; p=0.03). (1+)

TOE-guided cardioversion (US$ 2,774) costs less than TTE/TOE-guided cardioversion (US$3,070) and conventional strategy (US$3,106). Including the gains in QALYs, TOE-guided cardioversion is the least costly strategy with similar effectiveness (TOE accumulated 8.49 QALYs, TTE/TOE and conventional therapy both accumulated 8.48). The sensitivity analysis indicated that the results depend on a lower risk of cardioversion-related thromboembolism after negative TOE compared with conventional therapy.[399]

Overall, there was no significant difference in the mean costs per patient between TOE-guided and conventional care in the simulation model (US$3,503.09 versus US$3,423.52) and the hospital charge data from the ACUTE trial data (US$6,508 versus US$6,239, p=0.50). The analytic model indicated the initial treatment costs per patient were higher in the TOE group (US$2,639.67 versus US$2,429.01), but outcome-associated costs were lower (US$863.42 versus US$994.51). The decision model indicated that the TOE-guided strategy costs US$185 more than conventional therapy when all treatment and outcome data are included (US$7,090 versus US$6,905). An incremental cost per QALY of TOE-guided cardioversion was calculated at US$15,455.[240]

15.3.3 From evidence to recommendations

Overall, the clinical studies suggest that TOE-guided cardioversion is of comparable efficacy to conventional strategy.[239,397] Although bleeding was reduced in the TOE-guided strategy, this was perceived to be a result of the shorter time spent on anticoagulation, and therefore TOE-guided cardioversion could be deemed preferable in patients with an increased bleeding risk. The health economic studies suggested that TOE-guided cardioversion may be a cost-effective treatment strategy.

The theoretical advantage of early cardioversion being more likely to be successful was not supported by the current clinical trial data. However, the studies were underpowered to detect significant differences in this, and in mortality and embolic event rates. TOE-guided cardio-version was considered a specialised procedure requiring appropriately experienced staff and appropriate facilities. However, it was considered that TOE-guided cardioversion should be an available treatment, as some patients would prefer the option of not being on prolonged anticoagulation.

15.3.4 Recommendation

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

16 Maintenance of sinus rhythm

16.1 Introduction

When patients with atrial fibrillation (AF) are undergoing a rhythm control strategy, whether by cardioversion (electrical or pharmacological) or ablation, it is important to maintain long-term sinus rhythm following the intervention (Lip 2012[284]). In patients with paroxysmal AF, the objective is to reduce paroxysms of AF as well as maintain sinus rhythm long-term.

In general, drugs used for maintenance of sinus rhythm are usually the Class 1a (disopyramide), 1c (flecainide, propafenone) and III (amiodarone, dronedarone, sotalol) agents, although beta blockers (Class II antiarrhythmic agents) have often been used, due to relative safety. Often, a balance is made between drug efficacy and safety, especially since treatment may be long-term.

The objective of this chapter is to assess 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. The Class 1a drugs are rarely used in UK clinical practice, and will not be extensively reviewed in this chapter, although comparisons with disopyramide are included as it is licenced in the UK. Also, sotalol is a drug that has Class III antiarrhythmic properties only at doses of above 240mg/daily, and at the lower doses commonly used in UK practice, it essentially has beta-blocking properties.

The emphasis in this chapter is on the management of atrial fibrillation rather than of atrial flutter. The majority of studies included were of patients with atrial fibrillation. Studies were still included if they incorporated a mixed population of patients with atrial fibrillation and atrial flutter, but any studies which exclusively considered patients with atrial flutter were not included in the analysis. As the mechanisms of flutter and fibrillation differ, the GDG considered that the conclusions and recommendations of the chapter should not be extended to patients with atrial flutter. Additionally, it was considered that in contemporary management of atrial flutter, drug therapy for rhythm maintenance played a lesser role, as patients experiencing symptomatic recurrences of atrial flutter would be likely to be considered for flutter ablation.

16.2 Review question: 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?

For full details see review protocol in Appendix C.

Table 71: PICO characteristics of review question

Population	People with paroxysmal AF Persistent AF after cardioversion Sub-group analysis: • Heart failure (impaired LV function) • 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/s	Flecainide Propafenone Amiodarone Sotalol Beta-blockers (full list in rate control strategies protocol – Appendix C) Dronedarone (for comparative purposes only) Calcium channel blockers (should not be used) Digoxin (off label) Disopyramide (class 1a drug) Alone or in combination
Comparison/s	No treatment Any intervention listed above
Outcomes	Mortality (30 days and longest endpoint) Health-related quality of life Recurrence rate – proportion of time in AF 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
Study design	Randomised controlled trials (RCTs) Systematic reviews of RCTs

16.2.1 Clinical evidence

One Cochrane review[257] was included in the review. A modified version of this review has been included, with only the studies matching drugs specified in the NCGC protocol included: A-COMET-II 2006, [291] AFFIRM 2003,[7] Aliot 1996,[16] Bellandi 2001,[40] Benditt 1999,[42] Carunchio 1995,[80] Channer 2004[83] DAPHNE 2008,[76] Dogan 2004,[130] DYONISOS 2010,[265] EMERALD 2000,[69] FAPIS 1996,[90] GEFACA 2001,[167]Karlson 1988,[225] Kochiadakis 2000,[246] Kochiadakis 20004A,[249] Kochiadakis 2004B,[247] Kuhlkamp 2000,[256] Lloyd 1984,[289] Nergardh 2007,[329] Niu 2006,[332] PAFAC 2004,[145] PITAGORIA 2008,[178] Plewan 2001,[361] PRODIS 1996,[109] RAFT 2003,[366] Reimold 1993,[376] SAFE-T 2005,[408] Singh 1991,[410] SOPAT 2004,[351] Steinbeck 1988,[420] Stroobandt 1997,[424] Van Gelder 1989[439] and Villani 1992.[449] Dronedarone was not specifically considered for this review but has been included for comparative purposes only to assist in considering the clinical benefit and harms of the other included drugs. There is a NICE technology appraisal on dronederone[323] that was being incorporated into the guideline. Sotalol was reviewed separately from other beta-blockers.

Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 73**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 72: Summary of studies included in the review

Study	Population	Intervention/comparison	Outcomes
A-COMET II[291]	Symptomatic AF; persistent for >48 hours, <6 months duration N=658	Sotalol/ placebo/ (azimilide- not included in this review)	Mortality Recurrence rate Drug withdrawal due to side effects

Study	Population	Intervention/comparison	Outcomes
AFFIRM 2003[7]	AF	Amiodarone/ sotalol	Mortality Recurrence rate
Aliot 1996[16]	Paroxysmal AF documented any time before (70% in last year) N=97	Flecainide/ Propafenone	Mortality Stroke Recurrence rate Drug withdrawal due to side effects
Bellandi 2001[40]	Recurrent AF	Sotalol/ Propafenone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Benditt 1999[42]	AF or atrial flutter documented in the last 3 months. Type: paroxysmal or recent-onset 77%, persistent 23%. N=253	Sotalol/ placebo	Mortality Stroke Recurrence rate Drug withdrawal due to side effects
Carunchio 1995[80]	Recurrent AF with >3 episodes in previous year N=66	Flecainide/ sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Channer 2004[83]	Persistent AF (mean duration: 6 months) N=99	Amiodarone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
DAPHNE 2008[76]	Bradycardia-tachycardia sinus node disease with history of several episodes of AF/atrial flutter and needing a pacemaker	Sotalol/ beta-blockers (atenolol or metoprolol)	Recurrence rate Drug withdrawal due to side effects
Dogan 2004[130]	Recent onset and persistent AF	Propafenone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
DYONISOS 2010[265]	Documented AF for >72 hours	Amiodarone/ dronedarone	Mortality Recurrence rate Drug withdrawal due to side effects Patients developing heart failure
EMERALD 2000[69]	Persistent AF (1 week to 1 year, mean duration <6 months) N=535	Dofetilide/ Sotalol/ Placebo	Mortality Recurrence rate Drug withdrawal due to side effects

Study	Population	Intervention/comparison	Outcomes
FAPIS 1996[90]	Paroxysmal recurrent AF with>2 episodes in the last 4 months	Flecainide/ Propafenone	Mortality Recurrence rate Drug withdrawal due to side effects
GEFACA 2001[167]	Persistent AF lasting>2 months	Amiodarone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Karlson 1998[225]	Persistent AF	Disopyramide/ placebo	Mortality Stroke Adverse events AF recurrence
Kochiadakis 2000[246]	Any documented symptomatic previous or persistent AF. Type: paroxysmal or recent-onset 64%, persistent 34% (mean duration: 10 months). N=186	Amiodarone/ Sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Kochiadakis 2004A[249]	Any documented symptomatic previous or persistent AF. Type: paroxysmal or recent-onset 63%, persistent 37% (mean duration: 8 months). N=146	Amiodarone/ propafenone	Mortality Recurrence rate Drug withdrawal due to side effects
Kochiadakis 2004B[247]	Any documented symptomatic previous or persistent AF. Type: paroxysmal or recent-onset 59%, persistent 41% (mean duration: 8 months). N=254	Propafenone/ Sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Kuhlkamp 2000[256]	Persistent AF lasting 2 days to 1 year (mean duration: 3 months) N=394	B-blocker/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects

Study	Population	Intervention/comparison	Outcomes
Lloyd 1984[289]	Persistent AF lasting 1 month to 3 years (mean duration: NS). N=82	Disopyramide/ placebo	Mortality Stroke Recurrence rate Drug withdrawal due to side effects
Nergardh 2007[329]	Persistent AF of less than 1 year (mean duration: 5 months). N=168	B-blocker/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Niu 2006[332]	Any type of AF: 41% paroxysmal, 59% persistent (mean duration: NS). N=102	Amiodarone/ Sotalol	Mortality Recurrence rate Drug withdrawal due to side effects
PAFAC 2004[145]	Persistent AF lasting >7 days (mean duration: 15 months). N=848	Sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
PITAGORIA 2008[178]	Recurrent symptomatic AF in patients with sinus node disease and an indication for pace-maker. Type of AF: 53% paroxysmal, 46% persistent (mean duration NS). N=176	Amiodarone/ Class 1C (flecainide or Propafenone)/ Sotalol	Mortality Stroke Drug withdrawal due to side effects
Plewan 2001[361]	Persistent AF (mean duration: 9 months). N=128	Sotalol/ B-blocker	Mortality Recurrence rate Drug withdrawal due to side effects
PRODIS 1996[109]	Persistent AF (mean duration: 5 months). N=56	Disopyramide/ Propafenone	Mortality Recurrence rate Drug withdrawal due to side effects
RAFT 2003[366]	Previous symptomatic AF documented in the last year. Type: NS. N=523	Propafenone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Reimold 1993[376]	Any symptomatic AF or atrial flutter. Type: paroxysmal 46%, persistent 53% (mean duration:	Propafenone/ Sotalol	Mortality Recurrence rate Drug withdrawal due to side effects

Study	Population	Intervention/comparison	Outcomes
	36 months). N=100		
SAFE-T 2005[408]	Persistent AF lasting 3 days to 1 year (mean duration NS. N=655	Amiodarone/ Sotalol/ placebo	Mortality Recurrence rate
Singh 1991[410]	Persistent AF or atrial flutter lasting 2 weeks to 1 year (mean duration: 3 months). N=34	Sotalol/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
SOPAT 2004[351]	Paroxysmal AF documented in the last 1 month (mean duration: NS). N=1033	Sotalol/ placebo	Mortality Stroke Recurrence rate Drug withdrawal due to side effects
Steinbeck 1988[420]	Paroxysmal symptomatic AF of any duration (mean duration: 6 years). N=45	Flecainide (plus digoxin)/ digoxin	Mortality Recurrence rate Drug withdrawal due to side effects
Stroobandt 1997[424]	Recent-onset AF (46%) or persistent AF lasting>2 weeks (54%, mean duration: NS). N=102	Propafenone/ placebo	Mortality Recurrence rate Drug withdrawal due to side effects
Van Gelder 1989[439]	Any persistent AF or atrial flutter (mean duration: 12 months). N=73	Flecainide/ no treatment	Mortality Recurrence rate Drug withdrawal due to side effects
Villani 1992[449]	Symptomatic recent-onset AF lasting > 1 hour, being at least the second episode. N=76	Amiodarone/ disopyramide	Mortality Recurrence rate Drug withdrawal due to side effects

Table 73: Clinical evidence profile: mortality- antiarrhythmic versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic	Placebo	Relative (95% CI)	Absolute		
Individual antiarrhythmic - Class 1a: Disopyramide [226,289]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/75 (2.7%)	0/71 (0%)	OR 7.56 (0.47 to 122.66)	-	VERY LOW	CRITICAL
Individual antiarrhythmic - Class 1c: Flecainide [80,420,439]												
3	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/71 (0%)	0/78 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Individual antiarrhythmic - Class 1c: Propafenone [40,130,250,366,424]												
5	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[e]	none	0/720 (0%)	2/378 (0.5%)	OR 0.05 (0 to 1.02)	5 fewer per 1000 (from 5 fewer to 0 more)	LOW	CRITICAL
Individual antiarrhythmic - Class II: Beta-blockers [256,329]												
2	randomised trials	no serious risk of bias	serious[f]	no serious indirectness	very serious[b]	none	3/280 (1.1%)	1/282 (0.4%)	OR 2.75 (0.39 to 19.56)	6 more per 1000 (from 2 fewer to 62 more)	VERY LOW	CRITICAL
Individual antiarrhythmic - Class III: Amiodarone [83,167,246,408]												
4	randomised trials	serious[g]	no serious inconsistency	no serious indirectness	very serious[b]	none	13/428 (3%)	3/245 (1.2%)	OR 1.96 (0.68 to 5.67)	11 more per 1000 (from 4 fewer to 53 more)	VERY LOW	CRITICAL
								0%		-		
Individual antiarrhythmic - Class III: Sotalol [40,42,69,76,80,145,249,291,351,361,408,410]												
12	randomised trials	serious[h]	no serious inconsistency	no serious indirectness	serious[e]	none	34/1791 (1.9%)	5/1211	OR 2.47 (1.21 to	6 more per 1000 (from 1 more to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic	Placebo	Relative (95% CI)	Absolute	Quality	Importance
								(0.4 %)	5.05)	16 more)		

a. Allocation concealment was unclear in both studies
b. Confidence interval crossed both MIDs
c. Allocation concealment was unclear in 2/3 studies
d. Allocation concealment was unclear in 4/5 studies
e. Confidence interval crossed 1 MID
f. I2= 66%, p= 0.31
g. Allocation concealment was unclear in 3/4 studies
h. Allocation concealment was unclear in 8/12 studies

Table 74: Clinical evidence profile: mortality - antiarrhythmic versus antiarrhythmic

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute	Quality	Importance
Comparing antiarrhythmic drugs - Disopyramide versus other Class I drugs [110]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/60 (1.7%)	0/25 (0%)	OR 6.09 (0.12 to 313.90)	149 more per 1000 (from 32 fewer to 885 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Flecainide versus Propafenone [16,90]												
2	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/145 (0%)	1/152 (0.7%)	OR 0.14 (0 to 6.96)	6 fewer per 1000 (from 7 fewer to 37 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Class I drugs [7,178,249,449]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute		
4	randomised trials	serious[d]	very serious[e]	no serious indirectness	serious[f]	none	16/311 (5.1%)	28/332 (8.4%)	OR 0.59 (0.31 to 1.11)	33 fewer per 1000 (from 57 fewer to 8 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Dronedarone [266]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	5/255 (2%)	2/249 (0.8%)	OR 2.32 (0.52 to 10.32)	10 more per 1000 (from 4 fewer to 69 more)	LOW	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Sotalol [7,178,246,332,408]												
5	randomised trials	serious[g]	serious[h]	no serious indirectness	serious[f]	none	34/584 (5.8%)	39/529 (7.4%)	OR 0.77 (0.47 to 1.25)	16 fewer per 1000 (from 38 fewer to 17 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Sotalol versus Class I drugs other than quinidine [7,80,250,376]												
4	randomised trials	serious[i]	serious[j]	no serious indirectness	very serious[b]	none	15/243 (6.2%)	17/251 (6.8%)	OR 0.94 (0.44 to 1.99)	4 fewer per 1000 (from 37 fewer to 59 more)	VERY LOW	CRITICAL
								0%		-		
Comparing antiarrhythmic drugs - Sotalol versus Other Beta-blockers [77,361]												
2	randomised trials	serious[k]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/133 (0%)	0/130 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Comparing antiarrhythmic drugs - Class III versus Class I drugs [7,80,146,249,250,376,449]												
7	randomised trials	serious[l]	serious[m]	no serious indirectness	very serious[b]	none	42/1353 (3.1%)	39/1522 (2.6%)	OR 0.79 (0.49 to 1.26)	5 fewer per 1000 (from 13 fewer to 6 more)	VERY LOW	CRITICAL

a. Allocation concealment was unclear
b. Confidence interval crossed both MIDs
c. Allocation concealment was unclear in 1/2 studies

d. Allocation concealment was unclear in 3/4 studies
e. I2=85%, p=0.01
f. Confidence interval crossed 1 MID
g. Allocation concealment was unclear in 4/5 studies
h. I2=59%, p=0.09
i. Allocation concealment was unclear in 2/4/ studies
j. I2=57%, p=0.13
k. Allocation concealment was unclear in both studies
m. Allocation concealment was unclear in 4/8 studies
13 I2=42%, p=0.11

Table 75: Clinical evidence profile: withdrawal due to adverse events – antiarrhythmic versus control

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**antiarrhythmic**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Individual antiarrhythmic - Class 1a: Disopyramide [226,289]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	9/75 (12%)	2/71 (2.8%)	OR 3.85 (1.13 to 13.18)	72 more per 1000 (from 4 more to 248 more)	LOW	IMPORTANT
Individual antiarrhythmic - Class 1c: Flecainide [80,420,439]												
3	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/71 (9.9%)	0/78 (0%)	OR 9.14 (1.94 to 42.94)	-	MODERATE	IMPORTANT
Individual antiarrhythmic - Class 1c: Propafenone [40,130,250,366,424]												
5	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[b]	none	94/720 (13.1%)	23/378 (6.1%)	OR 1.69 (1.09 to 2.62)	38 more per 1000 (from 5 more to 84 more)	LOW	IMPORTANT
Individual antiarrhythmic - Class II: Beta-blockers [256,329]												
2	randomis	serio	no serious inconsistenc	no serious indirectnes	no serious imprecisio	none	22/280 (7.9%)	6/282	OR 3.38 (1.57 to	47 more per 1000 (from 12	MODER	IMPORT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antiarrhythmic	Placebo	Relative (95% CI)	Absolute		
	ed trials	us[a]	y	s	n			(2.1%)	7.25)	more to 115 more)	ATE	ANT
Individual antiarrhythmic - Class III: Amiodarone [83,179,246]												
3	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/161 (12.4%)	1/113 (0.9%)	OR 5.55 (2.24 to 13.72)	38 more per 1000 (from 11 more to 100 more)	MODERATE	IMPORTANT
Individual antiarrhythmic - Class III: Sotalol [40,42,70,77,80,146,248,291,352,361,410]												
11	randomised trials	serious[e]	serious[f]	no serious indirectness	no serious imprecision	none	251/1530 (16.4%)	102/1079 (9.5%)	OR 1.61 (1.25 to 2.06)	49 more per 1000 (from 21 more to 82 more)	LOW	IMPORTANT

a. Allocation concealment was unclear in both studies
b. Confidence interval crossed 1 MID
c. Allocation concealment was unclear in 2/3 studies
d. Allocation concealment was unclear in 4/5 studies
e. Allocation concealment was unclear in 7/11 studies
f. I2=52%, p=0.001

Table 76: Clinical evidence profile: withdrawals due to adverse events- antiarrhythmic versus antiarrhythmic drugs

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute	Quality	Importance
Comparing antiarrhythmic drugs - Disopyramide versus other Class I drugs [110]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	6/60 (10%)	12/53 (22.6%)	OR 0.37 (0.14 to 1.03)	129 fewer per 1000 (from 187 fewer to 5 more)	LOW	IMPORTANT
Comparing antiarrhythmic drugs - Flecainide versus Propafenone [16,90]												
2	randomised trials	serious[c]	very serious[d]	no serious indirectness	very serious[e]	none	12/145 (8.3%)	18/152 (11.8%)	OR 0.68 (0.32 to 1.43)	35 fewer per 1000 (from 77 fewer to 43 more)	VERY LOW	IMPORTANT
Comparing antiarrhythmic drugs - Amiodarone versus Class I drugs [7,178,249,449]												
4	randomised trials	serious[f]	very serious[7]	no serious indirectness	serious[b]	none	46/359 (12.8%)	62/293 (21.2%)	OR 0.55 (0.36 to 0.84)	83 fewer per 1000 (from 28 fewer to 123 fewer)	VERY LOW	IMPORTANT
Comparing antiarrhythmic drugs - Amiodarone versus Dronedarone [266]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[b]	none	45/255 (17.6%)	32/249 (12.9%)	OR 1.45 (0.89 to 2.35)	48 more per 1000 (from 12 fewer to 129 more)	MODERATE	IMPORTANT
Comparing antiarrhythmic drugs - Amiodarone versus Sotalol [7,178,246,332]												
4	randomised trials	serious[f]	serious[h]	no serious indirectness	very serious[e]	none	42/340 (12.4%)	31/278 (11.2%)	OR 1.19 (0.73 to 1.95)	18 more per 1000 (from 28 fewer to 85 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute	Quality	Importance
Comparing antiarrhythmic drugs - Sotalol versus Class I drugs other than quinidine [7,250,376]												
4	randomised trials	serious[i]	serious[j]	no serious indirectness	no serious imprecision	none	32/290 (11%)	56/277 (20.2%)	OR 0.45 (0.28 to 0.72)	100 fewer per 1000 (from 48 fewer to 136 fewer)	LOW	IMPORTANT
Comparing antiarrhythmic drugs - Sotalol versus Other Beta-blockers [77,361]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	15/133 (11.3%)	5/130 (3.8%)	OR 2.86 (1.15 to 7.11)	64 more per 1000 (from 6 more to 183 more)	LOW	IMPORTANT
Comparing antiarrhythmic drugs - Class III versus Class I drugs [7,80,146,249,250,376,449]												
7	randomised trials	serious[l]	very serious[m]	no serious indirectness	serious[b]	none	244/1448 (16.9%)	299/1527 (19.6%)	OR 0.79 (0.65 to 0.96)	34 fewer per 1000 (from 6 fewer to 59 fewer)	VERY LOW	IMPORTANT

a. Allocation concealment was unclear
b. Confidence interval crossed 1 MID
c. Allocation concealment was unclear in 1/2 studies
d. I2=72%; p=0.05
e. Confidence interval crossed both MIDs
f. Allocation concealment was unclear in 3/4 studies
g. I2=91%, p=<0.0001
h. I2=61%, p=0.05
i. Allocation concealment was unclear in 2/4 studies
j. I2=71%, p=0.05
k. Allocation concealment was unclear in both studies
l. Allocation concealment was unclear in 4/7 studies
m. I2=82%, p=<0.00001

Table 77: Clinical evidence profile: AF recurrence- antiarrhythmic versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antiarrhythmic	Placebo	Relative (95% CI)	Absolute		
Individual antiarrhythmic - Class 1a: Disopyramide [226,289]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	40/75 (53.3%)	49/71 (69%)	OR 0.52 (0.27 to 1.01)	153 fewer per 1000 (from 315 fewer to 2 more)	LOW	CRITICAL
Individual antiarrhythmic - Class 1c: Flecainide [80,420,439]												
3	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/71 (43.7%)	56/78 (71.8%)	OR 0.31 (0.16 to 0.6)	277 fewer per 1000 (from 114 fewer to 429 fewer)	MODERATE	CRITICAL
Individual antiarrhythmic - Class 1c: Propafenone [40,130,250,366,424]												
5	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	376/720 (52.2%)	276/378 (73%)	OR 0.37 (0.28 to 0.48)	230 fewer per 1000 (from 165 fewer to 299 fewer)	MODERATE	CRITICAL
Individual antiarrhythmic - Class II: Beta-blockers [256,329]												
2	randomised trials	no serious risk of bias	serious[e]	no serious indirectness	serious[b]	none	172/280 (61.4%)	203/282 (72%)	OR 0.62 (0.44 to 0.88)	105 fewer per 1000 (from 26 fewer to 189 fewer)	LOW	CRITICAL
Individual antiarrhythmic - Class III: Amiodarone [83,167,246,408]												
4	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	none	200/428 (46.7%)	209/245 (85.3%)	OR 0.19 (0.14 to 0.27)	329 fewer per 1000 (from 243 fewer to 405 fewer)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antiarrhythmic	Placebo	Relative (95% CI)	Absolute		
Individual antiarrhythmic - Class III: Sotalol [40,42,70,77,80,146,250,291,352,361,409,411]												
12	randomised trials	serious[g]	serious[h]	no serious indirectness	no serious imprecision	none	1197/1791 (66.8%)	955/1211 (78.9%)	OR 0.51 (0.43 to 0.6)	133 fewer per 1000 (from 97 fewer to 173 fewer)	LOW	CRITICAL

a. Allocation concealment was unclear in both studies
b. Confidence interval crossed 1 MID
c. Allocation concealment was unclear in 2/3 studies
d. Allocation concealment was unclear in 4/5 studies
e. I2=52%, p=0.15
f. Allocation concealment was unclear in 3/4 studies
g. Allocation concealment was unclear in 8/12 studies
h. I2=57%, p=<0.0001

Table 78: Clinical evidence profile: AF recurrence - antiarrhythmic versus antiarrhythmic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute		
Comparing antiarrhythmic drugs - Disopyramide versus other Class I drugs [110]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	26/60 (43.3%)	27/53 (50.9%)	OR 0.76 (0.36 to 1.6)	68 fewer per 1000 (from 237 fewer to 115 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Flecainide versus Propafenone [16,91]												
2	randomise	serious[c]	no serious	no serious	very	none	49/145	56/152	OR	32 fewer	VERY	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute		
	d trials		inconsistency	indirectness	serious[b]		(33.8%)	(36.8%)	0.87 (0.54 to 1.4)	per 1000 (from 129 fewer to 81 more)	LOW	
Comparing antiarrhythmic drugs - Amiodarone versus Class I drugs [7,179,249,449]												
4	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	none	142/311 (45.7%)	229/332 (69%)	OR 0.36 (0.26 to 0.5)	245 fewer per 1000 (from 163 fewer to 323 fewer)	MODERATE	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Dronedarone [266]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	116/255 (45.5%)	163/249 (65.5%)	OR 0.45 (0.31 to 0.63)	194 fewer per 1000 (from 110 fewer to 285 fewer)	HIGH	CRITICAL
Comparing antiarrhythmic drugs - Amiodarone versus Sotalol [7,179,246,332,409]												
5	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	284/584 (48.6%)	363/529 (68.6%)	OR 0.43 (0.34 to 0.54)	202 fewer per 1000 (from 145 fewer to 260 fewer)	MODERATE	CRITICAL
Comparing antiarrhythmic drugs - Sotalol versus Class I drugs other than quinidine [7,80,250,376]												
4	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[b]	none	150/243 (61.7%)	157/251 (62.5%)	OR 0.98 (0.67 to 1.45)	5 fewer per 1000 (from 97 fewer to 82 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antiarrhythmic 1	Antiarrhythmic 2	Relative (95% CI)	Absolute		
Comparing antiarrhythmic drugs - Sotalol versus Other Beta-blockers [77,361]												
2	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	very serious[b]	none	88/133 (66.2%)	83/130 (63.8%)	OR 1.1 (0.64 to 1.9)	22 more per 1000 (from 108 fewer to 132 more)	VERY LOW	CRITICAL
Comparing antiarrhythmic drugs - Class III versus Class I drugs [7,80,146,249,250,376,449]												
7	randomised trials	serious[g]	serious[h]	no serious indirectness	no serious imprecision	none	806/1353 (59.6%)	966/1522 (63.5%)	OR 0.89 (0.76 to 1.04)	27 fewer per 1000 (from 66 fewer to 9 more)	LOW	CRITICAL

a unclear allocation concealment
b CI crosses both MIDs
c unclear allocation concealment in 1/2 studies
d unclear allocation concealment in 3/4 studies
e unclear allocation concealment in 4/5 studies
f unclear allocation concealment in both studies
g unclear allocation concealment in 4/7 studies
h I2=69%; p=0.001

Table 79: Clinical evidence profile: quality of life

Quality assessment	No of patients	Effect	Quality	Importan

												ce
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antiarrhythmic 1**	**Antiarrhythmic 2**	**Relative (95% CI)**	**Absolute**		
Comparing antiarrhythmic drugs - Disopyramide versus other Class I drugs [110]												
0	No available evidence											CRITICAL

16.2.2 Economic evidence

Published literature

No relevant economic evaluations were identified.

Six economic evaluations relating to this review question were identified but were excluded due to a combination of limited applicability and methodological limitations. [81,138,187,294,388,428] These are summarised in Appendix K with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs of the drugs and associated monitoring were considered. The list prices for the drugs used for pharmacological cardio version can be found in appendix N.

16.2.3 Evidence statements

Clinical

Mortality: Drug versus placebo

Low quality evidence showed that propafenone may be clinically effective at reducing deaths compared to placebo, but there is also a potential that propafenone could increase deaths (five studies, N=1098).

Low quality evidence showed that sotalol is less clinically effective than placebo at reducing mortality (twelve studies, N=3002).

Low to very low quality evidence showed that disopyramide, beta-blockers and amiodarone may be less clinically effective at reducing deaths compared to placebo, but there is also a potential that disopyramide, beta-blockers, and amiodarone could decrease deaths (eight studies, N=1381).

A point estimate was not estimable for flecainide versus placebo as there were no deaths reported (six studies, N=149).

Mortality: Antiarrhythmic versus antiarrhythmic

Very low quality evidence showed that the following may be more clinically effective:

- Disopyramide compared to other class I drugs, but there is also a potential that other class I drugs could decrease deaths (one study, N=66)
- Flecainide compared to Propafenone but there is also a potential that propafenone could decrease deaths (one study, N=297).
- Amiodarone compared to class I drugs, but there is also a potential that amiodarone could decrease deaths (one study, N=643).
- Amiodarone compared to Sotalol, but there is also a potential that sotalol could decrease deaths (one study, N=1113).
- Class III drugs compared with class I drugs, but there is also a potential that class I drugs could decrease deaths (one study, N=2875).

Very low quality evidence showed that amiodarone may be less clinically effective compared to dronedarone, but there is also a potential that amiodarone could decrease deaths (one study, N=504).

Very low quality evidence showed that there may be no clinical difference between Sotalol and class I drugs other than quinidine, but the direction of the estimate of effect could favour either intervention (four studies, N=594).

A point estimate was not estimable for sotalol versus beta-blockers as there were no deaths reported (two studies, N=263).

Health-related quality of life
No evidence was found.

AF recurrence: drug versus placebo
Moderate to low quality evidence showed that flecainide, propafenone, amiodarone and sotalol are clinically effective compared with placebo (twenty-four studies, N=4249).
Low quality evidence showed that disopyramide and beta-blockers may be clinically effective compared with placebo (four studies, N=708).

AF recurrence: antiarrhythmic versus antiarrhythmic.
Evidence showed that amiodarone is more clinically effective compared with:

- class I drugs (Moderate quality evidence , four studies, N=643).
- sotalol (Moderate quality evidence , five studies, N=1113).
- Dronedarone (High quality evidence, one study, N= 504)

Very low quality evidence showed that there may be no difference between the following interventions (but the direction of the estimate of effect could favour either intervention):

- flecainide and propafenone (two studies, N=297).
- sotalol and class I drugs other than quinidine (four studies, N=594)
- sotalol and other beta-blockers (two studies, N=263).

Low quality evidence showed that there may be no difference between class III and class I drugs, but the direction of the estimate of effect favoured class III drugs (seven studies, N=1603).
Very low quality evidence showed that disopyramide may be more clinically effective compared with class III drugs, but the direction of the estimate of effect could favour either intervention (one study, N= 113).

Drug withdrawals due to adverse effects: drug versus placebo
Moderate to low quality evidence showed that there were more drug withdrawals due to adverse events with disopyramide, flecainide, propafenone, beta-blockers, amiodarone and sotalol (twenty-six studies, N=4838).
Drug withdrawals due to adverse effects: antiarrhythmic versus antiarrhythmic.
There were more drug withdrawals due to adverse events with:

- class I drugs compared with disopyramide (Low quality evidence, one study, N= 113).
- class I drugs compared with amiodarone (Very low quality evidence, four studies, N=652).
- amiodarone compared with dronedarone (Moderate quality evidence, one study, N= 504).
- class I drugs other than quinidine compared with sotalol in people with AF (Low quality evidence, four studies, N=567).
- sotalol compared with other beta-blockers in people with AF (Low quality evidence, two studies, N=263).

Very low quality evidence showed that there were more drug withdrawals due to adverse events with:

- Propafenone compared with flecainide, but the direction of the estimate of effect favoured propafenone (two studies, N= 297).
- Amiodarone and Sotalol but the direction of the estimate of effect favoured amiodarone (four studies, N=618).
- Class I drugs compared with class III drugs, but the direction of the estimate of effect favoured class III drugs (seven studies, N=>100).

Economic

No relevant economic evaluations were identified.

16.2.4 Recommendations and link to evidence

Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	The GDG agreed that the critical outcomes were motility, health related quality of life and recurrence rate. The GDG agreed that the most important outcome was improvement of symptoms, especially since the management of AF is very much patient centred and symptom directed. In many previous studies of drug efficacy, the best proxy was maintenance of sinus rhythm or recurrence rates as some of these patients were asymptomatic.
Trade-off between clinical benefits and harms	The evidence demonstrated a clinical benefit for maintenance of sinus rhythm with amiodarone, followed by flecainide and propafenone and then sotalol. Beta-blockers had a modest effect on maintenance. Side effects were found to be most harmful for flecainide, followed by amiodarone and then beta-blockers, propafenone and least for sotalol. When sotalol was compared with other beta-blockers there was a clinical benefit for beta-blockers, notwithstanding the dose considerations mentioned earlier (see Section 15.2.4) whereby a Class III antiarrhythmic effect was evident only at doses >240mg daily. The GDG weighed up the balance between the benefits of sinus rhythm maintenance against the side effects reported. The GDG agreed that the harm of the numerous side effects of drugs for rhythm control potentially outweighed the benefits. They recommended that if this treatment option is considered then beta-blockers would be the drug of first choice as they have the lowest side effects reported. In practice, in many cases patients will already have received beta blockers as part of a rate control strategy and under these circumstance a decision might be made to progress directly to another drug category. Associated comorbidities and patient preferences would need to be considered. When considering progressing to a rhythm control strategy with other rhythm control drugs if beta-blockers are unsuccessful or contraindicated, the GDG considered that co-morbidities and side potential side effects were the strongest determinant of drug choice amongst the class I and class III drugs. The GDG were concerned about potential harm with sotalol when compared to control for both mortality and withdrawal due to adverse events. The GDG had specific concerns when considering sotalol. Sotalol is used commonly in UK practice, although often at a lower dose than required for class III effects. The GDG were concerned that patients may have been maintained on sotalol for a long time without regular review. At the low doses commonly prescribed in the UK, sotalol has beta-blocker properties rather than Class III antiarrhythmic activity and perhaps another beta blocker could be considered to replace sotalol. The GDG considered that amiodarone was the only antiarrhythmic which could be recommended for use in patients with heart failure. The recommendation was not based on specific attributes of amiodarone in heart failure patients. Rather it was based on the fact that the presence of heart failure specifically contra-indicated the

	use of the class I anti-arrhythmics propafenone and flecainide, and of the class III agent dronedarone (see below recommendations from TA197[323]). In addition, the GDG considered that in view of the excess mortality which had been observed with d-sotalol in the SWORD study[453], in addition to their more general reservations on the use of sotalol, that sotalol should not be used. The recommendation for use of amiodarone in heart failure patients was therefore based on the non-availability of other anti-arrhythmics in this situation.
Economic considerations	There was no economic evidence of sufficient applicability or quality to inform this question. The GDG considered the pharmacological strategies, and agreed that the greatest cost was likely to arise from the adverse events of each strategy including pro-arrhythmia and the resultant hospitalisations. Therefore the clinical evidence was considered to inform the relative likelihood of such events. The GDG also considered the therapeutic monitoring required to mitigate the risk of harmful events occurring. Of all of the drugs considered, beta blockers appeared to have the least resource use in this regard and a relatively low acquisition cost and adverse effects profile. The GDG noted that sotalol needed to be initiated and doses increased in a facility capable of monitoring and assessing cardiac rhythm due to the possibility of pro-arrhythmic events. Renal function and electrolyte balance also needs to be assessed at initiation. Given that least relative benefit was found with sotalol, this is likely to be the least cost-effective drug on which evidence was reviewed. Likewise, propafenone is initiated in a specialist hospital setting, and requires ECG monitoring and BP measurement during initiation and dose titration. This is done at intervals of 3-4 days, until optimum dose is achieved. Oral flecainide should be initiated after structural heart disease has been ruled out, under direct hospital or specialist supervision and requires ECG and biochemical monitoring prior to initiation. Again, given a modest and unknown clinical benefit respectively, it is unlikely these drug will be optimal in terms of cost effectiveness if compared to beta-blockers. Amiodarone was found to have the most clinical benefit; however it has a greater adverse effect profile than beta blockers. Amiodarone can cause serious adverse 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 monitoring includes regular ECG. In comparison therefore, a pharmacological strategy of using amiodarone is likely to use substantially more health care resource than that of beta blockers. Therefore, amiodarone should be reserved for certain patient groups where beta blockers would not be appropriate. On balance, the GDG concluded that Beta Blockers were highly likely to be cost effective in comparison to the other drugs available to maintain rhythm.
Quality of evidence	The quality of evidence for the outcomes ranged from very low to high. However, the majority of outcomes had a low or very low quality with only one outcome comparison with a high quality.
Other considerations	These recommendations for patients with AF were based on the evidence and the experience and opinion of the GDG. The recommendations for patients with AF and structural heart disease, left ventricular impairment and heart failure were based on the experience and opinion of the GDG. The studies did not report separate analysis for people with AF due to reversible causes.

	The GDG have cross referenced to the related NICE technology appraisal on dronedarone for this chapter.

16.3 Treatment strategy for paroxysmal AF

In selected patients with recurrent paroxysmal AF, out-of-hospital initiation of antiarrhythmic drugs may be possible, allowing for earlier treatment, a shorter duration of AF and a presumed likelihood of restoring and maintaining sinus rhythm. A pill-in-the-pocket approach is used in those not taking drugs regularly due to infrequent symptoms/paroxysms, or can be taken as an 'extra' drug dose in those already on a low maintenance of that particular drug. This approach is different to the out-of-hospital use of antiarrhythmic drugs in patients with recurrent persistent AF, where the aim may be to achieve pharmacological cardioversion per se or to improve the likelihood of subsequent elective electrical cardioversion (see Chapter 15), or to maintain sinus rhythm (see Chapter 16).

The main concern with a pill-in-the-pocket approach is the risk of pro-arrhythmia often associated with antiarrhythmic drugs. Thus, the pill-in-the-pocket approach has generally been advocated only in those patients with a low risk of pro-arrhythmia and other adverse side effects. Such patients are typically those with no structural heart disease, absence of heart failure or left ventricular dysfunction, and where there is evidence that the antiarrhythmic drug used has previously worked successfully with no adverse effects (e.g. after at least one inpatient trial of the drug administered as a single oral dose, under ECG monitoring).

The antiarrhythmic drugs amiodarone and propafenone have both been considered in a number of trials comparing the safety and efficacy of a single oral dose of the drug with the intravenous administration of the same drug.[22,55,57,58] In all of these trials, patients were selected on the basis of relatively young age and the absence of any severe underlying structural heart disease. There was no incidence of ventricular pro-arrhythmia reported in either the intravenous or oral administration arms of these trials, and the incidence of successful cardioversion within 8 or 24 hours was comparable in most cases.

The objective of this section is to determine in which patients a single oral-dose antiarrhythmic drug may be safely used as a pill-in-the-pocket approach.

16.3.1 Methodological introduction

Studies were included if a comparison was made in terms of the safety, efficacy and impact on healthcare resources between the out-of-hospital self-administration of pharmacological cardioversion and the supervised, in-hospital administration in a well-defined patient cohort with either AF or supraventricular tachycardia (SVT). Studies were not included if the pharmacological agents were administered prophylactically.

Both of the included studies were based in Italy and compared the rates of hospital admission and emergency room treatment in a single cohort of patients in the period before and the period after the self-administration of antiarrhythmic drugs for the termination of either paroxysmal AF[13] or paroxysmal SVT.[14]

Neither study specified the treatment protocol during the period before the self-administration of antiarrhythmic drugs, or made a comparison between the two periods in terms of safety and efficacy.

16.3.2 Evidence statements

One study[13] found that the average number of admissions per month for emergency treatment was significantly lower during treatment of paroxysmal AF using a pill-in-the-pocket approach with Class Ic drugs than during conventional treatment (4.9 versus 45.6, $p<0.001$) in a population of patients with the following criteria: (2+)

- age 18 to 75

- left ventricular ejection fraction (LVEF) greater than 50%
- no history of severe heart disease
- systolic blood pressure (BP) greater than 100 mmHg
- heart rate greater than 70 bpm.

Another study found a similar result using similar selection criteria among patients with paroxysmal SVT.[14] (2+)

16.3.3 From evidence to recommendations

The limited evidence suggested that pill-in-the-pocket treatment was associated with a lower incidence of inpatient and emergency hospital admissions than conventional treatment.[13,14] It was uncertain whether the pill-in-the-pocket strategy was associated with more adverse events, or reduced episode duration when compared to in-hospital treatment.

Within the UK, the number of patients managed in this way is currently thought to be small, and patients need to be made more aware of this treatment option, although strict selection criteria are deemed necessary. In particular, it was considered that patient education in its use is vital.

Therapy for paroxysmal AF should be tailored to the patient. For example, episodes of AF for 1 to 2 minutes once a year or for 10 hours twice a day are both paroxysmal AF, but their impact on the patient's quality of life, if symptomatic, would be quite different. In patients with infrequent and brief paroxysms, the regular use of antiarrhythmic therapy may not be necessary (and is commonly not prescribed in current clinical practice). Such patients may be suitable for the pill-in-the-pocket approach. However, for infrequent but protracted and symptomatic paroxysmal AF, rapid cardioversion of each event and/or antiarrhythmic drug prophylaxis may be considered.

16.3.4 Recommendation

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

17 Left atrial ablation

This section was partially updated in 2021. See http://www.nice.org.uk/guidance/ng196/evidence for the 2021 evidence reviews.

17.1 Introduction

Although both left atrial surgical and catheter ablation are established therapies, the techniques and technologies have evolved since the last guideline was published and there is more evidence guiding us as to their efficacy. For this reason, this guideline has addressed three important questions: (1) What is the efficacy of catheter ablation, (2) What is the efficacy of surgical ablation and (3) How do the two techniques compare to one another?

Left atrial ablation may be used to treat patients with paroxysmal AF or persistent AF, but the outcome of ablation has long been recognised as being very different between these two clinical presentations. Furthermore, patients with coexistent heart failure may respond differently to ablation and may suffer different risks from the procedure. Therefore the questions seek to specifically examine the impact of ablation on these different patient groups.

It is critical that the patient's wishes and clinical history are taken into account when the patient and clinical team decide on the appropriate therapy for them.

Left atrial ablation in the context of cardiac arrhythmias describes the deliberate damage of discrete portions of cardiac tissue, such that the electrical activity of that tissue is eliminated. Left atrial ablation may be performed using catheters passed into the heart via the venous system, or surgically. Both catheter and surgical ablation have a number of different technologies available – these different technologies have not been compared in this guideline. Whether a catheter approach or a surgical approach is adopted, the primary aim is to electrically isolate the pulmonary veins which contain electrically active tissue that triggers the majority of AF. When AF is persistent, then most clinicians believe that ablation of other areas of the atria is also required in addition to isolation of the pulmonary veins. There are a number of practical differences between catheter and surgical ablation, therefore one of the questions examined in this guideline is a direct comparison of surgical and catheter ablation.

Left atrial catheter ablation is a minimally invasive technique that can be performed with local or general anaesthetic. Patients will usually be sent home the following day (although some units now perform day-case ablation). Left atrial catheter ablation is technically challenging, and one of the recognised limitations is that a significant minority of patients will require repeat procedures to achieve the best results. Surgical ablation may be performed either as part of another cardiothoracic operation or as a stand-alone procedure. Surgical ablation is always performed under general anaesthetic, although the patient stay in hospital may also be very short when done in isolation, particularly when using minimally invasive or thoracoscopic techniques. Both catheter and surgical ablation can be combined with procedures to close off the left atrial appendage, which is believed to be the source of clot for the majority of embolic strokes in AF patients with no cardiac valve disease.

The review questions examined in this guideline aim to aid clinicians in deciding which patients will benefit from left atrial ablation and whether surgical or catheter approaches are likely to deliver the best outcome. The assessment relates solely to left atrial ablation for atrial fibrillation and does not address the role of ablation management of classical atrial flutter originating in the right atrium.

17.2 Review question: What is the clinical and cost effectiveness of catheter ablation compared to non-ablation therapies in people with atrial fibrillation?

For full details see review protocol in Appendix C.

Table 80: PICO characteristics of review question

Population	People with paroxysmal, permanent or persistent AF
Intervention/s	Catheter ablation including percutaneous radiofrequency ablation
Comparison/s	Non ablation therapies: Rhythm control drugs Cardioversion Cardioversion and drug therapy Rate control drugs
Outcomes	Health related quality of life Mortality Recurrence of symptomatic AF Stroke or thromboembolic complications Hospitalisation (cardiovascular) Patients developing heart failure Necessity for concomitant antiarrhythmic drug therapy
Study design	Randomised controlled trials (RCT) Systematic reviews of RCTs

17.2.1 Clinical evidence

We searched for systematic reviews and RCTs comparing catheter ablation with non-ablative therapies.

A Cochrane systematic review [84] with 7 RCTs[14,17,26,32,34,40,45] (n=767) was included in the review. This compared catheter ablation with medical therapies (rhythm control) in patients with paroxysmal or persistent AF. In addition, one follow up study of an RCT included in the Cochrane review was included [348] and three RCT (n=706) comparing radiofrequency catheter ablation with medical therapies(rhythm control) in patients with paroxysmal atrial fibrillation[47105,345] were included.

Furthermore, one RCT (n=31) comparing radiofrequency catheter ablation with medical therapies (rate control) in patients with persistent AF, advanced heart failure and severe left ventricular systolic dysfunction[29] was included but reported separately due to the different patient population.

Another study[362] compared re-ablation with rhythm control drugs in patients who had a previously failed ablation.

Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 82**, **Table 83** and

Table 84). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 81: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes
Chen 2012[84]	Catheter ablation: 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 N=3 RCTS patients did not discontinue anti-arrhythmics before ablation procedure Medical therapies: Rhythm control	Paroxysmal or persistent AF	Mortality Fatal and non-fatal embolic complications Recurrence of AF Quality of life
Pappone 2011 [348]	Circumferential pulmonary vein ablation Medical therapies: Rhythm control Flecainide, sotalol and amiodarone	Paroxysmal AF	SF-36 Recurrence of AF
Wilber 2010[47]	Radiofrequency catheter ablation Medical therapies: Rhythm control Received a not previously administered medication (dofetilide, flecainide, propafenone, sotalol or quinidine) Amiodarone was not allowed	Paroxysmal AF Patients not to have responded to one antiarrhythmic drug	SF-36 Recurrence of AF
Pokushalov 2013 [362]	Re-ablation Medical therapies: rhythm control	Paroxysmal AF	AF/ AT free at 3 years
Packer 2013[345]	Cryoballoon ablation	Paroxysmal AF	Mortality Stroke

Study	Intervention/comparison	Population	Outcomes
	Medical therapies: antiarrhythmic drug therapy		Freedom from AF
Cosedis 2012[105]	Radiofrequency catheter ablation Medical therapies: Flecainide or propafenone. If contraindicated, amiodarone or sotalol	Paroxysmal AF	SF-36 mental and physical components Free from symptomatic AF Mortality Stroke Hospitalisation for heart failure
Advanced heart failure			
Macdonald 2011[29]	Radiofrequency catheter ablation Oral amiodarone was started at discharge and continued for three months Medical therapies: Rate control All patients had been receiving optimal heart failure treatment for three months. If mean heart rate was > 80 bpm over a 24 hour period then digoxin was added to treatment	Men and women aged 18-80 years with New York Heart Association functional class II-IV symptoms despite optimal heart failure treatment for at least three months, ejection fraction < 35%, persistent AF and no contraindication to cardiovascular MRI Exclusion criteria: paroxysmal AF	SF-36 Fatal and non-fatal embolic complications Maintenance of sinus rhythm

Table 82: Clinical evidence profile: catheter ablation versus medical therapies

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catheter ablation	Medical therapies	Relative (95% CI)	Absolute		
SF-36 mental (follow-up range from 3-24 months; Better indicated by higher values)[105,460]												
2	randomised trials	serious[a]	serious inconsistency[g]	no serious indirectness	no serious imprecision	none	236	187	-	MD 1.71 higher (0.02 to 3.45 higher)	LOW	CRITICAL
SF-36 mental (4 yrs.) (follow-up 4 years; Better indicated by higher values)[348]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	99	87	-	MD 10.4 higher (7.65 to 13.15 higher)	MODERATE	CRITICAL
SF-36 physical (follow-up range from 3-24 months; Better indicated by higher values)[105,460]												
2	randomised trials	serious[a]	serious inconsistency[g]	no serious indirectness	no serious imprecision	none	236	187	-	MD 4.03 higher (2.46 to 5.61 higher)	LOW	CRITICAL
SF-36 physical (4 yrs.) (follow-up 4 years; Better indicated by higher values)[348]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	99	87	-	MD 8.2 higher (5.9 to 10.5 higher)	MODERATE	CRITICAL
Recurrence of AF (follow-up 1-24 months)[105,148,210,254,343,345,347,418,455,460]												
10	randomised trials	serious[c]	serious[d]	no serious indirectness	no serious imprecision	none	188/791 (23.8)	(67.9%)	RR 0.33 (0.29 to 0.38)	455 fewer per 1000 (from 421 fewer to 482 fewer)	LOW	CRITICAL
Recurrence of AF (4 yrs.) (follow-up 4 years)[348]												
1	randomised trials	serious[e]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/99 (12.1%)	87/99 (87.9%)	RR 0.14 (0.08 to 0.24)	756 fewer per 1000 (from 668 fewer to 808 fewer)	MODERATE	CRITICAL
Mortality (follow-up 12 months) [105,345,418]												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[f]	none	5/377 (1.3%)	6/299 (2.0%)	RR 0.76 (0.24 to 2.41)	5 fewer per 1000 (from 15 fewer to 28 more)	LOW	CRITICAL
Fatal or non-fatal embolic complications (follow-up 6-12 months)[255,418]												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[f]	none	2/83 (2.4%)	2/84 (2.4%)	RR 1.01 (0.18 to 5.68)	0 more per 1000 (from 20 fewer to 111 more)	LOW	IMPORTANT
Stroke (follow-up 24 months)[105,345]												
2	randomised trials	serious[c]	no serious inconsistency	no serious indirectness	very serious[f]	none	5/309 (1.6%)	1/230 (0.4%)	OR 2.40 (0.44 to 13.00)	6 more per 1000 (from 2 fewer to 49 more)	VERY LOW	IMPORTANT
Hospitalisation for heart failure (follow-up 24 months)[105]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[f]	none	0/146 (0%)	2/148 (1.4%)	OR 0.14 (0.01 to 2.19)	-	LOW	IMPORTANT

a. Lack of blinding
b. Confidence interval crossed one MID
c. > 50% weighted studies at high risk of bias (unclear allocation concealment and randomisation)
d. i=73%. Heterogeneity 73% with random effects model. Considerable CI overlap and 7/8 studies suggest a benefit
e. Unclear allocation concealment and randomisation
f. Confidence interval crossed both MIDs
g. i>50% - heterogeneity detected

Table 83: Clinical evidence profile: catheter re-ablation versus medical therapies

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catheter ablation	Medical therapies	Relative (95% CI)	Absolute		
AF/ Atrial Tachycardia (AT) free (follow-up 3 years)[362]												
1	randomised trials	Very Serious[a]	N/A	no serious indirectness	Serious[b]	none	77	77	RR 1.43 (1.06 to 1.92)	195 more per 1000 (from 27 more to 418 more)	VERY LOW	IMPORTANT
Mortality												
0	No available evidence											
Recurrence of symptomatic AF												
0	No available evidence											

a. In the AAD group, 43 patients (56%) crossed over to undergo re-ablation. In re-ablation group, 21 of the patients with AF recurrences required treatment with antiarrhythmic drugs
b. Confidence intervals crosses one MID.

Table 84: Clinical evidence profile: catheter ablation versus medical therapies for AF with advanced heart failure

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Catheter ablation	medical therapies	Relative (95% CI)	Absolute		
SF-36 mental (follow-up 6 months; Better indicated by higher values)[295]												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	20	18	-	MD 5.5 lower (11.22 lower to 0.22 higher)	VERY LOW	CRITICAL
SF-36 physical (follow-up 6 months; Better indicated by higher values)[295]												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	20	18	-	MD 5 higher (0.37 to 9.63 higher)	VERY LOW	CRITICAL
Maintenance of sinus rhythm (follow-up 6 months)[295]												
1	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/20 (50%)	0/18 (0%)	Peto OR 12.31 (2.96 to 51.3)	500 more (from 270 more to 730 more)	MODERATE	CRITICAL
fatal or non-fatal embolic complications (follow-up 6 months)[295]												
1	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	1/22 (4.5%)	0/19 (0%)	Peto OR 6.45 (0.13 to 328.36)	50 more (from 80 fewer to 170	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
										more)		
Hospitalisation (cardiovascular) (follow-up 6 months)[295]												
1	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none	1/22 (4.5%)	0/19 (0%)	Peto OR 6.45 (0.13 to 328.36)	50 more (from 80 fewer to 170 more)	VERY LOW	IMPORTANT
Mortality												
0	No available evidence											CRITICAL

[b] Confidence interval crossed one MID
[c] Baseline differences
[d] Confidence interval crossed two MIDs

17.2.2 Economic evidence

Published literature

Two studies were included that compared ablation to alternative strategies as first line therapy for AF.[7,23] Three studies were included that compared ablation to alternative strategies as second line therapy for AF. [13,30,36,37] These are summarised in the economic evidence profile below and the economic evidence tables in Appendix H.

Ten studies that potentially met the inclusion criteria were selectively excluded, due to having less applicability than the included studies (for example, not considering quality of life information), or had more methodological limitations than the included studies (for example, deriving treatment effect and resource utilisation from observational and longitudinal studies)[31 43 15,16,18,22,25,27,31,46] – these are summarised in Appendix K, with reasons for their exclusion given.

See also the economic article selection flow chart in Appendix E.

Table 85: Economic evidence profile: Ablation versus no ablation (continued drug therapy) as first line treatment

Study	Applicability	Limitations	Other comments	Total cost (£)	Total effects (QALY gained)	Cost effectiveness (£ per QALY gained)	Uncertainty
Chan (2006), USA[82]	Partially Applicable (a)	Potentially serious limitations (b)	Markov model with results sub grouped according to age and stroke risk (c) Classification of AF not specified. Interventions: 1. RC+W 2. Ami + W 3. CA + W 4. RC+ASA 5. Ami+ASA 6. CA+ASA	**Moderate stroke risk 65 years | 55 years** 1: 24915|31947 2: 27424|36291 3: 33124|37558 **Low stroke risk 65 years** 4: 15522 5: 24304 6: 27221	**Moderate stroke risk 65 years | 55 years** 1: 10.81|13.95 2: 10.75|13.81 3: 11.06|14.26 **Low stroke risk 65 years** 4: 11.21 5: 11.02 6: 11.40	**Moderate stroke risk 65 years | 55 years** 1: Reference 2: Dominated by intvn 1|Dominated by intvn 1 3: 32764|18153 **Low stroke risk 65 years** 4: Reference 5: Dominated by intvn 4 6: £62555	Probabilistic Sensitivity Analysis indicated that CA 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 simulations using a $20K (£12650) 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 CA efficacy (i.e. annual risk of stroke in NSR would need to decrease by 42% to yield an ICER below $50,000). CA efficacy rates of less than 75% would require a >50% risk reduction in stroke with NSR. Lower CA efficacy rates are required for younger patients which are exposed to risks of anticoagulation for longer. Results for other parameter variation were not tabulated.
Khaykin (2009), Canada[23]	Partially applicable (d)	Potentially serious limitations (e)	Cost comparison study based on the RAAFT trial. Population with symptomatic	**Initial treatment cost:** 1: 5486 2: 1340 **1 year follow up** 1: 6722 2:3173 **2 year follow up**	**Not applicable**	**Incremental cost:** **Between year 1 and 2 of** the study: 1: 1236 2: 1830 **Between year 1 and 2 of the study:**	Costs of anticoagulation therapy, ablation, telemetry admission, days spent in hospital, timing of recurrence, 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 CA ranging from $13796 to $16810. However within each analysis

Study	Applicability	Limitations	Other comments	Total cost (£)	Total effects (QALY gained)	Cost effectiveness (£ per QALY gained)	Uncertainty
			AF (f) Interventions: 1: CA 2: AAD	1: 8022 2: 7544		1: 1300 2: 4371 Authors suggest therefore that between years 2 and 3 cost neutrality will occur	cost difference did not equate more than $1500. It remains uncertain when cost neutrality would occur.

Abbreviations: AF = Atrial fibrillation, ASA = aspirin, AMI = Amiodarone, AAD = antiarrhythmic drugs, ICER = Incremental Cost Effectiveness Ratio, INR = International Normalized Ratio, RC = rate control, CA = catheter ablation, W = warfarin, USA = United States of America,

a) A cost utility analysis using a probabilistic markov model from a USA provider perspective with a 3% discount rate.
RC therapy consisted of a combination of digoxin and atenolol, initial conversion rate to NSR of 38%, and a relapse rate of 5% thereafter. AMI therapy was not specified but had an overall conversion rate of 85% and a reversion rate of 30% in the first 6 months, and 5% thereafter. CA assumed efficacy of 80% with 30% redo rate in first year and a relapse rate of 2%.

b) A potentially serious limitation is that the model did not assess the reduction of symptoms and associated accumulated quality of life improvement. Inclusion of this parameter may have changed the conclusions of the analysis by improving cost effectiveness of ablation. Further, the assumption that ablation may impact on stroke risk may be flawed.

c) A moderate risk of stroke was defined as having one risk factor (hypertension, diabetes mellitus, coronary artery disease or congestive heart failure), a low risk of stroke was defined as having no risk factors, and a high risk of stroke (≥ two risk factors) was not examined.

d) A decision analytic model from a Canadian provider perspective to determine time of cost neutrality between compared interventions, with deterministic sensitivity analysis to assess uncertainty. A discount rate of 3% was applied.

e) 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 CA is assumed to be more clinically effective (in terms of symptom control and reduction in adverse events including stroke) than AAD.
Stroke risk not specified but patients were reported to keep within INR therapeutic range regardless of $CHADS_2$ score.

f) 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 crossed over to ablation if drug refractory. RFA therapy consisted of PVI with 3 months of warfarin anticoagulation for at least 3 months post ablation.

Table 86: Economic evidence profile: Ablation versus no ablation (continued drug therapy) as second line treatment

Study	Applicability	Limitations	Other comments	Total cost (£)	Incremental effects (QALY gained)	Cost effectiveness (£ per QALY gained)	Uncertainty
McKenna 2009, UK [30] Rogers 2008, UK[380]	Directly Applicable (a)	Potentially serious limitations (b)	Probabilistic markov model with lifetime horizon and UK perspective. Population was predominantly people with paroxysmal AF. Interventions: 1: CA (with no concurrent AAD) 2: AAD	**Lifetime horizon** **1:** $CHADS_2$ 0 = £25240 $CHADS_2$ 1 = £26027 $CHADS_2$ 2 = £26987 $CHADS_2$ 3 = £28343 **2:** $CHADS_2$ 0 = £14417 $CHADS_2$ 1 = £15367 $CHADS_2$ 2 = £16157 $CHADS_2$ 3 = £18107	**Lifetime horizon** **1:** $CHADS_2$ 0 = 12.37 $CHADS_2$ 1 = 12.14 $CHADS_2$ 2 = 11.87 $CHADS_2$ 3 = 11.49 **2:** $CHADS_2$ 0 = 10.98 $CHADS_2$ 1 = 10.77 $CHADS_2$ 2 = 10.52 $CHADS_2$ 3 = 10.19	**Lifetime horizon** $CHADS_2$ 0 = 7763 $CHADS_2$ 1 = 7780 $CHADS_2$ 2 = 7765 $CHADS_2$ 3 = 7910	The probability that the intervention for each $CHADS_2$ score using £20K/£30K threshold presented for a lifetime horizon: $CHADS_2$ 0 = 98.3%/99.6% $CHADS_2$ 1 = 98.1%/99.6% $CHADS_2$ 2 = 98.6%/99.9% $CHADS_2$ 3 = 99.2%/100% Scenario analysis suggests that duration of benefit is likely to be a key determinant of cost effectiveness, with treatment effects of less than 5 years likely to lead to a cost per QALY gained to be over £20,000. No scenario changed the conclusion of cost effectiveness using a lifetime horizon and a 20K threshold, including an annual probability of 15% reversion back to AF after CA.
Eckard 2009, Sweden[137]	Partially Applicable (c)	Potentially Serious Limitations (d)	Probabilistic Markov model with lifetime horizon Population was patients with paroxysmal or persistent drug refractory AF. Interventions: 1: CA	1:£15953 2: £19073	1: 9.46 2: 8.68	CA dominated AAD, being less costly and more beneficial.	Probabilistic sensitivity analysis was performed and inspection of cost-effectiveness plane suggests the majority of simulations showed CA to be a dominant strategy (no probability reported). Deterministic analysis of annual reversion post 12 months at 5%, 10% and 15% gave cost per QALY estimates of £5888, £16580 and £30271 respectively.

Study	Applicability	Limitations	Other comments	Total cost (£)	Incremental effects (QALY gained)	Cost effectiveness (£ per QALY gained)	Uncertainty
			2: AAD				
Reynolds 2009, USA[378]	Partially Applicable (e)	Potentially serious limitations (f)	Deterministic Markov model with 5 year horizon. Population was male at 60 years old and had drug refractory paroxysmal AF without severe structural heart disease Interventions: 1: CA 2: AAD	1: £16792 2: £12586 Incremental (Invn 1-2): £4206 (CI =NR ; p = NR)	1: 3.51 2: 3.38 Incremental (Invn 1-2): 0.13 (CI = NR; p = NR)	£32,531	Probabilistic analysis not undertaken A scenario whereby age and sex related background mortality was removed from the analysis reduced the cost per QALY to £29939 From inspection of graphs presented for deterministic sensitivity analysis it seems in comparison to base case values reduced ablation cost, increased rate control cost, single procedure success rate, decreased utility of the rate control and anticoagulation therapy states, and increased utility of the well post ablation states would be required in isolation or combination to infer cost effectiveness of CA using the £20,000 threshold. Results were not quantitatively reported from these analyses (see appendix for more detail)

Abbreviations: AF = Atrial fibrillation, ASA = aspirin, AMI = Amiodarone, AAD = antiarrhythmic drugs, ICER = Incremental Cost Effectiveness Ratio, INR = International Normalized Ratio, RC = rate control, CA = catheter ablation, , W = warfarin, USA = United States of America

a) *Rogers 2008 in an HTA and McKenna 2009 in a subsequent paper present a UK Economic evaluation comparing radiofrequency catheter ablation (CA) to long term antiarrhythmic drug (AAD) therapy using Amiodarone (200mg daily, per annum). The population was adults with AF refractory to at least one drug, and sub grouped according to $CHADS_2$ score. Evaluation conducted by construction of a decision tree feeding into Markov model which used findings from a systematic review and meta-analysis, with NHS reference costs supplemented with expert opinion and observational study costings where data standard sources not available. Treatment effect extrapolated post 5 years. SF36 quality of life scores mapped to EQ5D.*

b) *Probabilistic analysis was performed QoL values were mapped from SF36 questionnaire to the EQ5D and treatment effect was extrapolated post 5 years of follow up It was felt reasonable to assume that quality of life improvement would be sustained if the patient did not revert to AF. The key limitation was the assumption that stroke risk would be influenced by the use of catheter ablation, which runs counter to the evidence found in the clinical review. However, the fact that ablation was found to be cost effective at lower risk strata for stroke indicates it is unlikely this assumption would change conclusions regarding cost effectiveness of the intervention.*
c) *Eckard et al. present a cost utility analysis using a probabilistic Markov model over a lifetime horizon. It assumed no rate of reversion for CA after the first year. Quality of life was reviewed CA therapy had a 0.780 probability of being AF free at 12 months, and AAD had a 0.090 probability of being AF free at 12 months. Neither intervention was well specified, and assumed to be similar to the interventions specified in Stabile et al (2006).*
d) *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 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.*
e) *Reynolds et al. present a cost utility analysis using a Markov model from a USA provider perspective. No discount rate reported for the 5 year horizon of the model.*
f) *CA ± AAD therapy was not clearly specified but assumed to have a 60% efficacy rate, with 25% rate of repeat procedures and a 10% overall failure rate. AAD was assumed to have a 25% AF recurrence rate as first line treatment and 35% as second line treatment. Patients on AAD therapy could not cross over to ablation. Ablation assumed to have no benefit on stroke risk. 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. Assumes that ablation does not decrease risk of stroke. Takes into account differential utility for different treatment strategies.*

Economic evidence

Left atrial catheter ablation as first line therapy

Chan and colleagues[82]compared left atrial catheter ablation to rhythm control with amiodarone, and rate control with a combination of digoxin and atenolol , using data sources which estimated treatment effect using the interventions as a first line therapy. Patients also received antiplatelet or anticoagulant therapy; the choice of which was dependent on the risk of stroke. The benefit in this analysis was primarily driven by stroke reduction, and therefore the efficacy of the relative antithrombotic therapies are also an important driver of cost effectiveness. Where patients failed ablation or withdrew from amiodarone due to adverse effects, they crossed over to rate control therapies, assuming the same risks as the group that was commenced on rate control.

In patients with moderate and low risk of stroke, who are respectively on warfarin and aspirin as choice of antithrombotic therapy, treatment with amiodarone therapy was found to be more costly and less effective than rate control therapy (i.e. a dominated option that cannot be considered further in incremental analysis). Further, a cost comparison study by Khaykin et al. [23] suggested that the costs associated with rhythm control therapy would be greater than that of ablation therapy within three to four years in patients with symptomatic AF. Within a time frame of five years, it appears unlikely that rhythm control would be cost effective when compared to either rate control or ablation therapy.

For 65-year-old patients with AF at moderate and low risk of stroke and on warfarin therapy or aspirin therapy respectively, ablation (with an 80% efficacy rate) was estimated to be more effective but more costly than the next best option i.e. rate control[82]. In comparison to rate control, in both risk groups the cost per QALY gained was higher than £20,000 per QALY gained. For younger patients (55 years of age) with moderate risk of stroke, it is less certain whether rate control is the most cost-effective option for the same cost per QALY threshold.

A key limitation of the Chan et al study[82] is the lack of consideration given to the potential in the improvement of quality of life with the improvement of symptoms i.e. recurrent arrhythmias. Such symptoms are more probable than stroke in this population. The accumulative benefit of ablation therefore could be underestimated, especially as in the UK, ablation would normally be performed only on highly symptomatic patients. As Chan et al.[82] assessed ablation as a first line therapy, application of their results to assess cost effectiveness of ablation as a second line therapy could underestimate the cost effectiveness of ablation (as the relative effect of rate and antiarrhythmic pharmacological therapy may be overestimated).

Left atrial catheter ablation as second line therapy

When considering ablation as a second line therapy, general conclusions of all three analyses were consistent once the time horizon of the models had been taken into account. Where treatment effect had not been extrapolated beyond 5 years (i.e. in Reynolds 2009[378] and in the sensitivity analyses of McKenna 2009[30] and Rogers 2008[380]), ablation had a cost per QALY above the £20,000 threshold. In analyses where a lifetime horizon had been applied, ablation either dominated rhythm control (being less costly and more effective)[137] or achieved a cost per QALY gained below £20,000 in the range of sensitivity analysis explored[30,37]. This included testing an annual probability of 15% reversion back to AF after Catheter Ablation (CA).

Reynolds[378] did not consider prevention of stroke, whereas Eckard[137] regarded stroke prevention as a principle driver of cost effectiveness of ablation. McKenna and Rogers,[30,37] who stratified their results according to risk of stroke, stressed the importance of the differential in the quality of life between patients which have and have not had ablation. However, their results show that ablation is most cost effective and almost 100 per cent certain to be cost effective in patients with the highest stroke risk. However, the assumption that reversion to sinus rhythm reduces stroke risk is potentially flawed, with no evidence to date available to support this.

It is also important to note that all analyses compared ablation to antiarrhythmic drugs, where patients had already failed first line treatment.

Unit costs
In the absence of recent UK cost-effectiveness analysis, relevant unit costs were provided to aid consideration of cost effectiveness. The average NHS reference cost for a Percutaneous Complex Ablation (including that for Atrial Fibrillation or Ventricular Tachycardia) is £5,322 (HRG code EA29Z).

17.2.3 Evidence statements

Clinical

Atrial Fibrillation:

Moderate quality evidence showed left atrial catheter ablation is more clinically effective compared to medical therapies at:

- improving SF-36 physical and mental (4 years follow-up) scores compared to medical therapies (one study, N=186).
- reducing recurrence of AF (4 years follow-up) (one study, N=198).

Low to very low quality evidence showed there may be no clinical difference between left atrial catheter ablation and medical therapies in (but the direction of the estimate of effect could favour either intervention):

- reducing mortality (three studies, N=676).
- reducing stroke (two studies, N=539).
- reducing hospitalisation for heart failure (one study, N=294).

Very low quality evidence showed that re-ablation may be more clinically effective than medical therapies at reducing recurrence of AF in patients with paroxysmal AF and a previous failed ablation (one study, N=155).

Atrial fibrillation and advanced heart failure:

Very low quality evidence showed there may be no clinical difference between left atrial catheter ablation and medical therapies on SF-36 mental scores, the direction of the estimate of effect favoured medical therapies (one study, N=38).
Very low quality evidence showed left atrial catheter ablation may be more clinically effective at improving SF-36 physical scores when compared to medical therapies (one study, N=38).
Moderate quality evidence showed that left atrial catheter ablation is more clinically effective at maintaining sinus rhythm compared to medical therapies (one study, N=38).
Very low quality evidence showed there may be no difference between left atrial catheter ablation and medical therapies on fatal or non-fatal embolic complications, but the estimate of effect could favour either intervention (one study, N=41).

Economic
Ablation as first line therapy

- One cost–utility analysis found that catheter ablation with concurrent warfarin was not cost effective compared to rate control methods with concurrent warfarin for patients with low risk of stroke (ICER: £62555 per QALY gained) or for patients with moderate risk of stroke who are aged 65 and above (ICER: £32764 per QALY gained). The same study found that left atrial catheter ablation with concurrent warfarin may be cost effective compared to rate control methods with concurrent warfarin for patients with moderate risk of stroke and aged below 65 years (ICER:

£18153 per QALY gained). This is based on evidence of partial applicability and potentially serious limitations.

- One cost-minimization study found that left atrial catheter ablation may reach cost neutrality when compared to antiarrhythmic drugs between years two and three following treatment. This is based on evidence of partial applicability and potentially serious limitations.

Ablation as second line therapy

- One cost–utility analysis found that left atrial catheter ablation as a second line therapy was cost effective compared to second line rhythm control for patients with paroxysmal AF (ICER: £7763 to £7910 per QALY gained, dependent on stroke risk). This is based on evidence of direct applicability and potentially serious limitations.
- One cost–utility analysis found that left atrial catheter ablation as a second line therapy was dominant (less costly and more effective) compared to second line rhythm control. This is based on evidence of partial applicability and potentially serious limitations.
- One cost–utility analysis found that left atrial left atrial catheter ablation as a second line therapy was not cost effective compared to second line rhythm control (ICER: £32,531 per QALY gained). This is based on evidence of partial applicability and potentially serious limitations.
- No economic evidence was identified that compared left atrial catheter ablation as a second line therapy when compared to second line rhythm control in patients with persistent AF.

17.3 Review question: What is the clinical and cost effectiveness of surgical ablation compared to non-ablation therapies in people with AF?

For full details see review protocol in Appendix C.

Table 87: PICO characteristics of review question

Population	People with paroxysmal, permanent or persistent AF who are having pure ablation (lone ablation) or concomitant ablation (with other surgery) Sub-group analysis – age (if analysis reports results separately) Note patients that left atrial appendage removed
Intervention/s	Surgical ablation (with or without concomitant cardiac surgery); including Radiofrequency ablation Microwave ablation Cryoablation Ultrasound Cut and sew MAZE procedure Pulmonary Vein Isolation (PVI)
Comparison/s	Non ablation therapies: Surgery without ablation Rhythm control drugs Cardioversion Cardioversion and drug therapy Rate control drugs
Outcomes	All-cause mortality (reported at 30 days and longest endpoint) Maintenance of sinus rhythm/ Recurrence of atrial fibrillation Health related quality of life

	Stroke or thromboembolic complications Major bleeding including intracranial bleeding Re-hospitalisation (cardiovascular) Necessity for concomitant antiarrhythmic drug therapy
Exclusion	Heart transplant patients
Study design	Randomised controlled trials (RCTs) and systematic reviews

17.3.1 Clinical evidence

We searched for systematic reviews and RCTs comparing surgical ablation (with or without concomitant cardiac surgery) with non-ablative therapies.
Seventeen studies were included in the review [1-3,5,9-12,19-21,38,39,41,4363,214]. All of these studies involved surgical ablation concomitant with other cardiac surgery, and there were no studies found using stand-alone surgical ablation.
Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 89**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 88: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes
Abreu Filho 2005 [4]	Mitral valve (MV) surgery associated with a modified Maze III procedure using saline irrigated cooled tip radio-frequency ablation (SICTRA) versus MV surgery alone	Patients with permanent AF pre-existing for more than 1 year and rheumatic MV disease	Mortality; Rhythm status; Thrombo-embolic events.
Akpinar 2003 [11]	Port access mitral valve surgery plus modified radiofrequency (RF) Maze versus port access mitral valve surgery alone	Patients with persistent AF for more than 6 months and undergoing minimally invasive port access valve surgery	Mortality; Rhythm status; Functional capacity; Thrombo-embolic events.
Albrecht 2009[15]	Mitral valve surgery plus modified Maze (Cox maze III) or surgical isolation of the pulmonary veins (SPVI) versus mitral valve surgery alone	Patients with persistent AF and mitral valve disease requiring surgery	Mortality; Sinus rhythm; NYHA
Blomstrom-Lundqvist 2007[49]	Surgery plus epicardial left atrial cryoablation versus surgery alone	Patients aged 18-80 years with persistent AF for at least 3 months and mitral valve disease requiring surgery	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, morbidity and the incidence of predefined adverse events.
Budera 2012[63]	Coronary artery bypass graft	Indication cardiac	Death;

Study	Intervention/comparison	Population	Outcomes
	(CABG) and/or valve surgery plus left atrial surgical ablation, left atrial appendage surgical resection and three other lesions versus CABG and/or valve surgery alone	surgery and AF (paroxysmal, persistent, or long-standing persistent)	Stroke; Maintenance of sinus rhythm
Chevalier 2009[87]	MV surgery plus radio frequency ablation (RAF) versus MV surgery alone	Patients ≥ 18 years who were admitted for mitral valve disease requiring surgery that was associated with persistent AF evolving for more than six months, were eligible.	Mortality; Rhythm status; thrombo-embolic event
De Lima 2004[118]	MV surgery plus Maze III or PVI versus MV surgery alone	Patients referred for MV surgery between the ages of 18 and 75 years who had persistent AF lasting for more than 6 months before the surgery.	Mortality; Rhythm status; thrombo-embolic event; functional improvement as measured by the NYHA class; drug use
Deneke 2002[122]	MV surgery plus modified MA versus MV surgery alone	30 consecutive patients in whom mitral valve replacement and persistent AF were indicated by permanent AF for 1 year or at least two non-successful medical or electrical cardioversions 6 months before surgery.	Primary end-point was sinus rhythm at postoperative follow-up. Secondary end-points were clinical outcome, survival, atrial transport function and functional capacity at follow-up.
Doukas 2005[135]		97 patients requiring mitral valve surgery and who also had a history of persistent atrial fibrillation for at least 6 months which was unresponsive to medical treatment or cardioversion.	Primary end-point was sinus rhythm at 12 months. Secondary end-points included patient functional status and exercise capacity, left atrial contractility and left atrial and left ventricular dimension and function and plasma levels of B-type natriuretic peptide.
Jessurun 2003[212]	Surgery plus Maze III versus surgery alone	Patients <75 selected for mitral valve surgery with symptomatic AF, irrespective of type and duration of the arrhythmia	Sinus rhythm without AF; death, stroke and preserved sinus node function and quality of life.

Study	Intervention/comparison	Population	Outcomes
Johansson 2012[213]	MV surgery plus cryoablation versus MV surgery alone	Patients aged 18 to 80 years with persistent AF for at least 3 months and mitral valve disease requiring mitral valve surgery were eligible.	Restoration of sinus rhythm; left ventricular diastolic diameter; left ventricular ejection fraction.
Jonsson 2012[214]	MV surgery and atrial microwave ablation versus MV surgery alone	Scheduled for MV surgery with long-lasting AF of more than 12 months duration prior to surgery.	Maintenance of sinus rhythm; concomitant therapy; mortality; thromboembolic complications.
Khargi 2001[233]	MV surgery plus cooled tip radio-frequency maze versus MV surgery alone	Patients with documented persistent atrial fibrillation, pre-existing for more than 1 year and mitral valve disease	Mortality; Rhythm status
Schuetz 2003[394]	Surgery plus microwave energy plus atrial size reduction versus surgery alone	Patients with persistent AF who had been unsuccessfully treated who presented to clinic and required surgery for valvular disease or CABG	Mortality; Rhythm status
Srivastava 2008[417]	Surgery plus biatrial Maze Surgery plus left atrial Maze Surgery plus pulmonary vein isolation Maze versus surgery alone	Patients with rheumatic valvular heart disease in chronic atrial fibrillation (more than 3 months)	Mortality; Rhythm status – conversion to NSR; AF free survival at one-year duration
Van Breugel 2010[437]	Surgery plus ablation Surgery alone	Patients with a history of documented paroxysmal or persistent AF for at least three months prior to surgery	Mortality; Sinus rhythm; Recurrent AF; SF36 scores
von Oppell 2009[451]	Surgery plus biatrial modified radio-frequency Maze surgery versus surgery alone	Patients with persistent AF and mitral valve disease requiring surgical treatment	Sinus rhythm; Quality of life using SP-36; NYHA functional class; changes in antiarrhythmic and anticoagulant medication, adverse events; ECG and echocardiogram results

Table 89: Clinical evidence profile: surgical ablation versus surgery alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery + ablation	surgery alone	Relative (95% CI)	Absolute		
All-cause mortality reported at 30 days (follow-up 0-30 days; assessed with: Death) [4,11,15,50,63,87,118,122,135,212-214,234,394,417,451]												
16	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	None	30/643 (4.7%)	16/491 (3.3%)	RR 1.42 (0.82 to 2.47)	14 more per 1000 (from 6 fewer to 49 more)	LOW	CRITICAL
All-cause mortality at longest endpoint (follow-up 5 years; assessed with: Death) [4,11,15,50,63,87,118,122,135,212-214,234,394,417,451]												
16	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	None	40/621 (6.4%)	28/475 (5.9%)	RR 1.07 (0.69 to 1.68)	4 more per 1000 (from 18 fewer to 40 more)	VERY LOW	CRITICAL
All-cause mortality overall; Van Breugel (follow-up 12 months; assessed with: Death)[437]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	very serious[c]	None	2/65 (3.1%)	5/67 (7.5%)	RR 0.41 (0.08 to 2.05)	44 fewer per 1000 (from 69 fewer to 78 more)	VERY LOW	CRITICAL
Maintenance of sinus rhythm at longest time point (follow-up 6-60 months; assessed with: ECG)[4,11,15,50,63,87,118,122,135,212-214,234,394,417,437,451]												
17	randomised trials	serious[a]	serious[e]	no serious indirectness	no serious imprecision	None	437/640 (68.3%)	149/512 (29.1%)	RR 2.34 (1.86 to 2.94)	390 more per 1000 (from 250 more to 565 more)	LOW	CRITICAL
Recurrent AF at longest endpoint (follow-up 5 years; assessed with: ECG)[4,15,118,394,417,451]												
6	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	61/278 (21.9%)	91/162 (56.2%)	RR 0.40 (0.31 to 0.52)	337 fewer per 1000 (from 270 fewer to 388 fewer)	MODERATE	CRITICAL
SF-36 - Bodily pain; Von Oppell change scores (follow-up 1 years; measured with: SF-36; Better indicated by higher values)[451]												
1	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	None	24	23	-	MD 6.00 lower (8.34 to 3.66 lower)	MODERATE	CRITICAL
SF-36 - Role emotional; Von Oppell change scores (follow-up 1 years; measured with: SF-36; Better indicated by higher values)[451]												
1	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	no serious imprecision	None	24	23	-	MD 21 lower (24.42 to 17.58 lower)	MODERATE	CRITICAL
SF-36 - Mental health; Von Oppell, change scores (follow-up 1 years; measured with: SF-36; Better indicated by higher values)[451]												
1	randomised trials	serious[f]	no serious inconsistency	no serious indirectness	serious[g]	None	24	23	-	MD 7 lower (10.88 to 3.12 lower)	LOW	CRITICAL
SF-36 Physical functioning; Van Breugel end scores (follow-up 1 years; measured with: SF-36; Better indicated by higher values)[437]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[h]	None	63	62	-	MD 7.18 higher (1.07 lower to 15.43 higher)	LOW	CRITICAL
SF-36 Mental health; Van Breugel end scores (follow-up 1 years; measured with: SF-36; Better indicated by higher values)[437]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[i]	None	63	62	-	MD 3.70 higher (1.71 lower to 9.11 higher)	LOW	CRITICAL
SF-36 Physical pain; Van Breugel end scores (follow-up 1 years; measured with: Sf-36; Better indicated by higher values)[437]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[j]	None	63	62	-	MD 4.97 higher (2.84 lower to 12.78 higher)	LOW	CRITICAL

SF-36 Vitality; Van Breugel end scores (follow-up 1 years; measured with: Sf-36; Better indicated by higher values)[437]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	None	63	62	-	MD 1.37 higher (4.73 lower to 7.47 higher)	MODERATE	CRITICAL
SF-36 Role limitations due to emotional problems; Van Breugel end scores (follow-up 1 years; measured with: SF-36; Better indicated by higher values)[437]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	None	63	62	-	MD 2.59 higher (10.1 lower to 15.28 higher)	MODERATE	CRITICAL
SF-36 Social functioning; Van Breugel end scores (follow-up 1 years; measured with: SF-36; Better indicated by higher values)[437]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	no serious imprecision	None	63	62	-	MD 3.83 higher (3.95 lower to 11.61 higher)	MODERATE	CRITICAL
Thromboembolic events at longest endpoint (follow-up 1 years; assessed with: Scan)[4,12,15,50,63,87,214]												
7	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[c]	None	16/316 (5.1%)	17/264 (6.4%)	RR 0.78 (0.27 to 2.25)	14 fewer per 1000 (from 47 fewer to 80 more)	VERY LOW	IMPORTANT
Concomitant antiarrhythmic drug therapy at longest endpoint (follow-up 24 months; assessed with: Clinical record)[50,63,118,212,214]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	None	57/203 (28.1%)	37/164 (22.6%)	RR 1.22 (0.84 to 1.75)	50 more per 1000 (from 36 fewer to 170 more)	LOW	IMPORTANT
SF-36 Role limitations due to physical limitations; Van Breugel change from baseline (follow-up 1 years; measured with: SF-36; Better indicated by higher values)[437]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[k]	None	62	63	-	MD 0 higher (0 to 0 higher)	LOW	CRITICAL
SF-36 General Health; Van Breugel change from baseline (follow-up 1 years; measured with: SF-36; Better indicated by higher values)[437]												
1	randomised trials	serious[d]	no serious inconsistency	no serious indirectness	serious[k]	None	1	-	-	MD 0 higher (0 to 0 higher)	LOW	CRITICAL

a. Blinding not possible for surgical team. Randomisation and allocation concealment not consistently reported.
b. Confidence interval crossed one MID (1.25)
c. Confidence interval crossed two MIDs (0.75 and 1.25)
d. Allocation concealment not described.
e. Unexplained heterogeneity, I-squared >50% fixed and random effects models
f. Single blinding. Randomisation and allocation concealment not described.
g. Confidence interval crosses 3.39
h. Confidence interval crosses 11.93
i. Confidence interval crosses 8.73
j. Confidence interval crosses 10.97
k. Large difference in baseline scores makes measurement of imprecision not possible

17.3.2 Economic evidence

Published literature

Two studies were included with the relevant comparison.[28,42] These are summarised in the economic evidence profile below and the economic evidence tables in Appendix H. There were no excluded studies.

See also the economic article selection flow chart in Appendix E.

Table 90: Economic evidence profile: Concurrent cardiac surgery with ablation versus no concurrent ablation as part of cardiac surgery

Study	Applicability	Limitations	Other comments	Total cost (£)	Total effects (QALY gained)	Cost effectiveness (£ per QALY gained	Uncertainty
Lamotte 2007, [258] UK	Directly applicable(a)	Minor limitations b)	Markov model Population was patients with coronary or valvular disease undergoing CABG or valve replacement with concomitant AF	For Permanent| Persistent| Paroxysmal AF **No ablation:** 2513|2318|2317 **Classic maze:** 3233|3203|3173 **Surgical ablation:** 4567|4487|4457 **left atrial catheter ablation:** 5538|5497|5438	Permanent| Persistent| Paroxysmal AF **No ablation:** 2.5297|2.8835|2.8843 **Classic maze:** 3.0658|3.1385|3.1704 **Surgical ablation:** 3.0425|3.1747|3.2056 **Left atrial catheter ablation:** 2.9593|3.0665|3.1285	**INCREMENTAL ANALYSIS** Permanent| Persistent| Paroxysmal AF **Classic maze vs. no ablation:** 1343|3471|3471 **Surgical ablation vs. classic maze:** Dominated by classic maze|40,250 |36477 **Left atrial catheter ablation vs. surgical ablation:** Dominated by surgical ablation	Sensitivity analysis examined differential discount rate, utility, cost of interventions (by ±50%), complication rates of MAZE and a longer time horizon of 10 year.
Van Breugel,[438] Holland	Partial applicability c)	Potentially serious limitations d)	Within trial economic analysis with a population of patients with AF undergoing usual cardiac surgery.	**Ablation with surgery** 13 365 **Cardiac surgery without ablation** 10241 Mean difference: 3124 (95%CI: 2021 to 4308)	**Ablation with surgery** 0.75 **Cardiac surgery without ablation** 0.69 Mean difference: 0.06 (CI = NR)	£53,167 per QALY gained (via bootstrap) [95%CI: £33683 to £71800]	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

Study	Applicability	Limitations	Other comments	Total cost (£)	Total effects (QALY gained)	Cost effectiveness (£ per QALY gained	Uncertainty
							(inspection of graph).

Abbreviations: AF = Atrial fibrillation, CI = confidence Interval; ICER = Incremental Cost Effectiveness Ratio; NR =Not reported; QALY = Quality Adjusted Life Year

a) A deterministic Markov model from a UK NHS perspective. Classic Maze procedure is a type of treatment that has limited applicability in this review.

b) 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. It was felt reasonable to assume the difference in cost between the surgery with or without the concurrent MAZE procedure to be one day in ICU, whereas cost of surgical ablation was estimated using market averages quoted by industry. It is uncertain whether the definitions used for type of AF (permanent, persistent and paroxysmal AF) in the study are applicable to current understanding.

c) Deterministic within trial analysis from Dutch provider perspective. Comparator of cardiac surgery as usual poorly specified.

d) Reliant on one source for treatment effect and resource use, which is detailed in the clinical review [41]. Short time horizon of one year will not take into account downstream effects and cost, for example the event of stroke was not taken into account. However, as it is unclear whether ablation reduces the risk of stroke this may be a minor limitation in incremental analysis. The impact of adverse events was not detailed specifically.

Economic evidence continued

It is uncertain whether concomitant ablative surgery during other cardiac surgery is cost effective in comparison to usual surgery alone. One within trial analysis[42] suggested that the higher procedural costs of add on ablation during cardiac surgery would not be offset by the reduced cost of decreased number of general practitioner visits, emergency hospital visits and reduced medication costs. The QALY gain of the add-on ablation was not sufficient to justify the cost using a £20,000 threshold. This analysis only had a follow up period of one year; however as the reduction of healthcare resource use was minimal it is unlikely that the outlay cost would be offset in the lifetime of the patient, unless a difference in costly downstream events occurs i.e. stroke. Without a difference in the occurrence of downstream events, it would be the duration and magnitude of health benefit that would be important in determining cost effectiveness of the intervention over a longer time horizon.

A Markov model[258] evaluated different forms of concomitant surgical ablation, high intensity focused ultrasound (HIFU)-assisted surgical ablation or the MAZE procedure together with subsequent percutaneous left atrial catheter ablation and pharmacological treatment. This model showed the "cut and sew" maze procedure to be the most cost-effective option. The strategy of subsequent percutaneous ablation was dominated by HIFU assisted surgical ablation and the MAZE procedure, which the authors considered was due to the need for the subsequent procedure which incurs cost and additional risk of associated adverse events. The analysis shows however, that all add on procedures could be seen as cost effective in a pairwise comparison to pharmaceutical therapy.

The conflicting findings between the within trial analysis and Markov model may be in part be explained by the higher incremental QALY gains found with add on ablation accrued over a longer time horizon in the Markov model and the consideration of stroke as a downstream event.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs were provided to aid consideration of cost effectiveness. To note, no NHS reference cost was identified for surgical ablation as a lone intervention, however it may be coded as "Other Non-Complex Cardiac Surgery (EA40Z), which has a unit cost for elective inpatients of £5,998 (IQR of £3689 to £8173).

Table 91: Unit costs of surgical procedures with and without concomitant ablation.

Reference cost HRG	National average unit cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average cost of excess bed day	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Weighted national average	Weighted average length of stay	NOTES
Coronary Artery Bypass Graft (First Time) (EA14Z); as recorded for Elective Inpatients	£9,049	£7,806	£10,668	£322	£175	£385	£9,160	6.07	The number of data submissions for this code was 37, with 6924 units of activity.
Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention, Pacing, EP or RFA (EA16Z); as recorded for Elective Inpatients	£8,706	£7,780	£10,315	£459	£92	£872	£8,834	6.58	The number of data submissions for this code was 24, with 2445 units of activity.
Single Cardiac Valve Procedures (EA17Z); as recorded for Elective Inpatients	£10,795	£8,804	£12,234	£390	£221	£434	£10,931	6.63	The number of data submissions for this code was 35, with 3516 units of activity.
Single Cardiac Valve Procedures with Percutaneous Coronary Intervention, Pacing, EP or RFA (EA19Z); as recorded for Elective Inpatients	£12,071	£9,908	£12,527	£286	£50	£358	£12,195	8.37	The number of data submissions for this code was 29, with 1750 units of activity.
Other Complex Cardiac Surgery and Re-do's (EA20Z); as recorded for Elective Inpatients	£11,055	£8,799	£13,079	£264	£104	£330	£11,166	7.85	The number of data submissions for this code was 43, with 771 units of activity.
Other Complex Cardiac Surgery with Percutaneous Coronary Intervention, Pacing, EP or RFA (EA22Z); as recorded for Elective Inpatients	£16,938	£12,725	£24,766	£189	£53	£53	£17,090	10.72	The number of data submissions for this code was 16, with 130 units of activity.

17.3.3 Evidence statements

Clinical

Low quality evidence showed that surgical ablation with concomitant surgery is more clinically effective, compared to surgery alone at the longest endpoint recorded at:

- maintaining sinus rhythm (seventeen studies, N=1152).
- Reducing AF recurrence (seven studies, N=505)

Low and very low quality evidence showed there *may* be no clinical difference between surgical ablation with concomitant surgery, and surgery alone in:

- reducing mortality at 30 days (sixteen studies, N=1134)
- reducing mortality at longest endpoint after 30 days post-op (sixteen studies, N=1096].
- reducing thromboembolic events at longest endpoint, but the direction of the estimate of effect could favour either intervention (seven studies, N=580).
- reducing concomitant antiarrhythmic drug therapy at longest endpoint, the direction of the estimate of effect favoured surgery alone (seven studies, N=367).

Low and moderate quality evidence showed there is no clinical difference between surgical ablation with concomitant surgery and surgery alone for SF-36 scores (one study, N=47 or 125).

Economic

Ablation as a concurrent add on to cardiac surgery

- One cost–utility analysis found that for patients with AF in whom cardiac surgery is indicated, usual surgery alone and subsequent left atrial catheter ablation or pharmacological therapy is not cost effective in comparison to concurrent add on ablative surgery (ICER: £53,167 per QALY gained). This analysis was assessed as partially applicable with minor limitations.
- One cost–utility analysis found that cardiac surgery and subsequent left atrial catheter ablation was dominated by surgical ablation (with surgical ablation being less costly and more effective). This analysis was assessed as directly applicable with potentially serious limitations.

17.4 Review question: What is the clinical and cost effectiveness of surgical ablation compared to left atrial catheter ablation in people with AF?

For full details see review protocol in Appendix A.

Table 92: PICO characteristics of review question

Population	People with paroxysmal, permanent and persistent AF
Intervention/s	Surgical ablation
Comparison/s	Left atrial catheter ablation
Outcomes	Mortality - all-cause (reported at 30 days and longest endpoint given) Maintenance of sinus rhythm Heath related quality of life Stroke or thromboembolic complications

	Major bleeding including intracranial bleeding Re-hospitalisation (cardiovascular) Necessity for concomitant antiarrhythmic drug therapy Need for a pace maker
Study design	Systematic reviews and randomised controlled trials

17.4.1 Clinical evidence

We searched for systematic reviews and RCTs comparing surgical ablation with left atrial catheter ablation. One study was included in the review.[6] This compared surgical ablation with left atrial catheter ablation in patients with antiarrhythmic drug refractory atrial fibrillation referred for invasive treatment. Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 94**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

Table 93: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes
Boersma 2012[6]	Surgical ablation – bipolar radiofrequency isolation of the bilateral pulmonary vein, ganglionated plexia ablation and left atrial appendage excision with optional additional lines Left atrial catheter ablation – linear antral pulmonary vein isolation and optional additional lines.	People with antiarrhythmic drug refractory atrial fibrillation (33%) or failed prior left atrial catheter ablation (67%) referred for invasive treatment.	Freedom from left atrial arrhythmia; All-cause mortality (30 days); Stroke or thromboembolic complications; Major bleeding

Table 94: Clinical evidence profile: Surgical ablation versus left atrial catheter ablation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical	Catheter	Relative (95% CI)	Absolute		
Mortality (30 days) (follow-up mean 30 days)[52]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	0/61 (0%)	1.6%	RR 0.34 (0.01 to 8.29)	11 fewer per 1000 (from 16 fewer to 117 more)	LOW	CRITICAL
Freedom from left atrial arrhythmia (follow-up mean 12 months)[52]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[a]	none	40/61 (65.6%)	42.9%	RR 1.80 (1.24 to 2.61)	343 more per 1000 (from 103 more to 691 more)	MODERATE	CRITICAL
Stroke or thromboembolic complications (follow-up mean 12 months)[52]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	none	1/61 (1.6%)	4.8%	RR 0.34 (0.04 to 3.22)	32 fewer per 1000 (from 46 fewer to 107 more)	LOW	IMPORTANT
Major bleeding (follow-up mean 12 months)[52]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	1/61 (1.6%)	0%	RR 3.1 (0.13 to 74.58)	-	LOW	IMPORTANT
Quality of life												
0	No evidence available	-	-	-	-	-	-	0%	-	-	-	CRITICAL

a. Confidence interval crossed one MID

b. Confidence interval crossed two MIDs

17.4.2 Economic evidence

Published literature

No relevant economic evaluations comparing surgical ablation with left atrial catheter ablation were identified. There were no excluded studies.

See also the economic article selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided to aid consideration of this.

The NHS reference cost for Percutaneous Complex Ablation, including that for Atrial Fibrillation or Ventricular Tachycardia (HRG code EA29Z) for elective inpatients is £3,915 (IQR of £2599 to £5266).

To note, no NHS reference cost was identified for surgical ablation as a lone intervention, however this may be coded as "Other Non-Complex Cardiac Surgery (EA40Z) which has a unit cost for elective inpatients of £5,998 (IQR of £3689 to £8173).

17.4.3 Evidence statements

Clinical

Moderate quality evidence showed surgical ablation is more clinically effective at increasing freedom from left atrial arrhythmia in patients with antiarrhythmic drug refractory atrial fibrillation, or failed prior left atrial catheter ablation (one study, N=124).

Low quality evidence showed that it is unclear whether there is a difference between surgical and left atrial catheter ablation in reducing mortality, stroke and thromboembolic complications and major bleeding (one study, N=124).

There were no studies that reported health quality of life or maintenance of sinus rhythm.

Economic

No relevant economic evaluations were identified.

17.4.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	Although the most important outcome from AF ablation was considered a reduction in mortality or stroke, to date no study has demonstrated that any method of rhythm control has any impact on these. At present, the primary indication for ablation is improvement in symptoms associated with AF. For this reason in the absence of data adequately examining mortality and stroke risk, the GDG studied other important measurable endpoints including symptoms, quality of life, AF recurrence and AF burden.
Trade-off between clinical benefits and harms	**Left atrial catheter ablation versus medical therapies:** Left atrial catheter ablation was found to be more clinically effective than medical therapies at improving quality of life in paroxysmal AF and reducing recurrence of AF in paroxysmal and persistent AF patients. It was unclear whether there was a difference between left atrial catheter ablation and medical therapies in reducing mortality, stroke, hospitalisation for heart failure and embolic complications in AF patients. The GDG considered that left atrial catheter ablation improved quality of life and reduced symptomatic AF. These benefits should be explained to patients and set against the risk of complications. The success of left atrial catheter ablation was greater in patients with paroxysmal AF than in those with persistent AF. One small study[295] reported on patients with AF and advanced heart failure. The GDG considered that there was a clinical benefit from left atrial catheter ablation compared to medical therapies in improving maintenance of sinus rhythm and SF-36 physical scores. However, there was no clinical difference found in this study for SF-36 mental scores, hospitalisation or embolic complications. **Surgical ablation versus left atrial catheter ablation**: There were no RCTs comparing stand-alone surgical ablation with medical therapy. RCT information was limited to a single trial comparing left atrial catheter and surgical ablation in patients considered less amenable to left atrial catheter ablation, including patients with previous failed catheter ablation. The risks of stand-alone surgical ablation in the setting of heart failure are not clearly defined at this time. **GDG discussion** The GDG considered that in view of the reasonable success rates for left atrial catheter ablation in the management of paroxysmal AF, the relative lack of data on stand-alone surgical ablation and the more invasive nature of surgical ablation, that it was reasonable to recommend that catheter ablation should be offered in preference to surgical ablation in the first line ablation management of patients with paroxysmal AF. In the case of patients with persistent AF, as success rates (restoring and maintaining sinus rhythm) for left atrial catheter ablation are lower, the GDG thought it reasonable to consider both surgical and catheter ablation as options. The GDG

	recommended that the decision regarding which approach is used should be informed by patient preference and the skills and experience available. The GDG were of the opinion that the role of ablation in the management of patients with AF and heart failure was unclear, but that it was reasonable to consider ablation in patients amongst whom AF is considered to be a cause of or contributory to heart failure.
Economic considerations	The health economic evidence reviewed suggested that ablation was cost effective as a second line therapy in comparison to rhythm control as a second line therapy. The key economic trade-off identified in discussion was the high upfront cost of ablation versus the improved quality of life by reduction of symptoms of AF, the potential for reduced healthcare contacts and cost of continued pharmacological therapy as an alternative strategy. The economic studies identified, indicated that the incremental health benefit of ablation would need to be sustained for a period longer than 5 years (i.e. longer than the follow up of the trials) in order for the intervention to be cost effective. However, the GDG were confident this was highly likely given that even with a 15% probability of reversion to AF, post ablation left atrial catheter ablation as a second line option remained cost effective (as tested in a sensitivity analysis in the study of highest methodological quality and applicability (McKenna et al. 2009[310]). However, a key limitation of all models looking at catheter ablation was the implicit assumption that restoration of sinus rhythm via left atrial catheter ablation would necessarily lead to a reduced risk of stroke. This was not considered a reasonable assumption given the lack of evidence demonstrating that a reduction in AF correlates with a reduction in stroke risk. The group felt that as the clinical review did not find evidence to support this assumption, results of such models should be interpreted with caution. In particular, the group felt the Chan et al, model[82] to have potentially very serious limitations as this model, which looked at left atrial catheter ablation as a first line therapy, did not consider quality of life associated with the reduction of symptoms. As such the model results were in part driven by the implicit assumption regarding a reduction in stroke risk due to restoration of normal sinus rhythm, and therefore conclusions regarding cost effectiveness could be inappropriate should this assumption be incorrect. It was felt there was insufficient high quality evidence to base a recommendation in support of ablation as a first line therapy. The studies in principle looked at patients with paroxysmal AF, and the group felt that the cost effectiveness of left atrial catheter ablation as a means to treat persistent AF remains unclear. **Catheter versus surgical ablation:** There was no economic evidence to inform this question. The GDG considered the resource use for both catheter and surgical ablation. For both procedures it was noted devices excluded from the tariff would be used, for example a 3D mapping ablation device. Whilst left atrial catheter ablation might incur high costs for consumables, it was felt this would be offset by the reduced post-operative costs which are incurred with surgical ablation. Overall, and in light of the wide interquartile ranges given by the NHS reference costs, the GDG felt unable to comment which intervention was likely to be less costly. As a clear relative health benefit advantage of neither intervention could be ascertained from the clinical review, the relative cost effectiveness of these interventions remains unclear.
Quality of evidence	**Left atrial catheter ablation versus medical therapies:**

	There were eleven RCTs identified comparing left atrial catheter ablation to medical therapies. The quality of evidence was moderate to very low. Many trials were of small-moderate size, and had selected patients managed by specialist ablation centres. Treatment cross-over was also common. **AF and heart failure:** The study by MacDonald[295] reported outcomes for patients with advanced heart failure, and this study was analysed separately from the rest of the clinical evidence. The study had small numbers an event rates and as such the quality of evidence was very low for all outcomes with serious imprecision except for the maintenance of sinus rhythm that was moderate and had no imprecision. The economic evidence was thought to have potentially serious limitations due to the short time horizon in the within trial analysis (and the need for extrapolation within the model), as well as the assumption that freedom from AF as a surrogate for reduction in stroke risk, when the clinical review did not offer evidence to support this assertion. Despite these limitations however, the GDG concurred with the conclusion that ablation as a second line therapy in paroxysmal AF was a cost-effective strategy. It should be noted that many trials comparing ablation with medical therapy were of small-moderate size, and had selected patients managed by specialist ablation centres. Treatment cross-over was also common. **Surgical versus left atrial catheter ablation:** Only one RCT was identified for this systematic review. The quality of evidence was moderate to low. The study was conducted on two sites that used different techniques for ablation. In addition, length of stay after surgical ablation will varied between countries. This study had a small number of patients with the majority already having had a failed left atrial catheter ablation. The follow up was short and the GDG interpreted this study with caution. **Economic** The GDG regarded studies that used freedom from AF as a surrogate for reduction in stroke risk as poorer quality. This was not considered a reasonable assumption given the lack of evidence demonstrating that a reduction in AF correlates with a reduction in stroke risk.
Other considerations	**Catheter versus medical therapies:** At present, these recommendations will have little impact on current practice. However it should be noted that, given the uncertainty of the benefit of ablation for persistent AF compared to paroxysmal AF, it is reasonable that patients are referred for left atrial catheter ablation as soon as possible after medical therapy has been shown to be unsuccessful. This is because some patients will progress from paroxysmal AF to persistent AF if left untreated. **Surgical versus catheter ablation:** While there was one study demonstrating that surgical ablation is more effective than left atrial catheter ablation in patients who have failed catheter ablation or drug therapy, the view of the GDG was that stand-alone surgical ablation was in general inappropriate as a first line therapy for AF. The GDG agreed that the benefits and risk of left atrial ablation should be discussed

	with the patient. This would include the reduced need for antiarrhythmic drugs and the need to continue anticoagulation due to the risk of recurrence. The recommendation resulted from a combination of the evidence and the opinions and experience of the GDG.

Recommendations	**The current recommendations can be found at http://www.nice.org.uk/guidance/ng196**
Relative values of different outcomes	Although the most important outcome from AF ablation was considered a reduction in mortality or stroke, to date no study has demonstrated that any method of rhythm control has any impact on these. At present, the primary indication for ablation is improvement in symptoms associated with AF. For this reason in the absence of data adequately examining mortality and stroke risk, the GDG studied other important measurable endpoints including symptoms, quality of life, AF recurrence and AF burden.
Trade-off between clinical benefits and harms	Seventeen randomised controlled trials of surgical ablation concomitant to surgery were identified for this systematic review. The GDG agreed that the evidence showed less AF recurrence and improved maintenance of sinus rhythm with surgical ablation in addition to surgery compared to surgery alone. For mortality, stroke and concomitant use of antiarrhythmic drugs there were no clinical differences found between surgical ablation in addition to surgery and surgery alone. Quality of life outcomes for the Von Oppell study[451] favoured surgery alone but the quality of life outcomes reported from the Van Breugel study[437] favoured ablation with surgery. The GDG agreed that the quality of life outcomes showed no clinical difference due to the uncertainty of the results. The GDG agreed that the patient's quality of life could be affected by the concomitant surgery performed and have no bearing on the success of ablation. The GDG agreed that the benefit of symptom improvement (and reduction in recurrence) was considered to outweigh the harm of any increase in side effects. Therefore, the GDG recommended that symptomatic AF patients undergoing cardiothoracic surgery should be considered for surgical ablation at the same time.
Economic considerations	Based on the evidence presented to the GDG, it felt that the routine offer of concomitant surgical ablation would be highly cost effective for patients with symptomatic AF who were already scheduled for a cardiac surgery. This is in part due to the reduced need for an additional hospital based procedure if required for this subset of patients (alongside the reduced cost of providing pharmacological therapy as an alternative strategy). It was felt that the MAZE procedure was not applicable as a comparator in the UK setting, as it is rarely used, however the Lamotte study[258]clearly showed the concomitant surgical ablation strategy as dominant (being more effective and less costly) in comparison to left atrial catheter ablation subsequent to cardiac surgery, and cost effective in comparison to on-going pharmacological therapy. It was noted that the consideration of stroke in the model may have inferred an unrealistic advantage in favour of the ablative interventions; however, on the whole, the assumptions and model inputs appeared reasonable. The GDG considered the Van Breugel study[438]to have an insufficient time horizon to assess the potential benefit of ablation at the time of surgery. As the evidence was only partially applicable, the GDG also considered national average costs of surgery with and without ablation, noting that there did not appear to be on average a significant difference in cost (i.e. the interquartile ranges

	provided overlapped). The group noted that they would expect the cost for a single procedure to be less costly than a combined procedure, and therefore interpreted the costs with caution. In practice, concomitant surgical ablation is felt best reserved for those patients with a reasonable chance of maintaining sinus rhythm post-operatively so the additional costs of concurrent ablation can be offset. There was no economic evidence to review that included the comparator of surgical ablation as a stand-alone intervention, and as this is an uncommon procedure in the NHS it was not possible to obtain a national average cost. From clinical experience the GDG thought that it was likely the cost of stand-alone ablative surgery would fall within the interquartile range cited for the average cost of "Other Non-Complex Cardiac Surgery", i.e. between £3500 to £8000. Overall the group felt it unlikely that it would be a cost-effective first line intervention for the majority of patients due to the high upfront costs, and the cost effectiveness of surgical ablation as a stand-alone and second line procedure remains uncertain.
Quality of evidence	The quality of the evidence varied from very low to moderate. All the surgical ablation studies included in this review were as an add-on to another surgical procedure. The GDG discussed that the SP-36 quality of life outcomes reported should be considered together where possible. There was heterogeneity found in the thromboembolic complications outcome. Whilst all trial participants had anticoagulation the type, duration and dosages varied according to trial protocols. This could potentially explain the heterogeneity but would be impossible to analyse as the relevant data is not provided within the studies.
Other considerations	The recommendation came from the evidence and the GDG experience and opinion with expert advisor input. The GDG agreed that the benefits of surgical ablation outweighed any negative outcomes when the patient was already undergoing a surgical procedure. There was no evidence available to report age as a separate sub-group analysis.

18 Pace and ablate

18.1 Introduction

Some patients with atrial fibrillation (AF) may continue to be symptomatic due to high ventricular rates in AF, despite maximal rate-limiting drug therapy. Alternatively, the applicability of rate controlling drug therapy may be limited because of side effects or because of excessive bradycardia on some occasions contrasting with persisting tachycardia on others.

In these patients, pacing followed by atrioventricular (AV) node ablation presents an alternative strategy to pharmacological rate control. Using this approach, the AV node is ablated, rendering the ventricles immune to the high fibrillation rates persisting in the atria. A pacemaker is implanted to provide a maintenance heart rate. The pacemaker can also be programmed to detect a patient's exercise and to increase the paced heart rate appropriately in response.

While a pace and ablate strategy avoids excessive ventricular rates, it does not restore normality as the atria are still fibrillating. As a consequence, stroke risk persists and there is still a continuing need to consider anticoagulation.

This chapter considers the evidence for atrioventricular node ablation in comparison with usual care in the management of AF.

18.2 Review question: What is the clinical and cost effectiveness of atrioventricular node ablation and pacing compared to usual care in the treatment of AF?

For full details see review protocol in Appendix C.

Table 95: PICO characteristics of review question

Population	People with AF Sub-groups: age, heart failure and biventricular devices.
Intervention/s	Atrioventricular node ablation and pacing (rate control strategy) including; Biventricular Single ventricular pace maker
Comparison/s	Usual care (including left atrial catheter/surgical ablation) Rate control drugs
Outcomes	All-cause mortality (30 days and latest endpoint) Heart failure Health -related quality of life Stroke or thromboembolic complications Re-hospitalisation with a primary diagnosis of AF or heart failure Left ventricular function
Study design	Randomised controlled trials (RCT) Systematic reviews

18.2.1 Clinical evidence

Seven studies were included in the review. [59-62,231,274,305,456] Brignole 1999[60] and Brignole 1997[59] are the same study.

Evidence from these are summarised in the clinical GRADE evidence profiles below (**Table 97**, **Table 98**, **Table 99** and **Table 100**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

The following studies were identified:

- Two studies comparing **ablate and pace versus pharmacological therapies** in patients with paroxysmal AF,[59,60,305] one study in patients with chronic AF or flutter[61] and one study in patients with permanent AF[456]
- One study comparing **ablate and pace versus pharmacological therapies** in patients with paroxysmal AF and heart failure[62]
- One study comparing **ablate and pace versus pace and rate control** in patients with permanent AF[274]
- One study comparing **ablate and pace versus pulmonary vein (PV) isolation** in patients with AF and heart failure[231]

Table 96: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Ablate and pace versus pharmacological therapies control				
Brignole 1999[60] Brignole 1997[59]	**Ablate and pace** 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. DDDR mode-switching pacemaker Antiarrhythmic drugs stopped **Drug therapies** Antiarrhythmic drugs shown to have the best efficacy Month 6 No. of patients Amiodarone 2 Sotalol 10 Propafenone 3 Flecainide 4 Quinidine 1 Digitalis 5 Verapamil/diltiazem 2	Patients with intolerable, recurrent paroxysmal AF (≥3 episodes/last 6 months), not controlled with ≥3 antiarrhythmic drugs)	Living with Heart Failure NYHA class Hospitalisation or electrical cardioversion (1997)	
Brignole 1994[61]	**Ablate and pace**	Consecutive	NYHA class	

Study	Intervention/comparison	Population	Outcomes	Comments
	Complete, persistent AV block. Pacemaker was programmed in VVI mode at a basic rate of 70 beats/min and at an activity upper-sensor rate of 130 beats/min **Pace and drugs** VVIR pacemaker programmed at the lowest rate available No details of drug therapy Patients who did not respond underwent subsequent ablation (results not reported here)	patients affected by chronic (> 3 months) AF or flutter, with 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.	Specific Activity Class	
Marshall 1999[305]	**Ablate and pace** Antiarrhythmic drugs were discontinued 2 to 3 days before ablation and pacing Sub-randomised to slow mode switch or “fast” mode switch pulse generators **Drug therapies** No. of patients Amiodarone 3 Sotalol 8 Flecainide 9 Propafenone 9 Quinidine 4 Disopyramide 11 Digoxin 4 Others 6	Inclusion criteria: (i) Electrocardiographically documented paroxysmal atrial fibrillation at least 6 months 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	Psychological wellbeing questionnaire McMaster Health Index	
Weerasoonya 2003[456]	**Ablate and pace** 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	Patients (i) aged > 40 years (ii) symptomatic permanent AF (> 12 months or with failed cardioversion or medication therapy) with uncontrolled ventricular rate in which a good	Assessment of Quality of Life Questionnaire Sickness Impact Profile	

Study	Intervention/comparison	Population	Outcomes	Comments
	Drug therapies Drugs were prescribed to achieve satisfactory control of ventricular rate. Included digoxin, metoprolol, atenolol, verapamil, and diltiazem alone or combination	rate could be achieved by drugs during the three month screening period (iv) ability to perform a treadmill test		
Ablate and pace versus pharmacological therapies (heart failure)				
Brignole 1998[62]	**Ablate and pace** 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. **Drug therapies** Plus calcium-antagonists, sotalol and amiodarone Antithrombotic therapy	Consecutive patients affected by chronic AF (lasting > 6 months) who met all of the following criteria (i) clinically manifest heart failure responsible for episodes of congestive heart failure or pulmonary 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	Living with Heart Failure NYHA class Specific Activity Scale Mortality Hospitalisation	
Ablate and Pace versus PV isolation				
Khan 2008[231]	**Ablate and pace** 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	Patients with symptomatic AF and symptoms of NYHA class II or III heart failure, despite the use of antiarrhythmic drugs. Patients were included if they had	Living with Heart Failure	

Study	Intervention/comparison	Population	Outcomes	Comments
	P V Isolation	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		
Ablate and Pace versus Pace and Rate control				
Levy 2001[274]	**Ablate and pace** His bundle junction ablation plus pacemaker. The pacemaker was programmed to VVIR base rate 60 bpm, upper rate 85% of age predicted (220 minus age) **Pace plus drugs** 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.	Permanent AF (> 6 months).Symptomatic fast ventricular response rate to their AF that could not be controlled by drugs. Fully ambulant	Modified Karolinska Questionnaire Nottingham Health Profile	

Table 97: Clinical evidence profile comparing ablate and pace versus pharmacological therapies

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abl + Pace	Pharmacological therapies	Relative (95% CI)	Absolute	**Quality**	**Importance**
Mortality (follow-up 12 months)[456]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	None	2/49 (4.1 %)	2%	RR 2.04 (0.19 to 21.79)	21 more per 1000 (from 16 fewer to 416 more)	VERY LOW	CRITICAL
Living with heart failure questionnaire (follow-up 6 months; range of scores: 0-105; Better indicated by lower values)[60]												
1	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness	no serious imprecision	None	21	18	-	MD 23 lower (35.25 to 10.75 lower)	MODERATE	CRITICAL
Specific Activity Scale (follow-up 15 days; range of scores: I-IV; Better indicated by lower values)[61]												
1	randomised trials	very serious[d]	no serious inconsistency	no serious indirectness	Not assessed – categorical scale	none	12	11	-	Ablate and pace 1.7 (SD 0.5) Pharmacological therapies 2.1(0.7)	LOW	CRITICAL
McMaster Health Index - DDDR/MS pacemaker (follow-up 6-18 weeks; range of scores: 0-20; Better indicated by higher values)[305]												
1	randomised trials	very serious[f]	no serious inconsistency	no serious indirectness	Serious[e]	none	37	19	-	MD 0.4 higher (1.3 lower to 2.1 higher)	VERY LOW	CRITICAL
McMaster Health Index - VVIR pacemaker (follow-up 6-18 weeks; Better indicated by lower values)[305]												
1	randomised trials	very serious[f]	no serious inconsistency	no serious indirectness	very serious[g]	none	29	19	-	MD 0.1 lower (1.88 lower to 1.68 higher)	VERY LOW	CRITICAL
The Psychological General Well Being Questionnaire - DDDR/MS pacemaker (follow-up 6-18 weeks; range of scores: 0-110; Better indicated by higher values)[305]												
1	randomis	very	no serious	no serious	Serious[e]	none	37	19	-	MD 8.9 higher	VERY	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abl + Pace	Pharmacological therapies	Relative (95% CI)	Absolute	**Quality**	**Importance**
	ed trials	serious[f]	inconsistency	indirectness						(0.36 lower to 18.16 higher)	LOW	
The Psychological General Well Being Questionnaire - VVIR pacemaker (follow-up 6-18 weeks; range of scores: 0-110; Better indicated by higher values)[305]												
1	randomised trials	very serious[f]	no serious inconsistency	no serious indirectness	Serious[e]	none	29	19	-	MD 3.9 higher (5.89 lower to 13.69 higher)	VERY LOW	CRITICAL
Assessment of Quality of Life Questionnaire (follow-up 12 months; range of scores: 0-1; Better indicated by higher values)[456]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	47	-	MD 0.09 higher (0.01 to 0.17 higher)	MODERATE	CRITICAL
Sickness Impact Profile (follow-up 12 months; Better indicated by higher values)[456]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	serious[e]	none	34	47	-	MD 2.13 higher (0.96 lower to 5.22 higher)	LOW	CRITICAL
NYHA class (follow-up 15 days to 6 months; range of scores: 1-4; Better indicated by lower values)[60,61]												
2	randomised trials	very serious[i]	no serious inconsistency	no serious indirectness	Not assessed – categorical scale	none	33	29	-	Ablate and pace 2.0 (SD 0.6) Pharmacological therapies 2.4 (0.7)	LOW	CRITICAL
Hospitalisation or electrical cardioversion (follow-up 6 months)[59]												
1	randomised trials	Serious[c]	no serious inconsistency	no serious indirectness	Serious[e]	none	1/21 (4.8 %)	6/18 (33.3%)	RR 0.14 (0.02 to 1.08)	286 fewer per 1000 (from 326 fewer to 27 more)	LOW	IMPORTANT
Ejection fraction (follow-up 6 months; range of scores: 0-100%; Better indicated by higher values)[59]												
1	randomis	Serio	no serious	no serious	very	none	19	16	-	MD 1 lower	VERY	IMPORT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abl + Pace	Pharmacological therapies	Relative (95% CI)	Absolute		
	ed trials	us[c]	inconsistency	indirectness	serious[g]					(8.29 lower to 6.29 higher)	LOW	ANT

[a] *Lack of blinding. 13/49 dropped out after randomisation but before treatment in the ablate and pace group. Most dropped out because they 'felt too well'. Results therefore likely to be in favour of drug therapy group*
[b] *The 95% CI crosses the MID for benefit and harm*
[c] *Lack of blinding*
[d] *Lack of allocation concealment, 15 days follow up*
[e] *The 95%CI crosses the MID for either benefit or harm*
[f] *Lack of randomisation and blinding*
[g] *The 95%CI crosses the MID for benefit and harm*
[h] *The 95%CI crosses the MID for benefit or harm*
[i] *Lack of blinding (1994, 1999), lack of allocation concealment and 15 days follow up (1994)*

Table 98: Clinical evidence profile comparing ablate and pace versus pharmacological therapies (AF and heart failure)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abl + Pace	Pharmacological therapies (Heart failure)	Relative (95% CI)	Absolute		
Mortality (follow-up 12 months)[62]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	3/32 (9.4 %)	4/34 (11.8%)	RR 0.8 (0.19 to 3.29)	24 fewer per 1000 (from 96 fewer to 270 more)	VERY LOW	CRITICAL
Specific Activity Scale (follow-up 12 months; range of scores: I-IV; Better indicated by lower values)[62]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Not assessed – categorical variable	none	28	26	-	Ablate and pace 2.3 (SD 0.8) Pharmacological therapies 2.6 (0.9)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abl + Pace	Pharmacological therapies (Heart failure)	Relative (95% CI)	Absolute		
Living with heart failure questionnaire (follow-up 12 months; range of scores: 0-105; Better indicated by lower values)[62]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[c]	none	28	26	-	MD 5 lower (15.14 lower to 5.14 higher)	LOW	CRITICAL
NYHA class (follow-up 12 months; range of scores: 1-4; Better indicated by lower values)[62]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Not assessed – categorical variable	none	28	26	-	Ablate and pace 2.4 (0.5) Pharmacological therapies 2.5 (0.8)	MODERATE	CRITICAL
Hospitalisation or electrical cardioversion (follow-up 12 months)[62]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[b]	none	9/32 (28.1 %)	13/34 (38.2%)	RR 0.74 (0.37 to 1.48)	99 fewer per 1000 (from 241 fewer to 183 more)	LOW	IMPORTANT

[a] *Lack of blinding*
[b] *Confidence interval crossed two MIDs*
[c] *Confidence interval crossed one MID*

Table 99: Clinical evidence profile: ablate and pace versus pulmonary vein isolation (AF and heart failure)

Quality assessment							No of patients		Effect		Quality	Importance
No of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Abl +	P V	Relat	Absolute		

Quality assessment							No of patients		Effect		Qua	Importa
studies		bias				considerations	Pace	isolatio n	ive (95% CI)			
Living with heart failure (follow-up 6 months; range of scores: 0-105; Better indicated by lower values)[231]												
1	randomise d trials	very serious a	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	41	-	MD 22 higher (17.02 to 26.98 higher)	LO W	CRITICA L
Mortality												
0	No available evidence											CRITICA L
Health related quality of life												
0	No available evidence											CRITICA L

[a] *Lack of allocation concealment and blinding*

Table 100: Clinical evidence profile comparing ablate and pace versus pace and rate control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Abl + Pace	Pace + Rate control	Relative (95% CI)	Absolute		
Modified Karolinska Questionnaire (follow-up 12 months; range of scores: 0-140; Better indicated by lower values)[274]												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	16	16	-	MD 2 lower (14.13 lower to 10.13 higher)	VERY LOW	CRITICAL
Nottingham Health Profile (follow-up 12 months; range of scores: 0-600; Better indicated by lower values)[274]												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	16	16	-	MD 28 higher (34.49 lower to 90.49 higher)	VERY LOW	CRITICAL
Mortality												
0	No available evidence											CRITICAL
Living with heart failure												
0	No available evidence											CRITICAL

[a] *Lack of randomisation, allocation concealment and blinding*
[b] *Confidence interval crossed two MIDs*

18.2.2 Economic evidence

Published literature

No relevant economic evaluations comparing "ablate and pace" to an alternative strategy were identified. There were no excluded studies.

See also the economic article selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, the NHS reference costs for a single or dual chamber pacemaker or Implantable Diagnostic Device with Percutaneous Coronary Intervention, Electrophysiology or Radiofrequency ablation (EA48Z) are provided to aid consideration of cost effectiveness in **Table 101**.

Table 101: NHS reference cost for ablate and pace[123].

Reference cost HRG	National average unit cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average cost of excess bed day	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Weighted national average	Weighted average length of stay
Single or dual chamber pacemaker or Implantable Diagnostic Device with Percutaneous Coronary Intervention, EP or RFA (EA48Z (elective inpatients)) (a)	£3,675	£2,117	£5,215	£1,514	£1,514	£1,514	£3,686	2.08
Single or dual chamber pacemaker or Implantable Diagnostic Device with Percutaneous Coronary Intervention, EP or RFA (EA48Z (non elective long stay))(b)	£6,754	£5,098	£8,178	£240	£178	£277	£7,048	9.12
Single or dual chamber pacemaker or Implantable Diagnostic Device with Percutaneous Coronary Intervention, EP or RFA (EA48Z (non elective short stay))(c)	£2,705	£1,550	£3,776				£2,705	1.00
Single or dual chamber pacemaker or Implantable Diagnostic Device with Percutaneous Coronary Intervention, EP or RFA (EA48Z (day case)) (d)	£1,932	£1,448	£2,390				£1,932	1.00
Single or dual chamber pacemaker or Implantable Diagnostic Device with Percutaneous Coronary Intervention, EP or RFA (EA48Z (outpatient)) (e)	£2,250	£2,250	£2,250				£2,250	1.00
Weighted average across settings, including excess bed days:							**£4,970**	**4.12**

Abbreviations: EP = electrophysiology; RFA = radiofrequency ablation

(a) The number of data submissions for this code was 27, with 142 units of activity.
(b) The number of data submissions for this code was 27, with 58 units of activity.
(c) The number of data submissions for this code was 14, with 15 units of activity.
(d) The number of data submissions for this code was 16, with 24 units of activity.
(e) The number of data submissions for this code was 1, with 22 units of activity.

18.2.3 Evidence statements

Clinical

Atrial fibrillation

Low to very low quality evidence from one study showed no difference between atrioventricular junction ablation and pacing and pharmacological therapies in:

- reducing mortality rates.
- quality of life scores

Low and moderate quality evidence showed that atrioventricular junction ablation and pacing was clinically more effective than pharmacological therapies at:

- reducing hospitalisations
- quality of life (living with heart failure questionnaire and the assessment of quality of life questionnaire)

AF and heart failure:

Very low to moderate quality evidence from one study showed no clinical difference between atrioventricular junction ablation and pacing with pharmacological therapies in:

- mortality
- quality of life
- hospitalisation

Ablate and pace versus pace and PV isolation:

Low quality evidence showed that pulmonary vein isolation is clinically more effective than atrioventricular junction ablation and pacing in the quality of life (living with heart failure questionnaire) (one study, N=81)

Ablate and pace versus pace and rate control:

Very low quality evidence showed no difference between atrioventricular junction ablation and pacing and rate control and pacing in two quality of life scores (one study)

Economic

No relevant economic evaluations were identified.

18.2.4 Recommendations and link to evidence

Recommendations	The current recommendations can be found at http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	All-cause mortality, heart failure and quality of life were the critical outcomes for this comparison.
Trade-off between clinical benefits and harms	Four studies compared ablate and pace with pharmacological therapies. Two studies were in patients with paroxysmal AF (Brignole 1997,[59] Brignole 1999,[60] Marshall 1999[305]), one with chronic AF or flutter (Brignole 1994[61]) and one in permanent AF (Weerasooriya 2003[456]). The evidence reported hospitalisation and ejection fraction together and ejection fraction alone. There was a clinical benefit favouring ablate and pace for the hospitalisation and ejection fraction but no difference for the ejection fraction alone. From this it was deduced that there was a clinical benefit in reducing hospitalisation with pace and abate compared to medical therapies. There were seven quality of life scores reported and two found a clinical benefit favouring pace and ablate compared to pharmacological treatment. The other five scores found no difference between the two treatments. The evidence found no difference between pace and ablate and pharmacological treatment for mortality. The GDG regarded this as a positive outcome, indicating that ablate and pace was a safe last resort for symptomatic patients, as the procedure had not increased mortality. One study (Brignole 1998[62]) found no difference between any of the outcomes reported for ablate and pace compared to pharmacological therapies in patients with AF and heart failure. The GDG recognised the finality of a pace and ablate strategy as the last option in the pathway of AF management. They considered that it should only be adopted when a decision had been made that no further rate or rhythm control options were appropriate. While there is an evidence base for the pace and ablate strategy in patients with paroxysmal AF, the GDG were of the opinion that pace and ablate should only be considered after all other treatments, including pulmonary vein ablation, had been considered or in case of patient preference. The GDG recognised a role for a pace and ablate strategy in patients with left ventricular failure, when the left ventricular failure was thought to be a consequence of high ventricular rates. However, when there was thought to be a reasonable expectation of successful left atrial ablation and hence that the AF could be considered non-permanent, the GDG were of the opinion that left atrial ablation should be considered in the pathway before a pace and ablate strategy.
Economic considerations	There was no economic evidence retrieved to inform this question. The GDG considered the likely resource use associated with the strategy. As with ablation, the upfront costs of this strategy are relatively large, but over a period of time the cost may equalise to that which was spent on rate control drugs, meaning it may be cost saving if long term treatment effects are observed. However, with the costs in maintaining a pacemaker, the need for follow up checks and replacement, cost neutrality is not certain.

	In current practice ablate and pace is considered a second line rate control strategy. A recommendation in keeping with current practice would therefore affect symptomatic patients refractory to rate and rhythm control. The cost impact of the recommendation would not be significant. Overall the GDG felt that pace and ablate strategy was unlikely to be cost effective as a first line treatment.
Quality of evidence	In terms of quality of life, there appeared to be a clinically important benefit for atrioventricular node ablation and pacing over pharmacological therapies in the living with heart failure questionnaire and the assessment of quality of life questionnaire (moderate quality evidence). However, in the other five quality of life scores there was no clear advantage for either treatment (low to very low evidence). Mortality rates were very low quality evidence and hospitalisation or ejection fraction had a very low quality GRADE rating. For the study reporting AF and heart failure, outcomes were very low to moderate quality.
Other considerations	The GDG were of the opinion that, in view of the irrevocable nature of the pace and ablate strategy that it should be considered an option of last resort. In view of the consequential life-long dependence on pacing, it is an easier option to contemplate in older patients. The GDG agreed that in view of this and the potential for other co-morbidities, that the treatment was more suited to older patients. An informed discussion should take place with the patient outlining the irrevocable nature of pace and ablate treatment. The balance between benefits and harms should be fully discussed. <u>People with AF and heart failure</u> The GDG recognised that pacing may in some cases lead to deterioration in the left ventricular function and that this may be a cause for concern in patients with ventricular impairment put forward for a pace and ablate strategy. The GDG recognised that in these circumstances some clinicians would consider implanting a resynchronisation pacemaker to help protect against any deterioration in left ventricular function associated with single site ventricular pacing. The GDG did not consider the specific role of resynchronisation pacing in comparison with single site pacing following AV node ablation. The GDG similarly recognised that different indications for AV node ablation might apply to patients with AF and an existing resynchronisation pacemaker. It was recognised that additional issues may apply to this group in relation to a potential benefit of increasing percentage of resynchronisation pacing following AV node ablation. There was no sub-group analysis available to report age or biventricular devices separately in this review.

Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	All-cause mortality, heart failure and quality of life were the critical outcomes for this comparison.
Trade-off between clinical benefits and harms	One study (Levy 2001[274]) found that there was no clear advantage for atrioventricular junction ablation and pacing over rate control and pacing in two quality of life scores. The GDG considered that this was an approach, which was

	worth considering when deciding treatment options. The benefit of pacing and rate control is that this offers the possibility of further optimisation of rate control after pacing, as the pacemaker will protect against excessive bradycardia before committing to ablation. The GDG considered the benefits of having the pacemaker fitted before the ablation was performed. Although this would mean two procedures, it would allow the clinician's time to judge if the patients required the additional ablation. The GDG considered that there are other advantages and disadvantages of delaying proceeding to ablation after pacing. Delaying ablation reduces the risks arising from early pacing lead displacement, and also enables the clinician to ensure that the pacing wound has healed satisfactorily. On the other hand, it means a commitment to a second procedure and second hospital admission. The GDG thought that these advantages and disadvantages should be discussed with the patient.
Economic considerations	There was no economic evidence to inform this recommendation. The GDG discussed the benefits and costs which may result from a staged approach to pace and ablate, to that where the pace and ablate is undertaken in one procedure, in relation to the probability that a patient will require an ablation should pacing be successful in symptomatic relief. It is difficult to evaluate the relative costs of a staged approach to pacing and ablation in comparison with undertaking the two procedures during a single admission. On the one hand the hospital stay costs of a single admission are likely to be less than the hospital stay costs of two admissions in a staged approach. On the other hand, with the staged approach a proportion of patients will not require subsequent ablation with a consequent saving. Cost comparisons will depend critically on the number of patients avoiding the need for ablation and this is unknown. Thus the cost effectiveness of either approach remains unclear.
Quality of evidence	Both quality of life outcomes reported in this study were very low quality. The study (Levy 2001[274]) considered patients with bradycardia and tachycardia in AF who were already selected for a pacemaker. The GDG wanted to raise awareness of the value of pacing in this group and that these patients would not necessarily benefit from ablation.
Other considerations	The recommendation came from the evidence and the experience and opinion of the GDG. This was considered to be another option for this group of patients where the pacing was done initially to optimise rate control before considering ablation. This should be a patient led decision.

Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	All-cause mortality, heart failure and quality of life were the critical outcomes for this comparison.
Trade-off between clinical benefits and	One study (Khan 2008[231]) found a clinically important benefit in quality of life for pulmonary vein isolation (left atrial catheter ablation) compared to atrioventricular

harms	junction ablation and pacing in this group of patients with heart failure and AF. The GDG agreed that pulmonary vein isolation should be considered before ablate and pace in this patient group as this study found harm associated with ablate and pace for the quality of life score reported. The GDG considered that for patients with paroxysmal AF, in whom there was a reasonable expectation of successful ablation, that pulmonary vein isolation should be offered in the pathway before pace and ablate. Likewise in the case of patients with heart failure thought to be due to high ventricular rates and in whom there was a reasonable expectation of successful ablation, the GDG considered that left atrial ablation should be offered before a pace and ablate strategy.
Economic considerations	There was no economic evidence retrieved to inform this question. The GDG considered the likely resource use associated with the strategy. As with ablation, the upfront costs of this strategy are relatively large, but over a period of time the cost may equalise to that which was spent on rate control drugs, meaning it may be cost saving if long term treatment effects are observed. However, there are costs in maintaining a pacemaker, with need for follow up checks and replacement. In current practice ablate and pace is considered a second line strategy. A recommendation in keeping with current practice would therefore affect drug refractory patients rather than the whole AF population group. The cost impact of the recommendation would not be significant. Overall the GDG felt that pace and ablate strategy was unlikely to be cost effective as a first line treatment. Therefore ablation should be considered prior to pacing in patients who have paroxysmal AF. The GDG considered the clinical evidence and potential for harm when offering pacing to patients with persistent or permanent AF and heart failure. On this basis, it is unlikely offering pace and ablate to this subgroup will be cost effective, and ablation in isolation should be considered as an alternative strategy.
Quality of evidence	There was only one small study (Khan 2008[231]) reporting one low quality outcome.
Other considerations	The recommendation was based on the evidence and the experience and opinion of the GDG. Many patients with atrial fibrillation also have heart failure and this is likely to be particularly true of patients with poor rate control considered for AV node ablation. As most patients in this group will have persistent atrial fibrillation, ablation success rates will be lower and the need for repeat procedures higher. In view of these considerations, the relative merits of the two approaches require careful consideration on an individual patient basis. These issues should be carefully discussed with the patient to take account of their views in reaching a decision.

19 Acute atrial fibrillation (AF)

This section was partially updated in 2021. See http://www.nice.org.uk/guidance/ng196/evidence for the 2021 evidence reviews.

19.1 People that are presenting acutely and either have new onset AF or destabilisation of their existing AF

This chapter considers the management of patients presenting acutely with symptoms, signs of a tachyarrhythmia, and ECG findings diagnostic of atrial fibrillation.

Atrial fibrillation (AF) is a very common cause of acute presentation to hospital, either as a primary diagnosis in its own right or as a complication of other illness. In some cases the AF will be of new-onset. This is defined as a patient presenting to medical care with atrial fibrillation whose new or changing symptoms suggest that the episode of AF commenced less than 48 hours prior to presentation. In others, the acute presentation may be due to a deterioration of ventricular rate control in patients with pre-existing persistent or permanent AF. Typically patients will have a rapid ventricular response to the atrial fibrillation as it is this phenomenon that accounts for most of their symptoms and for their acute presentation.

Management strategies will vary with clinical circumstances. Issues to be considered include:

- the haemodynamic state of the patient
- whether the AF is likely to be a primary event
- the duration of AF and consequent thromboembolic risk if sinus rhythm is restored acutely
- accompanying co-morbidities and whether treating these will improve rate control or the likelihood of restoring and maintaining sinus rhythm.

It is essential that the overall management strategy addresses and treats accompanying co-morbidities and other concurrent physiological derangements, as rate or rhythm management in isolation is unlikely to be effective.

It is rare for AF to cause severe haemodynamic compromise necessitating immediate electrical cardioversion. More often the clinician will be able to reach a balanced clinical judgement based on an individual patient's circumstances of the most appropriate management strategy, and whether the primary objective should be restoration of sinus rhythm or control of ventricular rate.

This chapter accepts that when patients present acutely, the choice of rhythm or rate control strategies will be made on clinical grounds. The evidence base for the two strategies is therefore considered separately. For rhythm control, both electrical and pharmacological approaches are considered; for rate control only pharmacological approaches are relevant.

Finally, the acute management of thromboembolic risk is considered.

'Acute with unstable AF' is usually defined as less than 48 hours; however this definition varied between studies. We included 'acute with unstable AF' as defined by the individual study. Definitions of this according to each study can be found in the clinical evidence tables in Appendix G.

19.2 Review question: What is the clinical and cost effectiveness of using different rate control drug strategies in the pharmacological management of atrial fibrillation?

19.2.1 Introduction

In many patients presenting acutely with atrial fibrillation, the fibrillation may accompany intercurrent illness, such as a chest infection. The fibrillation may either be of new-onset, provoked by the intercurrent illness, or may be longstanding with acceleration of ventricular rate provoked by the intercurrent illness. In either case, the initial clinical strategy of choice is likely to be one of rate

control. Rhythm control is unlikely to be effective, either because the AF may be longstanding or, in cases of new-onset AF, because the intercurrent illness is still present and likely to cause relapse. In this common clinical situation, there are two treatment goals. One is to treat the precipitating illness; the other is to achieve improved control of ventricular response rate, through the use of pharmacological agents which slow conduction, through the atrioventricular (AV) node strategy.

For full details see review protocol in Appendix C.

Table 102: PICO characteristics of review question

Population	People with AF Report the following sub-groups separately: • Paroxysmal separate • Persistent/permanent • Unstable with acute AF • Heart failure (impaired LV function) This will include papers with a mixed population including atrial flutter but should not include paper with all atrial flutter patients.
Intervention/s	Rate-limiting calcium channel blockers Digoxin Beta-blockers Amiodarone Dronedarone (non-permanent AF only) Combinations of above interventions
Comparison/s	No treatment Any other intervention listed above
Outcomes	Mortality (long-term) Health-related quality of life Rate control – heart rate (time or amount of people) Stroke or thromboembolic complications Rate of discontinuation of drug due to side effects Rehospitalisation with a primary diagnosis of AF or heat failure Time to response Left ventricular function – number of people / ejection fraction as %
Exclusions	Population – atrial flutter only
Study design	Randomised controlled trials (RCT) Systematic reviews of RCTs

19.3 Review question: 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?

19.3.1 Introduction

In patients presenting with new-onset atrial fibrillation in whom the occurrence of atrial fibrillation is thought to be the primary problem responsible for their presentation, a rhythm control strategy may be preferable to rate control. Duration of AF and thromboembolic risk is central to this decision.

Other factors to be considered include co-morbidities together with their consequences for antiarrhythmic drug selection and the likelihood of maintaining sinus rhythm.
Restoration of sinus rhythm can be achieved by pharmacological cardioversion, electrical cardioversion, or by a combination of the two.
Vernakalent is not licensed in the UK and the GDG were not able to consider this drug for any of the recommendations. However, it was included in the review for comparative purposes only.
For full details see review protocol in Appendix C.

Table 103: PICO characteristics of review question

Population	People with persistent AF undergoing cardioversion (pharmacological or electrical or electrical with drugs). This definition may differ from studies. Include all AF patients. Report the following sub-groups separately: • Heart failure (impaired LV function) • Unstable with acute • Reversible causes including:
Intervention/s	Flecainide Propafenone Amiodarone Sotalol Beta-blockers Dronedarone (for comparative purposes only) Calcium channel blockers Digoxin Vernakalent (for comparative purposes only) Magnesium Combinations of the above interventions Electrical cardioversion alone or in combination with antiarrhythmic drug therapy
Comparison/s	No treatment or any other intervention listed above
Outcomes	Mortality (30 days and longest endpoint) Health-related quality of life Restoration of sinus rhythm/time to restoration for acute Stroke or thromboembolic events Rehospitalisation with a primary diagnosis of AF Patients developing heart failure Maintenance of sinus rhythm/Recurrence of AF
Study design	Randomised controlled trials (RCT) Systematic reviews of RCTs

19.3.2 Clinical evidence (rate control strategies)

Three studies were identified and included in the review: Demircan 2005[121], Jordaens 1997[215] and Hofmann 2006 [202]. Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 105**, **Table 106** and **Table 107**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.
We searched for systematic reviews and randomised trials comparing the effectiveness of different classes of rate control drugs with each other and against placebo in the pharmacological management of heart rate in atrial fibrillation. Crossover studies were excluded.

Table 104: Summary of studies included in the review- acute AF

Study	Intervention/comparison	Population	Outcomes	Comments
Demircan 2005[121]	Beta-blocker versus	AF with a	Rate control (mean %	Acute

Study	Intervention/comparison	Population	Outcomes	Comments
	diltiazem	ventricular rate ≥120 bpm and systolic BP≥95mmHg (acute AF)	decrease in ventricular rate over time)	treatment in emergency department
Hofmann 2006[202]	Amiodarone versus digoxin	Hospitalised AF with a ventricular rate >135 bpm	Rate control (mean ventricular rate)	Some patients were also taking beta-blockers and calcium channel blockers
Jordaens 1997[215]	Digoxin versus placebo	Recent onset AF	Rate control	Groups not comparable at baseline for duration of AF

Table 105: Clinical evidence profile: digoxin versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digoxin	Control	Relative (95% CI)	Absolute		
HR 30 min post treatment (Better indicated by lower values) [215]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	19	20	-	MD 21 lower (38.78 to 3.22 lower)	LOW	CRITICAL
Mortality												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
HR 30 min post treatment (Better indicated by lower values)[215]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	19	20	-	MD 21 lower (38.78 to 3.22 lower)	LOW	CRITICAL

a. Randomisation method unclear; groups not comparable at baseline for duration of AF
b. Confidence interval crossed one MID

Table 106: Clinical evidence profile: beta-blocker versus calcium channel blocker

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blocker	Calcium channel blocker	Relative (95% CI)	Absolute		
% decrease in VR at 20 min (Better indicated by lower values)[121]												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	20	20	-	MD 7 higher (1.42 to 12.58 higher)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	–	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	–	CRITICAL

a. randomisation method unclear
b CI crosses both MIDs

Table 107: Clinical evidence profile: digoxin versus Amiodarone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digoxin	Amiodarone	Relative (95% CI)	Absolute		
Mean ventricular rate (Better indicated by lower values)[202]												

1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	none	50	50	-	MD 11.1 lower (19.72 to 2.48 lower)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	–	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	–	CRITICAL

a. Randomisation method unclear; unclear blinding
b. Confidence interval crossed one MID

19.3.3 Clinical evidence (restoration of sinus rhythm)

We searched for randomised trials comparing the effectiveness of rhythm control drugs versus a rhythm control drug of another class or placebo for the pharmacological restoration of sinus rhythm. For the electrical restoration of sinus rhythm part of the review question, we searched for randomised controlled trials comparing electrical cardioversion (ECV) with pharmacological treatment, or electrical cardioversion combined with drugs to restore sinus rhythm.

Twenty-six studies were included for the review on pharmacological restoration of sinus rhythm: Azpitarte 1997,[34] Baldi 1990,[35] Balla 2011,[36] Bellandi 1995,[39] Blanc 1999,[48] Boriani 1997,[56] Camm 2011,[67] Capucci 1992,[73] Capucci 1994A,[72] Capucci 1999,[74] Chiladakis 2001,[88] Chu 2009,[93], Cybulski 2003,[112] Donovan 1991,[131] Donovan 1992,[132] Donovan 1995,[133] Falk 1987,[141] Galve 1996,[168] Ganau 1998,[169]Hassan 2007,[193] Hornestam 1997,[206], Joseph 2000,[216], Kochiadakis 1998,[244] Martinezmarcos 2000,[306] Peuhkurinen 2000[356] and Thomas 2004.[429]

One study was included for the review on electrical restoration of sinus rhythm: Bellone 2012[41].

Evidence from these are summarised in the clinical GRADE evidence profile below (**Table 109** -**Table 123**). See also the study selection flow chart in Appendix D, forest plots in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix J.

'Acute with unstable AF' is usually defined as less than 48 hours; however this definition varied between studies. We included 'acute with unstable AF' as defined by the individual study. Definitions of this according to each study can be found in the clinical evidence tables in Appendix G.

Table 108: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Azipitarte 1997[34]	Propafenone versus placebo	Acute AF	Restoration of sinus rhythm	Selection bias Trial stopped early Small numbers
Baldi 1990[35]	Flecainide versus digoxin	Recent-onset AF (≥3 days); VR >100bpm at rest	Restoration of sinus rhythm Time to restoration	Selection bias Small numbers
Balla 2011[36]	Flecainide versus placebo Flecainide versus amiodarone Flecainide versus propafenone Amiodarone versus placebo Propafenone versus placebo Amiodarone versus propafenone	Acute AF	Restoration of sinus rhythm	Small numbers
Bellandi 1995[39]	Propafenone versus placebo	Recent-onset AF	Restoration of sinus rhythm Time to restoration	
Bellone 2012[41]	Propafenone versus ECV	AF <48 hours	Restoration of sinus rhythm Patients in AF	Selection bias
Blanc 1999[48]	Propafenone versus	AF <2	Restoration of sinus rhythm	

Study	Intervention/comparison	Population	Outcomes	Comments
	amiodarone	weeks		
Boriani 1997[56]	Propafenone versus placebo	Recent-onset AF	Restoration of sinus rhythm	Selection bias
Camm 2011[67]	Amiodarone versus vernakalent	Symptomatic recent onset AF (3-48 hours)	Restoration of sinus rhythm	Selection bias Reporting bias
Capucci 1992[73]	Flecainide versus amiodarone Amiodarone versus placebo Flecainide versus placebo	AF <7 days	Restoration of sinus rhythm Time to restoration	Selection bias
Capucci 1994A[72]	Propafenone versus placebo Propafenone versus flecainide Flecainide versus placebo	AF <7 days	Restoration of sinus rhythm	Selection bias
Capucci 1999[74]	Propafenone versus digoxin Propafenone versus placebo Digoxin versus placebo	AF <48 hours; mean VR >70bpm; NYHA functional class <II	Restoration of sinus rhythm Time to restoration	Performance bias Reporting bias
Chiladakis 2001[88]	Magnesium versus calcium channel blocker	AF <12 hours; mean VR> 100 bpm	Restoration of sinus rhythm	Selection bias Small numbers
Chu 2009[93]	Magnesium versus placebo	Paroxysmal AF	Restoration of sinus rhythm	Selection bias Groups not comparable at baseline
Cybulski 2003[112]	Amiodarone versus placebo	New-onset AF <24 hours	Restoration of sinus rhythm Time to restoration	
Donovan 1991[131]	Flecainide versus placebo	Acute AF	Restoration of sinus rhythm	Selection bias Performance bias Attrition bias
Donovan 1992[132]	Flecainide versus placebo	Recent-onset AF ≥30min≤ 72 hours; ventricular response	Restoration of sinus rhythm	

Study	Intervention/comparison	Population	Outcomes	Comments
		≤120bpm		
Donovan 1995[133]	Flecainide versus amiodarone	Recent-onset AF ≥30min≤ 72 hours; ventricular response ≤100bpm	Restoration of sinus rhythm	Selection bias
Falk 1987[141]	Digoxin versus placebo	Acute AF	Restoration of sinus rhythm	Selection bias Baseline data not given Not all data could be analysed
Fresco 1996A[152]	Propafenone versus placebo	Paroxysmal AF (<72 hours onset)	Restoration of sinus rhythm	Small numbers
Galve 1996[168]	Amiodarone versus placebo	New-onset, acute AF	Restoration of sinus rhythm	All patients received digoxin
Ganau 1998[169]	Propafenone versus placebo	AF<72 hours; VR>110bpm	Restoration of sinus rhythm	
Hassan 2007[193]	Diltiazem versus beta-blocker	Acute/ paroxysmal AF and a rapid VR	Restoration of sinus rhythm Time to restoration	Selection bias Small numbers
Hornestam 1997[206]	Digoxin versus placebo	AF ≤7 days	Restoration of sinus rhythm Time to restoration	
Joseph 2000[216]	Sotalol versus amiodarone Sotalol versus digoxin Amiodarone versus digoxin	AF onset within 24 hours	Restoration of sinus rhythm Time to restoration Stroke	Small numbers Performance bias
Kochiadakis 1998[244]	Amiodarone versus propafenone Amiodarone versus placebo Propafenone versus placebo	AF < 48 hours	Restoration of sinus rhythm Time to restoration	All patients received digoxin Selection bias Performance bias Small numbers
Martinezmarcos 2000[306]	Flecainide versus propafenone	AF ≤48 ours	Restoration of sinus rhythm	Performance bias

Study	Intervention/comparison	Population	Outcomes	Comments
	Flecainide versus amiodarone Propafenone versus amiodarone			
Peuhkurinen 2000[356]	Amiodarone versus placebo	AF< 48 hours	Restoration of sinus rhythm	Selection bias Performance bias Attrition bias Reporting bias
Thomas 2004[429]	Sotalol versus amiodarone Sotalol versus digoxin Amiodarone versus digoxin	Acute AF	Restoration of sinus rhythm Time to restoration	Selection bias Performance bias

19.3.4 Pharmacological restoration of sinus rhythm

Table 109: Clinical evidence profile: Propafenone versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propafenone	Placebo	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF[34,35,39,56,72,152,169,244]												
8	randomised trials	very serious[a]	very serious[b]	no serious indirectness	no serious imprecision	none	386/515 (75%)	155/490 (30.8%)	RR 2.43 (1.81 to 3.25)	440 more per 1000 (from 249 more to 693 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias in 3 studies; trial stopped early in one study; small numbers in four studies; all patients also received digoxin in one study; performance bias in one study.
b. I2=73%; p=0.0004

Table 110: Clinical evidence profile: flecainide versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flecainide	Placebo	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF [36,72,73,131,133]												

5	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	154/205 (73.2%)	66/206 (35.3%)	RR 2.35 (1.90 to 2.91)	477 more per 1000 (from 318 more to 674 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias in three studies; performance and attrition bias in one study
b. I2=57%; p=0.07

Table 111: Clinical evidence profile: flecainide versus propafenone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Flecainide**	**Propafenone**	**Relative (95% CI)**	**Absolute**		
Restoration of sinus rhythm -Acute AF [36,72,306]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	125/148 (84.5%)	114/151 (72.1%)	RR 1.12 (1 to 1.25)	87 more per 1000 (from 0 more to 180 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												

0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Stroke or thromboembolic events												
0	no evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

a. Selection bias in one study; performance bias in one study
b. Confidence interval crossed one MID

Table 112: Clinical evidence profile: amiodarone versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amiodarone**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Restoration of sinus rhythm- acute AF [36,73,112,133,168,244,356]												
7	randomised trials	very serious[a]	very serious[b]	no serious indirectness	no serious imprecision	none	241/326 (73.9%)	116/277 (44.4%)	RR 1.71 (1.22 to 2.39)	297 more per 1000 (from 92 more to 582 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias in four studies; small numbers in one study; all patients received digoxin in two studies; performance bias, reporting bias and attrition bias in one study
b. I2=75%; p=0.0005
c. Selection bias in two studies; all patients also received digoxin in two studies

Table 113: Clinical evidence profile: amiodarone versus flecainide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amiodarone	Flecainide	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF [36,73,133,306]												
4	randomised trials	serious[a]	serious[b]	no serious indirectness	serious[c]	none	101/160 (63.1%)	141/168 (83.9%)	RR 0.76 (0.58 to 0.99)	216 fewer per 1000 (from 9 fewer to 378 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias in one study; performance bias in one study
b. I2=74%; p=0.02
c. Confidence interval crossed one MID

Table 114: Clinical evidence profile: Magnesium versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Magnesium	Placebo	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF [93]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/24 (8.3%)	6/24 (25%)	RR 0.33 (0.07 to 1.49)	167 fewer per 1000 (from 233 fewer to 123 more)	MODERATE	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a Selection bias; groups not comparable at baseline

Table 115: Clinical evidence profile: digoxin versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digoxin	Placebo	Relative (95% CI)	Absolute		
Restoration of sinus rhythm-acute AF [141,206]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	69/135 (51.1%)	64/120 (45.2%)	RR 1.12 (0.88 to 1.43)	54 more per 1000 (from 54 fewer to 194 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias; in one study baseline data were not provided and not all data could be analysed
b. Confidence interval crossed one MID

Table 116: Clinical evidence profile: amiodarone versus vernakalent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amiodarone	Vernakalent	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF [67]												
1	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60/116 (51.7%)	6/116 (5.2%)	RR 10 (4.5 to 22.23)	468 more per 1000 (from 182 more to 1000 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias; reporting bias

Table 117: Clinical evidence profile: magnesium versus calcium channel blockers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Magnesium	Calcium channel blockers	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF [89]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	13/23 (56.5%)	5/23 (21.7%)	RR 2.6 (1.11 to 6.11)	347 more per 1000 (from 24 more to 1000 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a Selection bias; small study
b Confidence interval crosses one MID

Table 118: Clinical evidence profile: propafenone versus amiodarone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propafenone	Amiodarone	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF [48,244,306]												
3	randomised trials	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	73/139 (52.5%)	79/141 (64%)	RR 0.97 (0.71 to 1.34)	19 fewer per 1000 (from 186 fewer to 218 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Performance bias in one study; selection bias in two studies; in two studies patients also received digoxin Selection bias; all patients received digoxin

Table 119: Clinical evidence profile: Amiodarone versus sotalol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amiodarone	Sotalol	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF [216,429]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57/91 (62.6%)	55/85 (66%)	RR 0.99 (0.8 to 1.22)	7 fewer per 1000 (from 132 fewer to 145 more)	MODERATE	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Small numbers in one study; selection bias in two studies; performance bias in one study.

Table 120: Clinical evidence profile: Amiodarone versus digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amiodarone	Digoxin	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF [216,429]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[b]	none	57/91 (62.6%)	42/78 (54.2%)	RR 1.17 (0.91 to 1.52)	92 more per 1000 (from 49 fewer to 282 more)	LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Small numbers in one study; selection bias in two studies; performance bias in one study.
b. Confidence interval crossed one MID

Table 121: Clinical evidence profile: Sotalol versus digoxin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sotalol	Digoxin	Relative (95% CI)	Absolute		
Restoration of sinus rhythm- acute AF [216,429]												
2	randomised trials	serious[a]	very serious[b]	no serious indirectness	serious[c]	none	55/85 (64.7%)	42/78 (54.2%)	RR 1.18 (0.70 to 2.01)	97 more per 1000 (from 162 fewer to 544 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Small numbers in one study; selection bias in two studies; performance bias in one study.
b. I2=74%; p=0.05
c. Confidence interval crossed one MID

Table 122: Clinical evidence profile: Beta-blocker versus calcium channel blocker

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	B-blocker	Ca ch blocker	Relative (95% CI)	Absolute		
Restoration of sinus rhythm at 24 hours -Acute AF [193]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	10/26 (38.5%)	10/24 (41.7%)	RR 0.92 (0.47 to 1.82)	33 fewer per 1000 (from 221 fewer to 342 more)	VERY LOW	CRITICAL
Mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Health-related quality of life												

0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias
b. Confidence interval crossed both MIDs

19.3.5 Electrical Restoration of sinus rhythm

Table 123: Clinical evidence profile: ECV versus propafenone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Propafenone	ECV	Relative (95% CI)	Absolute		
Successful cardioversion within 6 hours of intervention [41]												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	93/126 (73.8%)	108/121 (89.3%)	RR 0.83 (0.73 to 0.93)	152 fewer per 1000 (from 63 fewer to 241 fewer)	LOW	CRITICAL
Patients in AF at 60 days [41]												
1	Randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	None	21/74 (28.4%)	21/91 (26.4%)	RR 1.08 (0.65 to 1.77)	21 more per 1000 (from 92 fewer to 203 more)	VERY LOW	CRITICAL
Health-related quality of life												
0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

a. Selection bias

b. Confidence interval crossed both MIDs

19.3.6 Economic evidence

Published literature

No relevant economic evaluations comparing management strategies for acutely presenting AF were identified.

Two economic evaluations relating to this review question were identified but were excluded due to a combination of limited applicability and methodological limitations.[235,377] These are summarised in Appendix K with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs of the interventions were considered and can be found in Appendix N.

19.3.7 Evidence statements (rate control drug strategies)

Clinical

Low quality evidence from one study (N=47) showed that there is no clinical difference between digoxin and placebo at reducing heart rate 30 minutes post treatment.
Very low quality evidence from one study (N= 40) showed that IV diltiazem is clinically more effective than an IV beta-blocker at lowering ventricular rate.
Low quality evidence from one study (N= 100) showed that amiodarone is clinically more effective than digoxin at lowering ventricular rate.
No evidence was found for health-related quality of life or mortality.

Economic

No relevant economic evaluations were identified that looked at the AF presenting acutely.

19.3.8 Evidence statements (restoration of sinus rhythm)

Pharmacological restoration of rhythm

Low to very low quality evidence showed that propafenone and flecainide are clinically effective compared to placebo (thirteen studies, N=1416).

Very low quality evidence showed that amiodarone may be clinically effective compared to placebo (seven studies, N=603).

Moderate quality evidence showed that magnesium may not be clinically effective compared to placebo, but the direction of the estimate of effect could favour either intervention (one study, N= 48).

Low quality evidence showed that there may be no clinical difference between digoxin and placebo (two studies, N=275).

Restoration of sinus rhythm-Antiarrhythmic versus another antiarrhythmic

Amiodarone is more clinically effective than vernakalent (Low quality evidence, one study, N=232)

Magnesium is more clinically effective than calcium channel blockers (Low quality evidence, one study, N=46).

Evidence showed no clinical difference between:

- flecainide and propafenone (low quality evidence, three studies, N=299)
- amiodarone and sotalol (Moderate quality evidence, three studies, N= 176).

Evidence showed that there may be no clinical difference between:

- amiodarone and flecainide (Very low quality evidence, two studies, N=328) but the direction of the estimate of effect favoured flecainide
- amiodarone and digoxin (Low quality evidence , one study, N=169) but the direction of the estimate of effect favoured amiodarone.

Evidence showed that there *may* be no clinical difference between:

- amiodarone and propafenone (Low quality evidence, three studies, N=280)

- sotalol and digoxin (Very low quality evidence , two studies, N=163)
- beta-blockers and calcium channel blockers (Very low quality evidence , one study, N=50)

but the direction of the estimate of effect could favour either intervention

No evidence was found for health-related quality of life or mortality.

Pharmacological versus electrical

No clinical difference (one study, n= 247) was found between propafenone and electrical cardioversion in:

- successful cardioversions within 6 hours (Low quality evidence)
- the numbers of patients in AF at 60 days (Very low quality evidence).

No evidence was found for health-related quality of life or mortality.

Economic

No relevant economic evaluations were identified that looked at the AF presenting acutely.

19.3.9 Recommendation and link to evidence (rhythm control strategies)

Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	The GDG considered the following outcomes to be critical for decision making: mortality, health related quality of life and restoration of sinus rhythm or time to restoration. The only outcome reported for these studies was restoration of sinus rhythm. The studies that reported time to restoration did not provide the results in an appropriate form that could be used in the analysis. The time to restoration outcome was reported as a mean (SD) in all studies when a hazard ratio (HR) would have been more appropriate.
Trade-off between clinical benefits and harms	The GDG agreed that ECV is the optimum intervention in patients in acute AF that are haemodynamically unstable. The GDG recognised the clinical and logistical challenges inherent is delivering electrical cardioversion to patients presenting in acute haemodynamically unstable AF. There are major ethical problems in evaluating different therapies in patients who are acutely ill in whom the imminent risk of death is significant. In a situation of haemodynamic instability attributable to AF with a rapid, uncontrolled ventricular response it is essential that therapy should be: • prompt • have the highest probability of success • have the lowest probability of causing more malignant arrhythmias • avoid reducing cardiac output further (negative inotropy) The GDG discussed these issues and in the absence of any evidence to the contrary made the recommendation supporting electrical cardioversion as first line therapy in haemodynamically unstable AF. This is in line with standard current practice. Amiodarone, flecainide and propafenone are more clinically effective than placebo in

	restoring sinus rhythm for patients with acute AF. Flecainide was more clinically effective than amiodarone. Vernakalent was more clinically effective than amiodarone. Magnesium was more clinically effective than diltiazem (calcium channel blockers). The included studies found no clinical difference in the restoration of sinus rhythm between the following pharmacological drugs: • sotalol and amiodarone • sotalol and digoxin • beta-blockers and digoxin • beta-blockers and calcium channel blockers • amiodarone and propafenone • amiodarone and digoxin • flecainide and propafenone • digoxin and placebo • magnesium and placebo • electrical cardioversion and propafenone. The GDG agreed that there was a clinical benefit for amiodarone, flecainide and propafenone for restoration of sinus rhythm. Moreover, acute administration of these drugs is not associated with some of the side effects associated with more long term use. It was noted that propafenone is not available as an IV preparation in the UK. Therefore, amiodarone and flecainide were recommended for pharmacological cardioversion for new onset AF. However, the GDG discussed the implications of flecainide being contraindicated in patients with structural or ischaemic heart disease and the danger of inexperienced clinicians giving this drug to AF patients with unrecognised heart disease. The GDG agreed it was essential to ensure that clinicians administering this drug were knowledgeable of potential adverse effects and experienced in its use. The GDG discussed the comparative merits of electrical and pharmacological cardioversion in haemodynamically stable patients and recognised that whilst electrical cardioversion has a higher success rate, pharmacological cardioversion is often successful and does not require the patient to be sedated or anaesthetised. In addition patients may prefer a pharmacological technique. Magnesium was more clinically effective than calcium channel blockers but less effective than placebo. Therefore, the GDG considered these drugs showed harm and should not be used for cardioversion. The beta-blocker used in the referenced studies was sotalol given in high intravenous doses seldom used in the UK. The GDG agreed that sotalol had no proven benefit over other beta-blockers but did have a potential for specific adverse effects and should not be used.
Economic considerations	No economic evaluations were retrieved that compared different pharmacological rhythm control strategies to electrical cardioversion in patients with acute AF. In the absence of evidence, the GDG qualitatively weighed up the respective resource use against the potential net benefit. It was recognised that for patients in acute AF, both electrical and pharmacological cardioversion could take place in the acute setting and would require staff with sufficient expertise to administer both

	interventions. Therefore a hospital admission, and staff time, was likely to be involved for all strategies. The additional resource use involved in electrical cardioversion in comparison to pharmacological cardioversion, is the presence of an anaesthetist or an emergency physician trained in sedation techniques. The potential net clinical benefit of electrical cardioversion for patients, who are haemodynamically unstable was felt to outweigh this cost. Where pharmacological cardioversion is preferred, it is unclear which strategy is optimal. The GDG noted that the immediate costs of acute rhythm pharmacological control drugs were higher than for chronic control (as it involved IV infusion and hospital admission), however as drugs for chronic rhythm control would be taken over a life time rather than administered as a one off event, the economic implications of recommendations for chronic rate control was higher than that for acute rate control. As there was no economic evidence retrieved for use of the agents under consideration, the GDG felt cost effectiveness and overall conclusions were best considered by reference to clinical net benefit.
Quality of evidence	The evidence ranged for very low to moderate quality for the restoration of sinus rhythm outcome.
Other considerations	Vernakalent is not licensed in the UK and the GDG were not able to consider this drug for any of the recommendations. Definition of acute AF in studies was usually less than 48 hours but varied between studies. One study (Blanc 1999[48]) defined acute as less than 2 weeks. The recommendations came from the evidence and experience and opinion of the GDG. In situations where the patient and clinician are confident the rhythm onset was within 48hrs, it is appropriate to consider interventions to restore sinus rhythm. There is good evidence that the duration of atrial fibrillation is inversely related to the success of rhythm restoration strategies, and accordingly early intervention is of clinical benefit. In patients where the time of onset is either uncertain or greater than 48 hours the priority is to offer symptom control through rate control, and an assessment of stroke risk to enable appropriate consideration of anticoagulation therapy. The GDG also noted the use of the “pill in the pocket” approach to restoring sinus rhythm (see 16.3), which for selected patients, offers a means of restoring sinus rhythm following the acute onset of AF and can avoid the need to come to hospital. The recommendations from the 2006 guideline were included in this guideline as the GDG agreed they were still relevant to the AF clinical pathway (see evidence statements in section 16.3.3). In patients with an antegradely conducting accessory pathway (Wolff-Parkinson-White syndrome (WPW) syndrome) who develop AF, there is a dangerous acceleration of ventricular rate with a corresponding reduction in cardiac output and an increased risk of VF. The review did not report on this subgroup specifically and therefore evidence was not assessed, so the GDG did not feel it appropriate to make a formal recommendation. However they felt appropriate to advise that treatment of haemodynamically unstable AF and WPW is DC cardioversion. Flecainide IV is an

	acceptable alternative in patients with known WPW. AVN (Atrio-Ventricular Node) blocking drugs in such circumstances are potentially dangerous and should be avoided.

19.3.10 Recommendations and link to evidence (rate control strategies)

Recommendations	**The current recommendations can be found at** http://www.nice.org.uk/guidance/ng196
Relative values of different outcomes	The GDG considered the critical outcomes to be mortality, health related quality of life and heart rate to assess rate control.
Trade-off between clinical benefits and harms	One study[121] found a clinical benefit for calcium channel blocker diltiazem in percentage decrease in ventricular rate compared to beta-blocker. Diltiazem was given as an IV preparation in the study. In one study[215] heart rate 30 minutes post treatment showed a clinical benefit for digoxin when compared to placebo. The GDG discussed that you would expect to see an effect between 2-12 hours after treatment so it was unusual to see this positive treatment effect within 30 minutes. One study[202] compared digoxin and amiodarone. There was a clinical benefit in mean ventricular rate favouring amiodarone in hospitalised patients. The GDG summarised that there was a lack of evidence to support one drug over another and any of the treatments could be considered in the acute setting. The GDG were of the opinion that the decision to adopt a rate control strategy in patients presenting acutely with AF would be governed by a number of factors. Because of the stroke risk associated with reversion to sinus rhythm when AF duration exceeds 48 hours, a rate control strategy is indicated whenever the duration of AF exceeds 48 hours or in whom the time of onset is uncertain. For new onset AF within 48 hours, many factors will contribute to the rate/rhythm decision, including haemodynamic status of the patient, the presence of co-morbidities influencing the likelihood of AF recurrence (e.g. infection). Co-morbidities are likely to be similarly important in selecting a drug for acute rate control.
Economic considerations	There was no economic evidence to inform this recommendation. No economic evaluations were retrieved that compared different pharmacological rate control strategies in patients with AF. The GDG noted that the immediate costs of acute rate control drugs were higher than for chronic control (as it involved IV infusion and hospital admission), however as drugs for chronic rate control would be taken over a life time rather than administered as a one off event, the economic implication of recommendations for chronic rate control were higher than that for acute rate control. As there was no economic evidence retrieved for use of the agents under consideration for acute rate control, the GDG felt cost effectiveness was best considered by reference to the costs associated with long term rate control.
Quality of evidence	All the outcomes had a very low to low GRADE quality rating. In addition each of the three rate control drug comparisons only had one study to support the findings and only reported one relevant outcome.

	The GDG felt that there was not enough evidence to support one drug over another and recommended a choice of all the available drugs, to be used depending on the associated comorbidities and clinical presentation.
Other considerations	Diltiazem is not available in the UK by IV preparation and the oral preparation is licensed and used for AF in the UK. The recommendation came from low quality evidence and the experience and opinion of the GDG. The GDG recognised that in some patients the choice between rate and rhythm control strategies might be unclear and that amiodarone would offer efficacy in both strategies through both controlling ventricular rate and increasing the likelihood of restoring sinus rhythm. However, if using this approach, any possible thromboembolic risk consequent on restoration of sinus rhythm should be recognised and amiodarone should not be used if the duration of AF is greater than 48 hours, unless adequate thromboprophylaxis is in place.

19.4 Antithrombotic therapy for acute-onset AF

19.4.1 Introduction

The aim of this section is to examine which antithrombotic therapy, if any, is most effective in treating patients with acute-onset AF, including the postoperative setting.

The onset of AF is associated with a cluster of thromboembolic events,[461] but the development of intra-atrial thrombi, and the immediate risk of thromboembolism, is perceived to be minimal within the first 48 hours.

In one study of 357 patients with symptomatic acute-onset AF of less than 48 hour duration (of whom 250 converted spontaneously to sinus rhythm and 107 underwent cardioversion without any anticoagulation), thromboembolism only occurred in three patients.[457] In another series of 258 patients undergoing cardioversion for AF of less than 2 days duration, only one embolic event occurred out of 198 patients who did not receive pre- or post-cardioversion warfarin.[165] However, in a further study, patients with acute AF of an apparent duration of less than 3 days were found to have an intra-atrial thrombus detected by TOE in approximately 15% of cases.[421] This raises the possibilities that either the development of intra-atrial thrombus may be more rapid than previously suspected and/or that some cases of presumed recent-onset AF may have had the arrhythmia (possibly asymptomatically) for longer.

Thus, in patients presenting de novo with AF, a clear history of arrhythmia onset is necessary in order to guide appropriate antithrombotic therapy and, if performed, the safety of cardioversion.

19.4.2 Methodological introduction

No studies were found that addressed this clinical area.

19.4.3 From evidence to recommendations

Although no randomised trials have specifically addressed the issue of acute-onset AF, common clinical practice indicates that cardioversion may be safely performed without the need for oral anticoagulation if AF has been present for less than 48 hours.[407] However, in cases of uncertainty about arrhythmia onset, anticoagulation therapy is warranted.

The GDG discussed the use of intravenous unfractionated heparin and subcutaneous low molecular weight heparin (LMWH). Both drugs are routinely used in clinical practice in the acute and peri-cardioversion periods. It was agreed that anticoagulation with heparin could be started at the presentation of acute AF while the INR remains sub therapeutic during the initiating phase of oral anticoagulation.

Acute AF may present with a fast ventricular response, leading to haemodynamic instability, which may require urgent direct current (DC) cardioversion. Where the degree of haemodynamic instability is life threatening (for example, cardiogenic shock), DC cardioversion may need to be performed rapidly and in such cases would take priority over the need for anticoagulation.

19.4.4 Recommendations

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

20 Initial management of stroke and atrial fibrillation

Stroke is of major significance in relation to atrial fibrillation (AF). Whilst the original AF guideline included stroke recommendations, stroke was not in the new AF scope.

The GDG debated the original AF stroke recommendations from the previous NICE AF guideline. Part of the difficulty is that there were elements of the stroke and AF original recommendations that the GDG wanted to keep and elements that were out of date. Rather than represent incomplete stroke and AF recommendations the GDG elected to leave out all of the old AF recommendations pertaining to this area (section 1.8.2 and 1.8.3 of the previous NICE AF guideline) and in light of the NICE acute stroke guideline and the RCP National clinical guideline for stroke (4th edition, 2012), the GDG agreed to cross refer to the relevant NICE stroke guideline.

21 Postoperative AF

This section was partially updated in 2021. See http://www.nice.org.uk/guidance/ng196/evidence for the 2021 evidence reviews.

Postoperative AF (post-op AF) following cardiothoracic surgery is a significant problem, occurring in approximately 33% of patients after coronary heart surgery.[446] The occurrence following valvular heart surgery is even higher.[108]
Post-op AF is associated with a greater risk of mortality and morbidity.[17] Evidence is also emerging[277] that post-op AF predisposes people to a significantly increased risk of stroke and thromboembolism, suggesting that patients should be anticoagulated where post-op AF persists for more than 48 hours.[297]
Although post-op AF can be transient and generally self-limiting, treatment is indicated for those patients who remain symptomatic, become haemodynamically unstable, and develop cardiac ischaemia or heart failure. Conventional treatment strategies have included ECV, atrial overdrive pacing using temporary epicardial pacing leads (if atrial flutter is the dominant rhythm), pharmacological rate control and antithrombotic therapy. Cardioversion may also be attempted prior to hospital discharge.
Management of medical comorbidities (e.g. hypoxia) and the correction of underlying electrolyte imbalance (especially potassium and magnesium) is well recognised[126,387] in the prevention of post-op AF. Most units have strategies to maintain the serum potassium above 4 mmol per litre and some will often endeavour to maintain the serum potassium higher than 4.5 mmol per litre.[32] One recent meta-analysis[314] found that magnesium administration is an effective prophylactic measure for the prevention of post-op AF, but did not significantly alter length of stay or in-hospital mortality.
Currently, there is significant variation in the management of post-op AF. The aim of this chapter is to assess whether the perioperative administration of antiarrhythmic drugs is effective prophylaxis to prevent post-op AF (21.1), and in those cases where post-op AF develops, to determine which is the most effective treatment strategy (21.2).

21.1 Drug prophylaxis for postoperative AF

21.1.1 Methodological introduction

Of the studies considering prophylaxis, the majority concerned the prevention of post-op AF following cardiac surgery, and most of these results are summarised in a meta-analysis.[111] The other studies[18,19,38,54,261,443] considered non-cardiac thoracic procedures (e.g. pneumonectomy).
The reporting of side effects associated with antiarrhythmic drugs was not consistent, with many studies having too few participants to make any meaningful comparisons.
Studies were included if comparison was made between an antiarrhythmic drug or cardiac glycoside available in the UK, and a placebo or no-treatment control. The management of electrolyte imbalance (e.g. magnesium or potassium) was not assessed.
Five US studies[113,261,296,369,370] considering the cost effectiveness of drug prophylaxis were appraised and met quality criteria.
Two studies[369,370] estimated the mean cost per case of post-op AF avoided, of oral amiodarone prophylaxis versus no prophylaxis in patients undergoing coronary bypass grafting (CABG).
One study[296] estimated the cost per AF averted of intravenous amiodarone therapy in CABG, valve and CABG plus valve patients, according to their predicted risk of postoperative AF.
One study[261] estimated the median total hospital costs in patients with and without oral amiodarone prophylaxis based on the medical records of patients after pulmonary resection.
One study[113] estimated the total hospitalisation costs in a RCT of oral amiodarone prophylaxis versus placebo in patients undergoing cardiopulmonary bypass.

One study[370] estimated the total hospital costs in oral amiodarone prophylaxis versus placebo groups based on the Atrial Fibrillation Suppression Trial.

21.1.2 Evidence statements

21.1.2.1 Drug prophylaxis in cardiac surgery

Amiodarone

In a meta-analysis of 14 studies[111] which compared amiodarone with placebo or no treatment, amiodarone administered pre-, intra- or postoperatively was found to be associated with a reduced incidence of post-op AF or other supraventricular arrhythmia (OR 0.54, 95% CI 0.44 to 0.67; p<0.00001) (1+). Similar results were found in other primary studies.[33,208,219,228,236,242,419,434] (1++)

In one study[459] amiodarone was significantly associated with a reduced incidence of post-op AF lasting longer than 24 hours, and episodes that required treatment, compared with placebo. (1++)

One study[228] found that amiodarone resulted in a reduced duration of post-op AF compared with no treatment (11.0 versus 16.2 days; p<0.001) (2+). Two smaller studies[113,373] found no significant difference in the duration of post-op AF. (1++)

One study[459] found rapid preoperative amiodarone loading resulted in more nausea than placebo (31.3% versus 16.0%; p=0.018), this was not observed with slow loading (21.4% versus 16.0%) (1++). There was no difference reported in the incidence of hypotension for either strategy. (1++)

Beta-blockers (excluding sotalol)

One meta-analysis of 28 studies[111] found beta-blockers (excluding sotalol) resulted in less post-op AF and other supraventricular arrhythmias (OR 0.35, 95% CI 0.26 to 0.49; p<0.00001) (1+). This result is consistent with the results of other primary studies,[33,100,252,434,464] in one of which[33] there was a significant increase in postoperative symptomatic bradycardia (less than 40 bpm) compared with placebo (16.1% versus 3.1%; p<0.05). (1+)

Sotalol

A meta-analysis of eight studies[111] found sotalol reduced post-op AF and other supraventricular arrhythmias compared with control (OR 0.36, 95% CI 0.23 to 0.56) (1+). Two other primary studies[33,308] showed similar results, one of which[33] found a significant association between the use of sotalol (240 mg three times a day) and the incidence of postoperative symptomatic bradycardia (<40 bpm) compared with placebo (12.7% versus 3.1%; p<0.05) (1+). The study did not report any incidence of pro-arrhythmic side effects associated with sotalol.

Rate-limiting calcium channel blockers

Four studies[191,229,298,398] found the rate-limiting calcium channel blocker diltiazem to be significantly associated with a lower incidence of post-op AF compared with placebo or no treatment (1++). A similar result has also been found for the rate-limiting calcium channel blocker verapamil.[144] (1+)

Propafenone

One study[253] found propafenone administered at 675 mg/day (although not at 450 mg/day) decreased post-op AF compared with placebo. (1++)

Procainamide

One study[173] found no difference in the incidence of post-op AF between procainamide and placebo but did reduce the number of patient days spent in post-op AF (16 versus 19 days; p<0.05) (1++). It was found to be significantly associated with an increased incidence of nausea compared with placebo (64% versus 32%; p<0.01) (1++). Another smaller study[263] (N=46) found procainamide to be significantly associated with a reduced incidence of post-op AF compared with placebo (3.9% versus 10.6%; p<0.04). (1++)

Digoxin

A meta-analysis of two studies,[252] as well as another primary study[458] not included in the meta-analysis found digoxin did not reduce post-op AF when compared with no treatment. (1+)

21.1.2.2 Drug prophylaxis in thoracic (non-cardiac) surgery

Beta-blockers

One study[211] found beta-blockers to be effective in reducing post-op AF compared with placebo in favour of beta-blockers (6.7% versus 40.0%; p<0.05) (1+). Another[38] found a non-significant reduction in any arrhythmia requiring treatment but increased incidences of post-operative bradycardia and hypotension respectively (25% versus 4% compared with placebo; p=0.018; 49% versus 26% compared with placebo; p=0.003). (1++)

Rate-limiting calcium channel blockers

One study[19] found diltiazem did not significantly reduce the overall incidence of post-op AF; but when considering those over 60 years old only (15% versus 25%; p=0.05), or when other cardiac arrhythmias were included (14% versus 26%; p=0.03), diltiazem was effective (1++). Another study[443] did not find diltiazem effective compared with placebo (8% versus 15%). (1+)

Flecainide

One study[54] found flecainide effectively reduced all postoperative cardiac arrhythmia requiring treatment (including AF) compared with placebo (0% versus 6%; p<0.05). (1++)

Digoxin

One study[18] found no other treatments compared with digoxin in reducing the incidence of post-op AF following pneumonectomy (31% versus 28%). (2+)

Amiodarone

One study[261] found amiodarone reduced post-op AF compared with no treatment (9.7% versus 33%; p=0.025) following pneumonectomy. (2+)

21.1.2.3 Health economics

There was no significant difference in total hospital costs in oral amiodarone prophylaxis versus placebo (US$15,565 + US$9,832 versus US$16,126 + US$8,043, p=0.12) and a higher per cent of episodes of AF prevented (77% versus 62%).[370]

There was no significant difference between median total hospital costs (US$30,800 (20,400–96,900) in 50 patients without prophylaxis versus US$26,700 (11,000–55,900) in 31 patients with low dose oral amiodarone prophylaxis). Significantly less patients developed postoperative AF with low dose oral amiodarone (9.7% versus 33%, p=0.0253).[261]

One study[113] found a significantly lower mean total cost of hospitalisation in the oral amiodarone group compared with placebo in patients undergoing cardiopulmonary bypass surgery (US$18, 375 + US$13,863 versus US$26,491 + US$23,837, p=0.03).

One study[369,370] estimated the mean cost per AF event avoided was lower in the oral amiodarone group versus no prophylaxis (US$15,750, 95% CI US$15,591 to US$15,999 versus US$17,426, 95% CI US$17,252 to US$17,600). Multivariate sensitivity analysis indicated these findings were most sensitive to the cost of hospitalisation and frequency of AF.

One study[296] indicated the cost effectiveness of prophylactic intravenous amiodarone therapy varied according to the type of cardiac surgery and predicted risk of postoperative AF. As the risk of AF in the targeted patient's increases, the cost-effectiveness ratio improves.

- For CABG patients, the ICERs ranged from US$10,938 for the highest risk patients to US$55,854 per AF averted in the lowest risk patients.
- For valve replacement patients the ICERs ranged from US$4,219 in the highest risk patients to US$43,011 per AF averted in the lowest risk patients.
- For CABG and valve replacement patients the ICERs ranged from US$69 for the highest risk patients to US$39,698 per AF averted in the lowest risk patients.

21.1.3 From evidence to recommendations

Although no specific evidence was evaluated regarding the association between electrolyte balance and the incidence of post-op AF, it was agreed that scrupulous attention to electrolyte balance was important.

Drug prophylaxis to reduce the risk of post-op AF relates to the need to:

- continue existing medication (e.g. beta-blockers)
- administer a drug preoperatively (e.g. beta-blockers or amiodarone), or
- administer a drug in the immediate postoperative period (e.g. sotalol or amiodarone).

In many of the studies, the majority of patients were already taking beta-blockers pre-operatively, and these were either discontinued in the postoperative period or continued, despite the use of beta-blockers being recognised as an independent (negative) predictor of post-op AF.[184,307] In those studies where beta-blockers were continued postoperatively, the results may be confounded by this additional cardio-protective effect, which may be insensitive to additional antiarrhythmic medication, particularly beta-blockers, thus underestimating the effectiveness of the prophylaxis. Alternatively, in those studies where beta-blockers were discontinued, the incidence of post-op AF may be exaggerated by the withdrawal of the cardio-protective effects of beta-blockers, which in some patients may have been preventing the development of arrhythmias aetiologically independent from post-op AF.
For non-cardiac thoracic surgery, there was evidence for efficacy of the same drugs as used in cardiac surgery in the prevention of post-op AF.
It was agreed that beta-blockers, including sotalol, were effective prophylactic drugs, and that those patients who were receiving pre-existing therapy with these drugs would benefit from a reduced risk of post-op AF if those drugs were continued, unless there were compelling reasons to withdraw them (e.g. postoperative hypotension or bradycardia).
It was agreed that digoxin is not effective in preventing postoperative AF.[252,458]
Administering amiodarone slowly over 5 to 7 days preoperatively and continuing during the perioperative period is more effective and associated with fewer side effects than more rapid loading.[459]
There is an increased risk of bradycardia associated with the use of beta-blockers and nausea associated with procainamide, as well as with amiodarone when loaded rapidly in the pre-operative period.
Data from the USA suggest the prophylactic administration of amiodarone for the prevention of post-op AF is cost effective, particularly in high-risk patients, compared with no prophylaxis for certain cardiac procedures. It was noted that there may be cost differentials between the UK and the USA for antiarrhythmic drugs.

21.1.4 Recommendations

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

21.2 Treatment for postoperative AF

21.2.1 Methodological introduction

The results of nine studies considering the treatment of postoperative AF were included, all except one[400] were prospective RCTs. The other was placebo-controlled[102] with a 2x2 crossover study design with no reported wash-out period between crossover. Of the reported RCTs, none had the statistical power to identify effect sizes that may be considered clinically significant.
A rate-control strategy was defined as one which involved the administration of drugs to control heart rate; a rhythm-control strategy was defined as one which involved treatment with electrical or pharmacological cardioversion or the administration of drugs known to be effective in pharmacological cardioversion. In many studies the objectives of each treatment group were not explicitly reported, in which case a comparison of a rate-control treatment strategy with a rhythm-control treatment strategy was presumed based on the established differential actions of the

interventions considered. The duration of follow-up times varied between the studies (less than 1 hour to 30 days).
One study[102] compared rhythm control to no-treatment. All of the other studies compared rate control with pharmacological rhythm control. There were no studies comparing either rate control with rhythm control using electrical cardioversion or rate control versus no treatment.
None of the studies reported results for patients with post-op AF and haemodynamic instability requiring urgent medical intervention.

21.2.2 Evidence statements

In patients with post-op AF, where various rhythm- and rate-control strategies have been compared (see Table 124 and Table 125), rhythm control results in:

- greater cardioversion within 1 hour but not after 24 hours[68,97,102,200,416,452]
- shorter time for restoration of sinus rhythm[267]
- no difference in ventricular rate control[102,452]
- higher rates of therapeutic effectiveness[452]
- no difference in relapse rates.[267]

Table 124: Comparison of rhythm-control treatments for post-op AF with rate-controlling treatments or no treatment in terms of percentage of patients reverting to sinus rhythm

	Comparison	N	Period (hours)	Rhythm (%)	Control (%)	p
(1+)	Flecainide/digoxin[452]	29	1	60	0	<0.001
(1+)	Propafenone/placebo [102]	14	1	43	0	<0.001
(1+)	Procainamide/digoxin [200]	30	12	93	60	<0.05
(1+)	Sotalol/digoxin*[68]	40	12	85	85	NS
(1+)	Propafenone/various **[416]	32	24	35	50	NS
(1+)	Amiodarone/digoxin[97]	30	24	93	87	NS

**Digoxin with additional disopyramide if sinus rhythm was not restored within 2 hours.*
***Various = uncontrolled use of beta-blockers, calcium channel blockers or digoxin in both treatment arms.*

Table 125: Comparison of rhythm-control treatments for post-op AF with rate-controlling treatments or no treatment

	Outcome	N	Test/control	Test	Control	N
(1+)	Conversion time, hours	50	Rhythm-control drugs/ rate-control drugs*[267]	11.2	11.8	NS
(1+)	Therapeutic rate control	24	Propafenone/no treatment250	26%	11.2%	<0.0001
(1+)	Therapeutic rate control**	29	Flecainide/digoxin[452]	7%	14%	NS
(1+)	Therapeutic effectiveness	29	Flecainide/digoxin[452]	67%	14%	<0.0001
(1+)	AF recurrence at 1 week	50	Rhythm-control drugs/ rate-control drugs*[267]	24%	28%	NS
(1+)	AF recurrence at 4 weeks	50	Rhythm-control drugs/ rate-control drugs*[267]	6%	12%	NS

	Outcome	N	Test/control	Test	Control	N
(1+)	AF recurrence at 8 weeks	50	Rhythm-control drugs/ rate-control drugs*[267]	4%	9%	NS
(1+)	AF recurrence	40	Sotalol/digoxin†[68]	5%	35%	<0.05

**Rhythm-control drugs: sotalol, procainamide, propafenone or amiodarone. Rate-control drugs: diltiazem, verapamil, beta-blockers or digoxin.*
***HR <100 bpm within 45 minutes of administration.*
†Digoxin with additional disopyramide if sinus rhythm was not restored within 2 hours.

Two studies[267,400] of various rhythm-control versus rate-control strategies have shown shorter overall length of hospital stay with rhythm-control strategies but results for postoperative length of stay have been inconsistent (see Table 126).

Table 126: Comparison of rhythm-control and rate-control treatments in terms of length of stay (days)

	Study	N	LOS measure	Rhythm	Rate	p
(1+)	Lee et al[267]	50	Hospital	9.0	13.2	<0.05
(1+)	Lee et al[267]	50	Post-op only	7.4	9.7	<0.01
(2+)	Shah et al[400]	101	Post-op only	8.3	6.3	<0.01

LOS measure = length of hospital stay measure.

21.2.3 From evidence to recommendations

The GDG agreed that the evidence suggested a trend towards a strategy of rhythm control over rate control. The evidence suggested that rhythm control produced a decreased time to cardioversion, prolonged maintenance of cardioversion, and decreased length of overall hospital stay. [267] However, the data supported the use of a rhythm-control strategy in achieving sinus rhythm only in the short term. In the longer term, there is little difference in the maintenance of sinus rhythm between either strategy.[68,97,102,200,416,452] It was noted that the number of study participants was relatively small and the follow-up periods were relatively short. Overall, it was concluded that a rhythm-control strategy provided short-term benefits.

21.2.4 Recommendations

The current recommendations can be found at http://www.nice.org.uk/guidance/ng196

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23 Acronyms and abbreviations

ACC	American College of Cardiology
ADT	Antiarrhythmic Drug Therapy
AE	Adverse Events
AF	Atrial Fibrillation
AHA	American Heart Association
AT	Atrial Tachycardia
AUC	Area under the curve
AV	Atrioventricular
AVN	Atrioventricular node
BPM	Beats Per Minute
CABG	Coronary Artery Bypass
CAD	Coronary Artery Disease
CHD	Chronic Heart Disease
CHF	Chronic Heart Failure
CI	Confidence Interval
CNS	Central Nervous System
CPVA	Circumferential Pulmonary Vein Ablation
DDDR	Dual Chambers pace, Dual chambers sensed, Dual response to this, and rate modifiable pacemaker
ECG	Electrocardiogram
ECV	Electrical CardioVersion
EP	Electrophysiology
ESC	European Society of Cardiology
GDG	Guideline Development Group
Hb	Haemoglobin
HD	Heart Disease
HIFU	High intensity focused ultrasound
HR	Heart Rate
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
INR	International Normalised Ratio
IQR	Interquartile range
ITT	Intention To Treat
IV	Intravenous
LA	Left Atrial
LAA-V	Left atrial appendage velocity
LAAO	Left Atrial Appendage Occlusion
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVF	Left Ventricular Failure
MI	Myocardial Infarction
MV	Mitral Valve

MVR	Mitral Valve Rate
N	Population Size
n	Sample Size
NR	Not Reported
NRI	Net Reclassification Index
NSAID	Non-Steroid Anti-Inflammatory Drug
NSR	Normal Sinus Rhythm
NYHA	New York Heart Association
OAC	Oral Anticoagulation
OECD	Organisation of Economic Co-operation and Development
P	Probability/Significance testing
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
Pm	Pacemaker
PTR	Prothrombin Time Ratio
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QALY	Quality Adjusted Life Year
RFA	Radiofrequency Ablation
RCT	Randomised Clinical Trial
RF	Radio Frequency
RR	Relative Risk
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEM	Standard Error of the Mean
SF-36	Short Form (36) Quality of Life
SICTRA	Saline-irrigated, cooled tip radiofrequency ablation
SPVI	Surgical Pulmonary Vein Isolation
TIA	Transient Ischaemic Attack
TTR	Time in therapeutic range
VKA	Vitamin K Antagonist
VVI	Paces and senses the ventricle and is inhibited by a sensed ventricular event.
WPW Syndrome	Wolff-Parkinson-White Syndrome

24 Glossary

Absolute risk	Measures the probability of an event or outcome occurring (for example, an adverse reaction to the drug being tested) in the group of people under study. Studies that compare two or more groups of patients may report results in terms of the Absolute Risk Reduction.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acute presentation	Patients presenting to secondary or tertiary medical care on account of new or recurrent symptoms which my either be due to new onset AF or to deterioration in rate control of existing AF.
Adjusted Dose	The situation where the dosage of a drug is adjusted to attain a particular physiological value, e.g. the dosage of warfarin may be adjusted to attain a particular INR value.
AF burden	A measure of the degree to which the presence of AF has a detrimental effect on the patient's quality of life. It is normally measured either as the proportion of time spent in AF, or the number of AF episodes per unit time.
AF recurrence	The recurrence of an episode of AF following one or more prior episodes of the arrhythmia in either its paroxysmal or persistent form.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Ambulatory-ECG	An ECG monitoring tool in which a continuous ECG recording is made while the patient remains able to walk around freely and pursue most normal daily activities
Antiarrhythmic	A drug or interventional procedure that has a therapeutic effect against cardiac arrhythmias.
Anticoagulation	A form of thromboprophylaxis involving the use of anticoagulant drugs such as warfarin that inhibit the coagulation/clotting of blood.
Antiplatelet therapy	A form of thromboprophylaxis involving the use of antiplatelet drugs (such as aspirin) that inhibit the formation of blood clots.
Antithrombotic therapy	See 'thromboprophylaxis'.
Aortic plaque	The deposits of atherosclerotic plaque within the aorta. The extent of aortic plaque is classified as 'simple', 'moderate' or 'complex'
Aortic stenosis	An abnormal narrowing of the aortic valve
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm
Arrhythmia	An irregularity in the coordinated rhythm of the heart.
Arrhythmia surgery	Antiarrhythmic surgical interventions to treat the abnormal heart rhythm
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Atrial arrhythmias	Cardiac arrhythmias that originate in the atria. AF is an atrial arrhythmia. See also 'arrhythmia'.

Atrial contractile function	A measurement of the contractile function of the atria. This is normally measured using echocardiography.
Atrial fibrillation (AF)	An atrial arrhythmia characterised by an absence of regular P waves on an electrocardiogram, and normally resulting in a fast ventricular response. See also ‘atrial arrhythmia’.
Atrial filling fraction	A measurement of the contractile function of the atria. This is normally measured using echocardiography
Atrioventricular node ablation	Use of energy (usually radiofrequency) to destroy tissue of the atrioventricular node to alter conduction of electrical signals through this part of the heart.
Atrioventricular-blocking drug	A drug that inhibits the ability of the atrioventricular node to conduct electrical signals to the ventricles.
Audit	See ‘clinical audit’.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers/doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Bradycardia	A slow heartbeat. The occurrence of bradycardia is often recorded as an adverse event to some antiarrhythmic or chronotropic drugs. Such occurrences are referred to as bradycardic events.
Cardioembolic stroke	An embolic stroke whose aetiology is presumed to be the embolization of an intra-cardiac thrombus.
Cardiomegaly	An abnormal enlargement of the heart. It is normally measured in terms of the cardiothoracic ratio from a chest X-ray or by measurement using echocardiography.
Cardiomemo	An event recorder that records cardiac rhythm when activated by the patient
Cardiothoracic ratio (CTR)	See ‘cardiomegaly’.
Cardioversion	In the context of AF, cardioversion is the process of restoring normal sinus rhythm. There are two commonly used forms of cardioversion: electrical cardioversion and pharmacological cardioversion. The former involves the administration of a transthoracic electrical shock; the latter involves the administration of antiarrhythmic drugs.

Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Cerebral infarction	Damage to the brain following a reduction of blood supply to that area, resulting in a stroke.
Cerebrovascular disease	Disease of the blood vessels within the brain. Cerebrovascular disease can be caused by blocked or otherwise damaged blood vessels and is the cause of strokes. See also ‘stroke’.
Chronotropic	In the context of pharmacology, the ability of a therapeutic intervention to control heart rate.
Chronotropic incompetence	The inability of the body to appropriately alter heart rate during periods of physical exertion. See also ‘chronotropic’.
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Clinically significant	The result of a study is clinically significant if it is felt that the demonstrated difference in outcomes between the different arms of the study have the potential to inform and change clinical practice. A result may be statistically significant but not clinically significant, and vice versa.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.

Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Congestive heart failure (CHF)	Heart failure characterised by the inability of the heart to adequately support the body's physiological requirements.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Conventional anticoagulation	The use of oral anticoagulation as a means of thromboprophylaxis, aiming for a target INR (usually 2.5, range 2–3) with monitoring and dose adjustment in an anticoagulation clinic.
Coronary artery disease	A disease which affects the arteries of the heart, normally through atherosclerosis of the coronary arteries, reducing the supply of blood to the heart and causing ischaemia and angina. See also 'ischaemic heart disease'.
Cost–benefit analysis (CBA)	Cost-benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost–consequences analysis	Cost-consequence analysis is one of the tools used to carry out an economic

(CCA)	evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost-benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost effectiveness	A measure of effectiveness that is relative to cost. For example, the cost effectiveness of antithrombotic therapy to prevent strokes may be measured in terms of the cost per stroke prevented. See also cost-effectiveness analysis and cost-effectiveness model.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost function	A function that describes the relationship between the input prices such as labour costs, drugs, hospital stay and the quantity of outputs (health outcomes). It describes the opportunity cost, that is, what needs to be sacrificed in monetary terms in order to gain certain outcomes.
Cost–utility analysis (CUA)	Cost-utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Coumarin derivative	An anticoagulant drug that is derived from coumarin. Examples of coumarin derivatives include the anticoagulant warfarin.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Crossover study	A study design in which the participants are first administered the control intervention, followed by the test intervention, or vice versa. In between these two study phases there is normally a wash-out period in the case of drug trials, so that the levels of the control or test drug falls to negligible amounts before the next phase of the study begins.
Cryoablation	Use of cold energy (‘freezing’) to destroy tissue within the heart in order to alter conduction of electrical signals through this part of the heart.
CT scan	Computed tomography scan, an imaging technique using X-rays.
Day case	In the context of cardioversion, a day case refers to the discharge of patients following elective cardioversion on the same day on which they were admitted.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Decision analytic model/techniques	A way of reaching decisions, based on evidence from research. This evidence is translated into probabilities and then into diagrams or decision trees that direct the clinician through a succession of possible scenarios, actions and outcomes.
Defibrillator	In the context of AF, a device used to deliver the electrical shock used in electrical cardioversion.
Diagnostic accuracy	The degree to which a diagnostic (or screening) tool or procedure is able to distinguish between cases and non-cases. See also ‘sensitivity’, ‘specificity’,

	'negative predictive value' and 'positive predictive value'.
Diastolic	Relating to the phase of the cardiac cycle where the chambers of the heart fill with blood prior to being pumped out during the subsequent systolic phase. See also 'systolic'.
Discounted survival	See 'discounting'.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Drug-eluting stents	Special metallic devices which are placed within the coronary artery to reduce the likelihood of coronary stenosis recurring following angioplasty (balloon dilatation of the coronary artery). Drug eluting stents have special drugs within their structure that greatly reduce the recurrence of stenosis.
Dyspnoea	Breathlessness.
Echocardiogram	An examination of the heart using ultrasound-imaging techniques. An echocardiogram may be performed by placing the ultrasound device across the chest (transthoracic echocardiography), or by inserting it down the gullet to view the heart from behind (transoesophageal echocardiography).
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits - health effects - relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost-benefit analysis, cost-consequence analysis, cost-effectiveness analysis, cost-minimisation analysis and cost-utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Electrical cardioversion (ECV)	See 'cardioversion'.
Electrocardiograph (ECG)	A device which traces the electrical activity of the heart by recording the electrical potentials at electrodes placed at various locations around the chest. The recording produced by the electrocardiograph is referred to as an electrocardiogram.
Electrolyte abnormalities	Abnormalities or an imbalance in one or more of the body's salts or other

	chemicals in the blood circulation.
Embolic	The passage within the blood stream of a body (e.g. blood clot), which has formed somewhere and ends up elsewhere within the body (e.g. brain).
Endpoint	In the context of study design, an endpoint is a pre-defined event or events whose occurrence represents the end of follow-up. A composite endpoint is one where more than one event is pre-defined, and the occurrence of any one of them represents the end of follow-up. A primary endpoint is the occurrence of the event, which is the main outcome of interest.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Event-ECG recorder	An ECG recording device, which only produces an ECG recording when susceptible electrical activity is detected. It may be triggered automatically or by the patient upon the occurrence of symptoms. See 'cardiomemo'.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exercise tolerance	A measure of a patient's capacity for physical exertion.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more cost effective and should be preferred, other things remaining equal.
Extra cellular fluid volume	A term that refers to the fluid bathing the body's cells.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Focal AF	AF secondary to a focus of abnormal cells (e.g. near the pulmonary veins) that can initiate AF.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Functional heart disease	Abnormalities of cardiac function – either in systole or diastole.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Guideline development group (GDG)	The guideline development group agrees the clinical questions for the guideline, considers the evidence and develops the recommendations. The GDG membership is multidisciplinary comprising clinicians, patients and/or carers and technical experts.
Haemodynamic function	An assessment of cardiac function.

Haemodynamic instability	Where cardiac function is compromised so that the patient becomes clinically unstable.
Haemorrhagic death	Death caused by a haemorrhagic event such as an intracranial haemorrhage.
Haemorrhagic stroke	Stroke secondary to cerebral haemorrhage.
Haemorrhagic transformation	The situation where there is bleeding into a (usually large) cerebral infarction, especially in the early phase of a stroke.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Health technology assessment (HTA)	These consider the effectiveness, appropriateness and cost of technologies and are funded by the NHS Research and Development Division.
Heart failure	See 'congestive heart failure'.
Heart murmur	An audible sound with or without a stethoscope, which relates to abnormal flow within the heart or an abnormal communication within the circulatory system.
Heart rate	The rate at which the heart performs a complete cycle of coordinated muscular contraction. It is measured in beats per minute (bpm).
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Holter monitor	An ambulatory ECG recording device.
Hyperadrenergic state	Situations where there is abnormal circulating adrenaline (and similar hormones) and/or activation of the sympathetic nervous system e.g. 'fight or flight' reaction.
Hypertension	Abnormally high blood pressure.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Incidence	The rate at which an event occurs. Incidence normally measures the rate at which people within a population develop a particular disease or experience other adverse events.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Inconclusive	A series of study results are inconclusive when the evidence of different studies do not conflict with each other, but nonetheless lack the strength to be able to reach a definite conclusion.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental cost per QALY	The additional cost incurred for each additional QALY. See also 'incremental cost-effectiveness ratio'.

Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Independent predictor	A variable whose value predicts the occurrence of an event independent of the values of other variables.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Infarction	An ischaemic lesion. Cerebral infarctions can result in stroke, and myocardial infarctions can result in a heart attack. See also 'myocardial infarction'.
Informed dissent	The situation whereby a patient elects to abstain from receiving the optimal therapeutic intervention in the knowledge that this could cause them harm.
Inotropic	Drugs that can stimulate the contraction of the heart
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
International normalised ratio (INR)	A measure of the clotting ability of blood, usually following use of anticoagulant drugs. It is calculated as the ratio of the length of time it takes blood to clot over the time it would take the blood of a normal subject to clot.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intra-cardiac	Occurring within the chambers of the heart.
Intracranial haemorrhage	A bleeding event within the brain, which may result in a haemorrhagic stroke.
Intraoperative	The period of time during a surgical procedure.
Intubation	Being intubated with a transoesophageal breathing tube connected to a mechanical ventilator.
Ischaemic heart disease	Heart disease characterised by a reduced supply of blood to the heart. See also 'coronary artery disease'.
Ischaemic stroke	Stroke caused by cerebral infarction.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Lacunar infarction	Stroke secondary to blockage of the small vessels especially at the border of zones supplied by different arteries.
Left atrial appendage velocity	A measurement of the blood flow within the left atrial appendage, usually on TEE
Left ventricular dysfunction (LVD)	Impaired function of the left ventricle.
Left ventricular ejection fraction (LVEF)	The percentage of blood within the left ventricle that is ejected at each contraction.
Left ventricular end diastolic diameter (LVEDD)	A measurement of the size of the heart on echo, referring to the internal dimension of the heart in diastole.

Left ventricular end systolic diameter (LVESD)	A measurement of the size of the heart on echo, referring to the internal dimension of the heart in systole.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Lone AF	AF that occurs in the absence of any comorbid cardiovascular disease or other precipitants of AF.
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Magnetic resonance imaging (MRI)	A non-invasive imaging technique allowing detailed examination of the heart.
Management strategy	The overarching plan on how to treat a particular patient. In the context of AF, there are two main management strategies – rate control and rhythm control.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Maximum workload	A measure of exercise tolerance. See 'exercise tolerance'.
Medically refractory	In the context of AF, a patient is medically refractory if successive trials of different drugs and attempts at cardioversion fail to adequately control the symptoms or pathophysiology of AF.
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Methodological limitations	Features of the design or reporting of a clinical study which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.
Mitral annular abnormalities	Echo abnormalities of the mitral valve ring/annulus, such as mitral annular calcification.
Mitral regurgitation	A backwards flow of blood through the mitral valve normally caused by a dysfunctional mitral valve disease. Mitral regurgitation is classified as 'mild', 'moderate' or 'severe'.
Mitral stenosis	An abnormal narrowing of the mitral valve. It can be measured echocardiographically by the mitral valve area.
Mitral valve calcification	Deposition of calcium on the mitral valve.
Mitral valve disease	Common generic term for disease of the mitral valve.
Mitral valve prolapse	Condition where one or more mitral valve leaflets do not appose correctly and there is backward movement of the valve into the atrium, leading to mitral regurgitation.
Mitral valvuloplasty	Stretching of the mitral valve, at surgery or using a balloon technique.
Monotherapy	In the context of drug therapy, the administration of a single drug for a particular indication.
Multivariate	Involving multiple variables. See also 'univariate'.
Multivariate model	A statistical model for analysis of the relationship between 2 or more

	predictor (independent) variables and the outcome (dependent) variable.
Myocardial infarction (MI)	Heart attack.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct.
National Institute for Health and Clinical Excellence (NICE)	NICE is the independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.
National Service Framework (NSF)	A series of reports recommending service levels and targets for particular disease groups in the UK.
Negative predictive value	The proportion of individuals with a negative test result who do not have the disease.
Negative predictor	A variable whose values are inversely related to the likelihood of an event occurring.
New onset atrial fibrillation	A patient presenting to medical care with atrial fibrillation whose new or changing symptoms suggest that the episode of AF commenced less than 48 hours prior to presentation.
New York Heart Association (NYHA)	A score graded between 1 and 4 that measures cardiac function. Those patients with a score of 4 are considered to have severe heart failure; those with a score of 1 are considered to have asymptomatic or mild heart failure.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
Nurse-led cardioversion	Practice where the cardioversion procedure is organised, performed and patient follow-up undertaken by specialist nurses.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups - in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio.

Open-label	In the context of study design, a study in which the physicians or investigators are not blinded to which patients are allocated to which treatment arm.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Pacing	The situation where a device (a pacemaker) complements or replaces the natural conducting system of the heart.
Palpitations	The experience of one’s own heartbeat as an awareness of the heart beating or a thumping sensation originating in the chest.
Paroxysmal AF	AF which terminates spontaneously within seven days of onset and most often within 48 hours of onset.
Patent foramen ovale	A ‘hole in the heart’ where there is a congenital connection between the left and right atria.
Percutaneous coronary intervention (PCI)	Any procedure on the heart undertaken by insertion of a device (e.g. stent) through a small hole in an artery (e.g. radial artery, femoral artery).
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Peripheral artery disease	Atherosclerotic vascular disease involving the peripheral arteries .
Permanent AF	AF which is accepted without attempted cardioversion or which cannot be terminated by cardioversion.
Persistent AF	AF present continuously for seven days or more or terminated by cardioversion.
Pharmacological cardioversion (PCV)	See ‘cardioversion’.
Pill-in-the-pocket	A management strategy for paroxysmal AF involving the patient self-administering antiarrhythmic drugs only upon the onset of an episode of AF.
Placebo	A fake (or dummy) treatment given to participants in the control group of a

	clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had - over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Platelet-thrombus	Blood clot that is rich in platelets rather than fibrin.
Pneumonectomy	Removal of whole or part of a lung.
Polypharmacy	The use or prescription of multiple medications.
Pooled analysis	The aggregation of patient data from multiple separate studies with the objective of increasing the likelihood of being able to detect significant associations that would otherwise have been missed.
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Precipitant	A disease process, toxin, or physiological abnormality which is known to predispose towards development of AF. In many cases, AF precipitants may not be identifiable, in other cases there are identifiable precipitants such as heart failure or alcohol excess.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	The proportion of people within a population who have a particular disease.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Pro-arrhythmic	Pre-disposing to the development of cardiac arrhythmias.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prophylactic	Having a preventative action against one or more adverse events
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.

Pulmonary vein isolation	Procedure where ablation is used to create a scar that isolates the tissue of the pulmonary vein from the rest of the heart – thus, if a focus precipitating AF is from within the pulmonary veins, the abnormal electrical impulses cannot reach the heart.
Pulse palpation	The act of feeling for, and counting, the pulse.
QT prolongation	The prolongation of the QT interval on an electrocardiogram
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Rapid atrial fibrillation	AF that is associated with a very fast heartbeat.
Rate control	The attempt to treat AF not through the restoration of sinus rhythm, but through the control of the ventricular rate and the management of stroke risk. See also 'rhythm control'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Regression equation	An equation that assigns weights (co-efficients) to different variables according to the degree to which they are able to predict the occurrence of a particular event or value.
Relative risk (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely

	to have the event happen. A relative risk of less than one means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio.
Relative risk reduction (RRR)	The percentage reduction in the relative risk gained by a particular therapeutic intervention in comparison to another. See also 'relative risk'
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Rhythm control	The attempt to treat AF through the restoration and maintenance of sinus rhythm and the management of stroke risk. See also 'rate control'.
Right bundle branch block (RBBB)	A conduction abnormality of the heart due to impaired conduction down the right bundle of His.
Risk stratification	The process of allocating patients to different levels of risk of an adverse event occurring, based on their clinical or other characteristics.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Self-management	In the context of anticoagulation, the process of the patient testing their own blood and making dose-adjustments where necessary.
Self-testing	In the context of anticoagulation, the process of the patient testing their own blood and their treating physician recommending dose-adjustments where necessary.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or

	methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Side effect	An adverse event that occurs because of a therapeutic intervention.
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Sinus rhythm	The normal pattern of electrical activity (and subsequent muscular contraction) of the heart.
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Spontaneous cardioversion	The process of cardioversion that occurs in the absence of any therapeutic interventions.
Spontaneous echo contrast	Smoke-like appearance within the chambers of the heart – usually on TOE – which indicates stasis of blood within the chamber.
Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
Structural heart disease	The presence of abnormalities of the heart valves, muscle, chambers etc.
Sudden cardiac death syndrome	The condition whereby a patient dies suddenly and unexpectedly with no obvious precipitants.
Supervised management	In the context of anticoagulation management, supervised management refers to the situation where a clinician determines any dose adjustments and takes blood measurements.
Supraventricular	Pertaining to the atria, e.g. supraventricular arrhythmia is an abnormal heart rhythm originating in the atria.
Systemic emboli	Emboli that has reached the systemic circulation, potentially causing a systemic embolism. See 'embolic'.
Systematic review	A review, in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Systolic	Relating to the phase of contraction of the chambers of the heart during

	which they eject blood following the diastolic phase. See also ‘diastolic’.
Tachycardia-induced cardiomyopathy	A form of cardiomyopathy (damage to the heart muscle cells) caused by an excessive heart rate.
Temporal pattern	The pattern distinguishing between different subtypes of AF.
Thromboembolic stroke	Thrombus that has travelled to the brain circulating leading to blockage of an artery and causing a stroke. See ‘embolic’, ‘stroke’.
Thromboembolism	The embolisation (disloading and transportation in the blood) of a thrombus.
Thromboprophylaxis	The administration of antithrombotic therapy (anticoagulation, antiplatelet therapy) for the prevention of thrombus formation.
Thrombus	Blood clot.
Thyrotoxicosis	A disease caused by the hyperactivity of the thyroid glands.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
TOE-guided cardioversion	In the context of cardioversion, the management of pericardioversion thromboembolic risk through the use of transoesophageal echocardiography (TOE) to screen for intra-cardiac thrombi alongside parenteral anticoagulation. See also ‘conventional anticoagulation’.
Torsades de pointes	A type of ventricular arrhythmia, which is a polymorphic ventricular tachycardia characterised by ‘twisting of points’ and commonly associated with a prolonged QT interval on the ECG.
Transoesphageal echocardiography	See ‘echocardiogram’.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Treatment failure	Failure of the prescribed drug regimen to work. Demonstrated by a lack of clinical improvement or reduction in arrhythmia, etc.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost-utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).
Valvular heart disease	Diseases of heart valves, e.g. mitral valve disease.
Vascular death	Death caused by a cardiovascular disease or adverse cardiovascular event such as an acute myocardial infarction.
Vascular disease	Disease of the vascular system, including both coronary and peripheral blood vessels.
Vaughan-Williams	A classification system of antiarrhythmic drugs, depending on whether the drugs activity is as a sodium-channel blocker (Class I), a beta-blocker (Class II), a repolarisation-prolonging agent (Class III), or a calcium-channel blocker (Class IV).
Ventricular arrhythmias	Cardiac arrhythmias that originate in the ventricles. See also ‘arrhythmia’.
Ventricular rate control	See ‘rate control’.
Volume loss	A term that usually refers to the amount of blood lost.
Wall motion index (WMI)	An echocardiographic measure of the contractile function of the ventricles.
Wash-out period	A period between the different experimental phases of a crossover study to ensure that no significant traces of previously administered drugs are left in the body to confound the results.

Appendices A–P are in a separate file.