

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Centre for Clinical Practice

### *Review consultation document*

#### Review of Clinical Guideline (CG) – CG36 Atrial Fibrillation

## 1. Background information

Guideline issue date: 2006

2 year review: 2008

5 year review: 2011

National Collaborating Centre: National Collaborating Centre for Chronic Conditions

## 2. Consideration of the evidence

### Literature search

From a high-level randomised control trial (RCT) search, new evidence was identified related to the following clinical areas within the guideline:

- Cardioversion
- Treatment for Persistent Atrial Fibrillation (AF)
- Treatment for Permanent AF
- Treatment for Paroxysmal AF
- Treatment for AF (not specified sub type)
- Treatment for acute-onset AF

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- Antithrombotic therapy
- Monitoring and referral

Through this stage of the process, a sufficient number of studies (257) relevant to the above clinical areas were identified from the high level RCT search to allow an assessment for a proposed review decision and are summarised in table 1 below.

From initial intelligence gathering, qualitative feedback from other NICE departments, the views expressed by the Guideline Development Group, as well as the high-level RCT search, an additional focused literature search was also conducted for the following clinical area:

- Factors that impact on treatment outcomes and should be included risk stratification for thromboprophylaxis in patients with AF

The results of the focused search are summarised in table 2 below. All references identified through the high-level RCT search, initial intelligence gathering and the focused searches can be viewed in [Appendix 1](#).

**Table 1: Summary of articles from the high level RCT search**

<b>Clinical area 1: Cardioversion</b>		
<b>Clinical question</b>	<b>Summary of evidence</b>	<b>Relevance to guideline recommendations</b>
<p>Q: What is the most effective method for cardioversion in patients with AF?</p> <p><b>Related clinical questions from the guideline;</b> Does electrical conversion versus pharmacological conversion affect rates of thromboembolism, quality of life, exercise capacity, failure rates?</p>	<p>Through the high level search 56 studies relevant to the clinical question were identified.</p> <p><b><u>Pharmacological Conversion (PCV) (18 RCTs)</u></b></p> <p>18 studies were identified that have evaluated pharmacological agents for cardioversion (CV) in Atrial Fibrillation (AF).</p> <p>PCV was evaluated as the initial treatment option for AF (presenting at emergency rooms) for cardioversion in the following 3 RCTs</p> <ul style="list-style-type: none"> <li>• Two RCTs assessed the new agents in this context. Intravenous metoprolol was found to be effective and safe in</li> </ul>	<p>Potential new evidence that may change current guideline recommendation(s).</p>

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<p>In patients with persistent AF, is amiodarone better than a) flecainide or b) propafenone for use in cardioversion?</p> <p>In patients with AF is amiodarone better than sotalol for use in cardioversion?</p> <p>What is the safety and efficacy of the adjunctive administration of antiarrhythmic drugs for use in electrical and cardioversion in comparison to electrical cardioversion without adjunctive antiarrhythmic drugs?</p> <p>Is a conventional</p>	<p>comparison to cedilanid, and diltiazem did not decrease the likelihood of spontaneous conversion of AF to sinus rhythm.</p> <ul style="list-style-type: none"> <li>• In line with the guideline, one RCT found an intravenous bolus of amiodarone was more safe and effective than digoxin for heart rate control and conversion to sinus rhythm in patients with AF and a rapid ventricular rate.</li> </ul> <p>For recent onset AF five RCTs were identified that have assessed PCV:</p> <ul style="list-style-type: none"> <li>• Four RCTs have demonstrated the new therapy vernakalant's efficacy for cardioversion against either placebo or active comparator (amiodarone). Vernakalant also demonstrated a rapid and high rate of cardioversion for individuals with AF or AF flutter in one study.</li> <li>• One RCT indicated that intravenous diltiazem was safe and effective in achieving VR control to improve symptoms compared to digoxin and amiodarone.</li> </ul>	
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<p>anticoagulation strategy for elective cardioversion as effective as a transoesophageal comparative studies and echocardiogram plus anticoagulation?</p> <p><b>Relevant section of guideline</b> (5.0 Cardioversion)</p> <p><b>Recommendations</b> (R7, R8, R9, R10)</p>	<ul style="list-style-type: none"> <li>• Oral propafenone and quinidine were both equally effective in conversion to sinus rhythm but propafenone was quicker acting in patients with paroxysmal AF.</li> <li>• One study compared the efficacy and safety PCV by nibentan, a newer class III antiarrhythmic agent to ECV in patients with persisting AF and atrial flutter. The two strategies were equally effective.</li> </ul> <p>In addition the following unlicensed agents have been found to be effective for PCV in AF; procainamide was effective for recent onset AF compared to active comparators (two RCTs), combination therapy with Ibutilide and either esmolol or propafenone (two RCTs), AZD7009 in individuals with either persistent or flutter AF (two RCTs) and pilsicainide in patients with persistent AF.</p> <p>The unlicensed drug bepridil demonstrated some efficacy for treatment of persistent AF. However, a high rate of AF recurrence</p>	
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	<p>and substantial drug-related adverse effects, including sudden death, raised caution about use of this drug.</p> <p><b><u>Complementary cardioversion (two RCTs)</u></b></p> <p>Two RCTs have indicated that acupuncture is more effective in preventing arrhythmic recurrences after cardioversion in patients with paroxysmal AF in comparison to sham acupuncture or amiodarone.</p> <p><b><u>Electrical Cardioversion (ECV) (36 RCTs)</u></b></p> <p>In total 36 RCTs were indentified that have evaluated electro-cardioversion (ECV) in atrial fibrillation including; ECV characteristics (waveform (nine RCTs), paddle position (nine RCTs), energy protocol (two RCTs), concurrent drug therapy (nine RCTs), thrombosis prevention (four RCTs) and the use of implantable cardioverter defibrillators (three RCTs). The type of AF</p>	
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	<p>was detailed in 37.5% of these studies (three flutters, one acute, eight persistent).</p> <p><b>ECV and antiarrhythmic therapy</b></p> <p>Propafenone and amiodarone both aided cardioversion and maintained sinus rhythm (SR) post ECV in one RCT. However compared with amiodarone, propafenone may be preferred as it is associated with a shorter hospital stay.</p> <p>Three RCTs have confirmed that amiodarone and sotalol facilitated successful ECV; however amiodarone was more effective at maintaining a SR post ECV. These agents had no effect on the total number of energy steps used but successful ECV was associated with lower BMI , biphasic shocks and AF history of less than or one year. A fourth RCT indicated that pre treatment with amiodarone was more effective than diltiazem for preventing early AF recurrences following ECV.</p>	
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	<p>The VERDICT trial indicated that acute ECV was not superior in the long term in comparison to routine ECV strategies and that verapamil was not beneficial with regards to ECV.</p> <p>Non-licensed agents have been evaluated in three RCTs within this context. Pre-treatment with ibutilide was shown to lower energy requirements in transthoracic biphasic cardioversion. A further RCT found cibenzoline was a more effective ADT than pilsicainide for patients previously refractory to ECV. The efficacy of pre ECV azimilide for prevention of AF recurrence was slightly superior to placebo but significantly inferior to sotalol in patients with persistent AF.</p> <p><b>ECV characteristics</b></p> <p>Biphasic waveforms were found to be more effective than monophasic waveforms in all eight RCTs that have assessed this aspect of ECV. In particular a more rapid restoration of sinus beat (one RCT); fewer shocks (one RCT) and less energy (five RCTs)</p>	
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	<p>resulted in cardioversion using biphasic compared to monophasic waveforms. Only one RCT did not show a decrease in total energy for biphasic in comparison to monophasic ECV using escalating transthoracic shocks.</p> <p>A further RCT assessing internal ECV found low waveform tilt for defibrillation to be superior to conventional waveform in cardioversion for atrial fibrillation.</p> <p>Six studies assessing the efficacy of various electrode positions for elective ECV in AF have been identified;</p> <ul style="list-style-type: none"><li>• apex-anterior electrode positions were more effective than left anterior posterior for elective ECV (one RCT)</li><li>• Anterior-posterior versus anterior-lateral pad positions has been assessed in four RCTs with differing outcomes. In two studies the positions were comparable, however one RCT has shown that anterior-posterior positioning to be more</li></ul>	
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	<p>effective in achieving restoration of sinus rhythm in lower energy shock levels compared to the anterior-lateral position and another RCT that anterior-lateral increased efficacy and required less energy and fewer shocks in AF flutter patients.</p> <ul style="list-style-type: none"> <li>• Transoesophageal and transthoracic electrical cardioversion have been compared in two RCTs and found to be comparable under moderate sedation. However, transoesophageal electrical cardioversion showed lower levels of delivered and effective energies for SR restoration and had enhanced tolerability. A comparison of transthoracic cardioversion to internal cardioversion indicated that sinus rhythm rates and major clinical events were similar between the two approaches (one RCT).</li> </ul> <p>Two RCTs compared the efficacy and safety of an escalating energy protocol with a non-escalating energy protocol. High initial energy increased success rates and decreased the number of</p>	
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	<p>shocks but resulted in similar cumulative energy delivery, sedation use and patient tolerability compared with a conventional step-up protocol.</p> <p><b>Implantable cardioverter defibrillators</b></p> <p>Dual chamber implantable cardioverter defibrillators were found to be for efficacious than single chamber (one RCT). The adjunctive use of bolus propafenone was found to be safe and effective and improve patient tolerance of this devise based AF therapy in one RCT. However, a coronary sinus coil did not improve atrial defibrillation efficacy by implantable cardioverter defibrillators in another RCT.</p> <p><b>Transesophageal echocardiography guided cardioversion</b></p> <p>Transesophageal echocardiography (TOE)-guided ECV strategy in patients with AF was a clinically effective alternative to a conventional anticoagulation strategy for these patients (three</p>	
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	<p>RCTs). TEE guided ECV with anti-thrombotic agents enoxaparin and unfractionated heparin has also been assessed in the ACUTE II trial. There was no difference in safety outcomes between the two strategies.</p> <p><b>Summary</b></p> <p>The guideline recommends for pharmacological cardioversion using an intravenous Class 1c antiarrhythmic drug in the absence of structural heart disease and amiodarone for AF patients with structural heart disease.</p> <p>The evidence base in the original guidance for ECV with concomitant ADT assessed the efficacy of digoxin, diltiazem, verapamil, propranolol in comparison to amiodarone peri-ECV. Amiodarone, digoxin, diltiazem, sotalol, flecainide were also assessed for efficacy as pre-ECV therapies. The resulting recommendation was for concomitant amiodarone or sotalol if ADT was required prior to ECV. The evidence regarding ADT and</p>	
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	<p>defibrillation energy requirements was inconclusive and current practice was noted to vary in published papers for ECV. During the guidance development it was noted that biphasic defibrillators were used more in clinical practice but this had not at the time reflected in the evidence base.</p> <p>Overall, the identified new evidence indicates a potential benefit for new agents including the Class III agent vernakalant not covered by the guideline for PCV. A NICE Technical appraisal for vernakalant for the treatment of rapid conversion of recent onset atrial fibrillation is in development. The high level search identified further studies comparing the relative efficacy of agents and treatment strategies for ECV and concomitant ADT. In addition, new evidence relating to defibrillator characteristics which effect ECV outcomes have been identified including; waveform paddle positions, monophasic and biphasic waveforms, shock energy and shock strategy.</p>	
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<b>Clinical area 2: Treatment for Persistent AF</b>		
<b>Clinical question</b>	<b>Summary of evidence</b>	<b>Relevance to guideline recommendations</b>
<p>Q: What is the most effective treatment option for patients with persistent AF?</p> <p>Related clinical questions from the guideline;</p> <p>In which patients with persistent AF does rate control result in improved mortality/ morbidity/ quality of life over rhythm control?</p> <p>In which patients with persistent AF does rhythm control result in</p>	<p>Through the high level RCT search 27 studies relevant to the clinical question were identified.</p> <p><b><u>Rate or Rhythm control</u></b></p> <p>1 meta-analysis and 12 reports from RCTs have been identified that have addressed the issue of treatment strategies of rhythm control and rate control, for persistent AF (in some cases the clarification of AF type was unclear from the abstract).</p> <p>A Cochrane systematic review indicated that there is no evidence that PCV of AF to sinus rhythm (SR) was superior to rate control with regards to the annual risk of stroke, peripheral embolism, and mortality. Rhythm control was associated with more adverse effects and increased hospitalisation and did not</p>	<p>Potential new evidence that may change current guideline recommendation(s).</p>

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<p>improved mortality/ morbidity/ quality of life over rate control?</p> <p><b>Relevant section of guideline</b> (6.0 Treatment for persistent AF)</p> <p><b>Recommendations</b> (R12, R13, R14, R15, R16)</p>	<p>reduce the risk of stroke. It was noted that the conclusions cannot be generalised to all people with AF as the majority of the patients included in the analysis were relatively older (&gt;60 years) with significant cardiovascular risk factors.</p> <ul style="list-style-type: none"> <li>• The AFFIRM trial found no significant difference in mortality, hospitalization, and NYHA class with either strategy.</li> <li>• A post-hoc analysis of the RACE study found no differences in terms of cardiovascular events with regard to morbidity, mortality, and quality of life between rate control and rhythm control throughout follow-up. However, a further report on the RACE study indicated that for patients with hypertension a rhythm control approach is associated with higher cardiovascular morbidity and mortality in this sub population.</li> <li>• A further RCT also compared both strategies in patients</li> </ul>	
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	<p>with hypertension and found that restoring and maintaining SR had a beneficial effect on exercise capacity but no significant effects in terms of the total mortality and embolic event rates.</p> <ul style="list-style-type: none"><li>• One RCT found that rhythm control with long-term anticoagulation therapy was superior to rate control in terms of embolic events. It is concluded that patients with AF duration &gt; 48 h might benefit considerably from rhythm restoration and long-term warfarin therapy.</li><li>• Two RCTs have shown that rhythm control was associated with improvements in QoL measures compared to rate control in patients with chronic heart failure (one RCT) or without chronic heart failure (one RCT).</li><li>• The VALIANT study compared a rate control to an anti-arrhythmic-based rhythm control strategy for the treatment of AF following myocardial infarction. This study found that rhythm control was associated with</li></ul>	
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	<p>excess mortality compared with rate control, but was not associated with increased mortality beyond the immediate peri-infarct period. These results identify a sub-group in whom the use of anti-arrhythmic drug therapy may cause an increased risk of death.</p> <ul style="list-style-type: none"> <li>• A further RCT has evaluated the relationship between the presence of SR and outcomes in patients with a history of congestive heart failure and AF. They determined that a rhythm-control strategy or the presence of sinus rhythm was not associated with better outcomes in patients with AF and CHF compared to rate control.</li> <li>• Two RCTs investigating patients with persistent AF and left ventricular ejection dysfunction (heart failure), found no significant differences between the rate and rhythm control strategies in terms of outcomes.</li> </ul> <p>One cost-effectiveness study compared rhythm to rate control over a 12 month period, both strategies were equally effective</p>	
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	<p>however the rate control strategy was less costly due to the lower hospitalization costs.</p> <p><b><u>Rhythm control</u></b></p> <p>16 studies (three meta-analysis and 14 RCTs) have been identified that have assessed various treatments for maintaining SR in patients with persistent AF following ECV or PCV.</p> <p>A meta-analysis concluded that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have equivalent preventive effects for maintaining SR in this population.</p> <p>Amiodarone was found to be the most effective basic treatment drug. The second meta-analysis evaluated amiodarone and concluded that this drug was a safe and effective method to achieve and maintain SR in patients with persistent AF. The third systematic review indicated that current evidence did not</p>	
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	<p>suggest that statins are associated with increased probability of maintaining SR following ECV.</p> <p>10 RCTs were identified that related to treatments not specified within the guideline:</p> <ul style="list-style-type: none"><li>• The use of rosuvastatin was found to decrease recurrence of AF following ECV in one RCT.</li><li>• Metoprolol (extended release) prior to CV and in combination with prompt second CV in cases of early relapse significantly increases the proportion of patients in SR during six months of follow-up compared to placebo.</li><li>• An active comparator trial indicated that dronedarone was less effective than amiodarone in decreasing AF recurrence, but had a better safety profile within this population.</li><li>• One RCT investigating combination therapy of amiodarone and irbesartan was identified. Combination therapy was found to be superior to amiodarone monotherapy for</li></ul>	
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	<p>maintaining SR after CV in rheumatic heart disease patients with persistent AF.</p> <ul style="list-style-type: none"> <li>• One RCT indicated that acupuncture treatment prevents arrhythmic recurrences after CV in patients with persistent AF.</li> <li>• Atorvastatin was not superior to placebo with regards to maintaining SR 30 days after CV.</li> <li>• Supplementation with polyunsaturated fatty acids in addition to the usual antiarrhythmic treatment does not reduce recurrent AF.</li> <li>• In three RCTs candesartan had no effect on the recurrence rate of AF at six months post CV for patients with persistent AF compared to placebo.</li> </ul> <p>Further evidence for drugs detailed in the guideline was identified in one RCT. The episodic treatment with amiodarone showed a significantly increased rate of AF recurrence, all-</p>	
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	<p>cause mortality and cardiovascular hospitalizations compared to continuous amiodarone treatment for patients with persistent AF.</p> <p><b>Summary</b></p> <p>The original guidance summarised that overall rate and rhythm control were equivalent for many outcomes for the majority of AF patients. The level of evidence was stated as poor in many cases as patients did not receive anti-thrombic medication in many studies. Subgroups of patients with co-morbidities were identified that would benefit from particular strategies.</p> <p>For rhythm control in persistent AF an escalating approach to ADT based on associated co morbidity with a beta-blocker in first instance was recommended.</p> <p>New evidence has been retrieved that identifies patient</p>	
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	<p>populations with co morbidities in whom the use of rhythm control strategy may cause an increased risk of death. These co morbidities were not previously included in the strategy stratification in the guideline. In addition, there is new evidence that contradicts strategy choice for patients with and without congestive heart failure.</p> <p>For rhythm control treatment, the identified new evidence indicates a potential benefit for new formulations and new agents not covered by the guideline both in mono and combination therapy. In addition there were further studies comparing the relative efficacy of treatments currently recommended. This indicated that amiodarone, the second line treatment, was the most effective treatment option in this group.</p>	
<p><b>Clinical area 3: Treatment for Permanent AF</b></p>		

Clinical question	Summary of evidence	Relevance to guideline recommendations
<p>Q: What is the most effective treatment option for patients with permanent AF?</p> <p>Related clinical questions from the guideline:</p> <p>In patients with permanent AF, what is the efficacy of rate-limiting calcium antagonists compared with digoxin in rate control?</p> <p>In patients with permanent AF, what is the efficacy of beta-blockers compared with rate-</p>	<p>Through the high level RCT search three studies relevant to the clinical question were identified</p> <ul style="list-style-type: none"> <li>• One RCT investigated monotherapy options in relation to quality of life (QOL) in permanent AF patients. Verapamil was superior to beta-blockers (bisoprolol, atenolol or metoprolol) or digitalis for short-term improvement of QoL and exercise tolerance in patients.</li> <li>• The second study investigated the stringency of rate control in preventing cardiovascular morbidity and mortality in patients with permanent AF in patients. The study concluded that lenient rate control was as effective as strict rate control and was easier to achieve.</li> <li>• Dronedarone significantly reduced heart rate compared to placebo in patients with permanent AF (ERATO trial).</li> </ul>	<p>Potential new evidence that may change current guideline recommendation(s).</p>

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<p>limiting calcium antagonists in rate control?</p> <p>In patients with permanent AF, what is the efficacy of rate-limiting calcium antagonists in combination with digoxin compared with rate-limiting calcium antagonists monotherapy in rate control?</p> <p>In patients with permanent AF, what is the efficacy of beta-blockers in combination with digoxin compared with beta-blocker monotherapy in rate control?</p> <p><b>Relevant section of guideline</b></p>	<p><b>Summary</b></p> <p>The guideline recommends beta-blockers or rate limiting calcium antagonists as monotherapy for rate control in patients with AF. For patients where monotherapy is inadequate the addition of digoxin is recommended.</p> <p>Overall, the identified new evidence indicates a potential benefit for a new agent not covered by the guideline. In addition there is new evidence concerning the stringency of rate control required for therapeutic benefit.</p>	
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<p>(7.0 Treatment for permanent AF)</p> <p><b>Recommendations</b> (R23, R24)</p>		
<p><b>Clinical area 4: Treatment for Paroxysmal AF</b></p>		
<p><b>Clinical question</b></p>	<p><b>Summary of evidence-</b></p>	<p><b>Relevance to guideline recommendations</b></p>
<p>Q: What is the most effective treatment option for patients with paroxysmal AF?</p> <p>Related clinical questions from the guideline:</p>	<p>Through the high level RCT search 14 studies relevant to the clinical question were identified.</p> <p><b>Rhythm control (13 studies)</b></p> <p>The RHYTHM study found no significant differences between rate and rhythm control strategies with regard to mortality and cardiovascular morbidity between the two strategies for paroxysmal</p>	<p>Potential new evidence that may change current guideline recommendation(s).</p>

<p>In patients with paroxysmal AF, is flecainide/ propafenone better than beta-blockers in reducing the frequency of paroxysms?</p> <p>In patients with paroxysmal AF, is amiodarone or sotalol better than beta-blockers in reducing the frequency of paroxysms?</p> <p>In patients with paroxysmal AF, is flecainide/ propafenone better than amiodarone or sotalol in reducing the frequency of paroxysms?</p> <p>In which patients should pill-in-</p>	<p>AF.</p> <p>Seven RCTs have evaluated newer treatments either in monotherapy or combination therapy relating to prevention of AF episodes:</p> <ul style="list-style-type: none"> <li>• One RCT indicated that acupuncture treatment prevents arrhythmic recurrences after CV in patients with paroxysmal AF.</li> <li>• Low dose amiodarone in combination with losartan or perindopril (not licensed) were found more effective than amiodarone monotherapy for SR maintenance in paroxysmal AF or lone AF (two RCTs).</li> <li>• The addition of spironolactone to B blocker treatment was more effective than monotherapy or the addition of enalapril in preventing AF episodes in patients with normal left ventricular function and a history of refractory paroxysmal AF in one RCT.</li> </ul>	
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<p>the-pocket therapy be recommended?</p> <p><b>Relevant section of guideline</b> (8.0 Treatment for paroxysmal AF)</p> <p><b>Recommendations</b> (R28, R29, R30, R32, R33)</p>	<ul style="list-style-type: none"> <li>• The combination of irbesartan and amiodarone was found to be more effective than amiodarone alone for SR maintenance in paroxysmal AF in one RCT.</li> <li>• One RCT found that valsartan plus amlodipine was more effective than an atenolol plus amlodipine combination in preventing the recurrence of AF in hypertensive diabetic patients. Both combinations showed a similar blood pressure reduction.</li> <li>• Treatment with valsartan alone was not associated with a reduction in the incidence of recurrent AF compared to placebo.</li> <li>• Omega-3-fatty acids compared with placebo did not reduce recurrent AF over six months in one RCT.</li> </ul> <p>Further evidence for drugs detailed in the guideline was identified in two RCTs. The episodic treatment with amiodarone showed a significantly continued SR maintenance which was associated with</p>	
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	<p>an improvement in QOL in the episodic in comparison to continuous amiodarone treatment. One placebo controlled RCT indicated that flecainide exerted a significant dose-dependent effect on the prevention of symptomatic paroxysmal AF recurrence and with no inter-ethnic differences in the clinical effect.</p> <p>In addition two RCTs evaluating non licensed drugs were identified. Azimilide showed a non significant trend toward efficacy in maintaining SR in patients with AF in comparison to placebo. The preventive effects of pilsicainide and cibenzoline were compared in patients that were defibrillated at &lt;48 h or &gt;or=48 h after onset. Cibenzoline was considered to be more effective in preventing the recurrence of paroxysmal AF in the electrically remodelled atria than pilsicainide.</p> <p><b>Pill-in-the-pocket therapy</b></p> <p>A meta-analysis investigated the clinical effectiveness and cost</p>	
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	<p>effectiveness of prescribing the pill-in-the pocket (PiP) approach for the treatment of patients with paroxysmal AF which additionally developed an economic model to assess the cost-effectiveness of PiP compared with in-hospital treatment (IHT) or continuous ADT was identified. The developed model indicated that a PiP strategy was slightly less effective than ADT and IHT, but was associated with cost savings. In addition, the PiP strategy seems to be more efficacious and cost effective than a continuous ADT strategy in men over 65 years and women over 70 years. They concluded that self-management was safe and reliable in patients who also have long-term oral anticoagulation.</p> <p><b>Summary</b></p> <p>For patients with paroxysmal AF who have few symptoms and infrequent paroxysms a no drug treatment or PIP strategy was recommended by the guideline for consideration. Whereas for symptomatic AF patients a standard beta-blocker was recommended as first line treatment, with second line treatment</p>	
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	<p>including a Class Ic agent or sotalol. Recommended, third line treatment options were amiodarone or referral for non-pharmacological intervention in this group of patients.</p> <p>Overall, the identified new evidence indicates a potential benefit for new agents not covered by the guideline for preventing AF episodes in combination therapy. In addition there were further studies comparing the relative efficacy of treatments currently recommended and treatment strategies. New evidence that may address a research recommendation (CG36/4) in the guideline relating to the clinical and cost effectiveness of 'pill-in-the-pocket' treatment for those with paroxysmal AF compared to hospital-based administration or continuous antiarrhythmic therapy was also identified.</p>	
<p><b>Clinical area 5: Treatment for AF (not specified sub type)</b></p>		
<p><b>Clinical question</b></p>	<p><b>Summary of evidence</b></p>	<p><b>Relevance to guideline</b></p>

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		<b>recommendations</b>
<p>Q: What is the most effective treatment option for patients with AF?</p> <p><b>Relevant section of guideline</b> (6.0 Treatment for persistent AF, 7.0 Treatment for permanent AF, 8.0 Treatment for paroxysmal AF)</p> <p><b>Recommendations</b> (R12, R13, R14, R15, R16, R28, R29, R30, R32)</p>	<p>Through the high level RCT search 13 studies relevant to the clinical question were identified.</p> <p>A number of RCTs were identified that either stated the population as AF and did not specify type or included more than one sub-type of AF (i.e. persistent and paroxysmal) in the abstract. The results from these 13 studies are summarised below.</p> <p>A Cochrane systematic review was indentified which assessed the effect of long-term treatment with antiarrhythmic drugs on death, stroke and embolism, adverse effects, pro-arrhythmia and recurrence of AF in patients who had recovered SR after CV. The review concluded that class Ia drugs were associated with increased mortality compared with controls. Other antiarrhythmic drugs did not modify mortality. Several class Ia (disopyramide, quinidine), Ic (flecainide, propafenone) and III (amiodarone, dofetilide, dronedarone, sotalol) drugs significantly reduced</p>	<p>Potential new evidence that may change current guideline recommendation(s).</p>

	<p>recurrence of AF, but all increased withdrawals due to adverse affects. All drug treatments assessed increased pro-arrhythmia with the exception of amiodarone and propafenone. The second meta-analysis evaluated dronedarone and concluded dronedarone was less effective than amiodarone for the maintenance of SR, but has fewer adverse effects.</p> <p>Individual studies (eight RCTs) on numerous newer agents were identified and summarised below:</p> <ul style="list-style-type: none"><li>• Dronedarone has been evaluated in a number of RCTs identified in the current high level search. This new agent has been approved for use in non-permanent AF in a NICE technological appraisal.<ul style="list-style-type: none"><li>○ In the ATHENA trial, cardiovascular death and hospitalization was significantly reduced in patients with AF and additional risk factors.</li><li>○ In the DIONYSOS trial amiodarone was superior to</li></ul></li></ul>	
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	<p>dronedarone to maintain SR in patients with AF and atrial flutter.</p> <ul style="list-style-type: none"><li>○ In EURDIS and ADONIS trials dronedarone was significantly more effective than placebo in maintaining SR and in reducing the ventricular rate during recurrence of arrhythmia.</li><li>○ The ANDROMEDA trial was stopped because dronedarone increased early mortality in advanced heart failure.</li><li>● Atorvastatin was associated with a significantly reduced risk of recurrent AF in comparison to placebo post ECV in one RCT.</li><li>● Ramipril was effective in preventing relapses of AF following CV in comparison to placebo in one RCT.</li><li>● The AFFIRM trial indicated that lipid lowering therapy decreased mortality and adverse cardiovascular events in patients with AF.</li><li>● Valsartan treatment was not associated with a reduction in the incidence of recurrent AF in one RCT.</li></ul>	
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	<p>Further evidence for drugs detailed in the guideline was identified in one RCT. A very low dose of amiodarone was found to result adequate long-term efficacy and was safe for maintaining SR rhythm post successful CV in patients with chronic AF and rheumatic heart disease.</p> <p>In addition one RCT evaluating the non licensed drug azimilide was identified. Azimilide did not demonstrate clinically important or statistically significant efficacy in reducing the risk for AF recurrence in patients with structural heart disease post CV.</p> <p><b>Summary</b></p> <p>Overall, the identified new evidence indicates a potential benefit for patients with AF utilising new agents not covered by the guideline.</p>	
<p><b>Clinical area 6: Treatment for acute-onset AF</b></p>		

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Clinical question	Summary of evidence	Relevance to guideline recommendations
<p>Q: What is the most effective treatment option for patients with acute onset AF?</p> <p>Related clinical questions from the guideline: In haemodynamically unstable patients presenting with acute AF, what is the best treatment strategy (ECV, PCV or acute (iv) rate control)?</p> <p><b>Relevant section of guideline</b> (90. Treatment of acute-onset AF)</p>	<p>Through the high level RCT search 10 studies relevant to the clinical question were identified.</p> <p>Five studies have evaluated PCV as the initial treatment option for AF (presenting at emergency rooms) for CV. New agents assessed include;</p> <ul style="list-style-type: none"> <li>• Intravenous (IV) metoprolol was found to be both effective and safe in comparison to cedilanid in this setting.</li> <li>• Procainamide and amiodarone which were equally effective and safe in restoring SR (although procainamide acts quicker in the loading phase) after administration of digoxin for ventricular rate control.</li> <li>• IV infusion of vernakalant showed efficacy in rapidly converted recent onset AF to SR in comparison to placebo.</li> <li>• Diltiazem did not decrease the likelihood of spontaneous</li> </ul>	<p>Potential new evidence that may change current guideline recommendation(s).</p>

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<p><b>Recommendations</b> (R36, R38)</p>	<p>conversion of AF to SR in comparison to esmolol.</p> <p>In line with the guideline, one RCT found that an IV bolus of amiodarone was relatively safe and more effective than digoxin for heart rate control and conversion to SR in patients with AF and a rapid ventricular rate.</p> <p>A further five RCTs were identified that have assessed PCV for recent onset AF:</p> <ul style="list-style-type: none"> <li>• The new therapy vernakalant has shown superior efficacy for CV in comparison to either placebo (one RCT) or active the comparator amiodarone (one RCT).</li> <li>• One RCT demonstrated that amiodarone and propafenone were more effective than IV procainamide. However, IV procainamide and propafenone were faster at reducing symptoms in responders.</li> <li>• IV diltiazem was safe and effective in achieving acute ventricular rate control compared to digoxin, and amiodarone in</li> </ul>	
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	<p>one RCT.</p> <ul style="list-style-type: none"><li>• Combination therapy esmolol and ibutilide was more effective in conversion of rapidly conducting AF back to sinus rhythm than ibutilide monotherapy.</li></ul> <p><b>Summary</b></p> <p>The current recommendations for acute onset AF for patients with deterioration in hemodynamic stability, either life threatening or not, is for ECV. If ECV is delayed then IV amiodarone is recommended in this patient group. For patients with known permanent AF who are hemodynamic instable then urgent rate-control with IV beta-blockers or rate limiting are recommended. Where these agents are ineffective then IV amiodarone should be considered.</p> <p>Evidence relating to new effective agents both in monotherapy and combination therapy for the rapid PCV of acute AF has been identified.</p>	
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<b>Clinical area 7: Treatment of post-operative AF</b>		
<b>Clinical question</b>	<b>Summary of evidence</b>	<b>Relevance to guideline recommendations</b>
<p>Q: What is the most effective treatment option to prevent post operative AF?</p> <p>Related clinical questions from the guideline:            What is the best treatment strategy (rate or rhythm control 10.2 or no treatment) for patients with postoperative AF?</p> <p>Is the peri-operative administration of antiarrhythmic drugs effective prophylaxis for</p>	<p>Through the high level RCT search 57 studies relevant to the clinical question were identified.</p> <p><b><u>Post-Operative AF</u></b></p> <p>A large number of studies were identified by the high level search relating to post-operative AF this included five meta-analyses, two cost-effectiveness studies and 50 RCTs. The majority of these studies related to coronary artery bypass grafting (CABG) or other types of cardiac surgery.</p> <p>Four systematic reviews on the use of statins for prevention of post-operative AF were identified. Two of the reviews on pre-operative statin dosing concluded that statin therapy was associated with a reduction in the incidence of post-operative AF.</p>	<p>Potential new evidence that may change current guideline recommendation(s).</p>

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<p>post-operative AF?</p> <p><b>Relevant section of guideline</b> (10.0 Treatment of post-operative AF)</p> <p><b>Recommendations</b> (R44, R45, R46, R47)</p>	<p>The remaining two reviews did not specify the period of statin use included in their analysis but they also concluded that statin use reduced the incidence of post-operative AF. The remaining review identified investigated the effects of corticosteroids and concluded that the use of these agents reduced the incidence of post-operative AF and length of hospital stay.</p> <p>Two studies addressed the cost effectiveness of postoperative amiodarone as prevention of AF for patients undergoing cardiac surgery. The routine use of postoperative prophylactic intravenous bolus and subsequent five days of oral amiodarone therapy after CABG was found to reduce the risk of AF and decreases the total costs of care in one study. The second study pooled data from 4 previous meta-analyses and concluded that amiodarone prophylaxis was cost neutral and resulted in a decrease in the length of stay, the main cost driver in postoperative AF.</p> <p><b><u>Pre-Operation drug prophylaxis</u></b></p>	
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	<p>Six RCTs evaluated the following treatments for pre-operation drug prophylaxis for post operative AF prior to CABG. Atorvastatin (three RCTs), metoprolol (one RCT) reduced the incidence of post-operative AF. Whereas Omega-3 PUFA (one RCT) and dexamethasone (one RCT) did not show any efficacy in comparison to placebo.</p> <p><b><u>Intra-operative drug prophylaxis</u></b></p> <p>Two RCTs have indicated that the use of a single intra-operative dose of amiodarone during cardiac surgery was effective in reducing AF associated events post surgery.</p> <p><b><u>Peri-operative administration of drug prophylaxis</u></b></p> <p>Ten studies were identified that have investigated the peri-operative administration of drug prophylaxis for post-operative AF. Oral amiodarone (one RCT), intravenous (one RCT), low dose (one RCT), plus propranolol (one RCT) all indicated that</p>	
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	<p>amiodarone prophylaxis significantly reduced the incidence of AF following CABG in comparison to placebo or control. Likewise atorvastatin (one RCT), ascorbic acid (one RCT), dofetilide (one RCT) all significantly decreased the incidence of AF following CABG in comparison to placebo or control. There was conflicting evidence with regards to PUFA (two RCTs) as one RCT indicated an IV infusion of PUFA reduced the incidence of post-operative AF however a second RCT found that PUFA capsules were not effective.</p> <p><b><u>Intra-and post operative prophylaxis</u></b></p> <p>13 studies were identified that have investigated the intra and post-operative administration of drug or a treatment for prophylaxis of post-operative AF.</p> <ul style="list-style-type: none"> <li>• Five RCTs have investigated the use of temporary pacing, either by biatrial pacing (four RCTs) or Bachman bundle pacing in comparison to atrial pacing (one RCT). Temporary pacing reduced the incidence of post-operative</li> </ul>	
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	<p>AF; however, Bachman bundle pacing was found to be superior to atrial pacing in one study.</p> <ul style="list-style-type: none"> <li>• Two RCTs have concluded that retention of the anterior fat pad and addition of anti-arrhythmic drugs may prove beneficial in preventing post operative AF.</li> <li>• Posterior pericardiotomy (one RCT) and the use of polymethoxyethylacry late-coated circuits and leukocyte filters (one RCT) significantly reduced the incidence of AF after CABG.</li> <li>• Two RCTs were identified that have examined successful drug prophylaxis treatments for intra-and post operative delivery. Digoxin was found to independently decrease the risk of AF following CABG surgery in patients with high risk factors for AF. In addition an RCT indicated amiodarone prophylaxis significantly reduces the incidence of AF after anatomic pulmonary resection.</li> <li>• Ventral cardiac denervation (one RCT) and transvenous</li> </ul>	
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	<p>intracardial cardioversion (one RCT) both did not significantly reduce the rate of post-operative AF following CABG.</p> <p><b><u>Post-operative drug prophylaxis</u></b></p> <p>17 studies were identified that have investigated the post-operative administration of drug prophylaxis for post-operative AF. The following drugs were all found to be effective in reducing the incidence of post-operative AF following either CABG, mitral valve replacement or cardiac surgery; Amiodarone (six RCTs), Bisoprolol , particularly in the elderly (two RCTs), oral carvedilol was superior to metoprolol, one RCT), IV metoprolol (two RCTs), hydrocortisone (one RCT), betaxolol was superior to metoprolol (one RCT), cibenzoline was superior to disopyramide (one RCT), vernakalant (one RCT), N-acetylcysteine (one RCT) and angiotensin receptor blocker (one RCT). One RCT compared a rhythm versus rate control strategy following percutaneous mitral balloon valvotomy. The optimal strategy which increased QOL was</p>	
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	<p>a rhythm control.</p> <p><b>Summary</b></p> <p>Prophylaxis with amiodarone, beta-blockers, sotalol or rate-limiting calcium antagonist is recommended for patients undergoing cardiothoracic surgery. The treatment for post-operative AF due to cardiothoracic surgery should follow a rhythm control strategy and for other surgery types be managed as for acute-onset AF. Pre, post and peri-prophylaxis for the prevention of AF following surgery is recommended.</p> <p>Overall, evidence was identified which indicates a potential benefit for new agents/procedures for pre-, intra, peri and post- operative for prophylaxis of post-operative AF not covered by the guideline. In addition there were further studies comparing the relative efficacy of treatments currently recommended and treatment strategies.</p>	
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<b>Clinical area 8: Thromboprophylaxis for AF</b>		
<b>Clinical question</b>	<b>Summary of evidence</b>	<b>Relevance to guideline recommendations</b>
<p>Q: What is most appropriate thromboprophylaxis strategy for patients with AF?</p> <p>Related clinical questions from the guideline: At the diagnosis of AF does immediate anticoagulation (comparison is absence of immediate Tx or later, delayed Tx result in reduced rates of morbidity mortality, without increasing patient anxiety, while still being cost effective</p>	<p>Through the high level RCT search 43 studies relevant to the clinical question were identified.</p> <p>This included six systematic reviews, a number of large RCTs including; SPORTIF II and IV, BAFTA, ACTIVE , CHARISMA, RELY, ACUTE II, ESTEEM large RCTs. Many of these trials have undertaken numerous sub-population outcome and post-hoc analyses.</p> <p>Not all studies report fully the patient population in the abstract hence categorisation into the subgroups detailed in the guideline has not been possible.</p> <p><b>Antithrombotic therapy following stroke or TIA</b></p>	<p>Potential new evidence that may change current guideline recommendation(s).</p>

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<p>in people with AF what are the risks of long-term oral treatment outcomes, anticoagulation administration as thromboprophylaxis?</p> <p>In patients with AF, what are the risk factors associated with stroke/TIA and thromboembolism?</p> <p>What is the efficacy of anticoagulation therapy versus placebo for stroke prevention in persistent/permanent/paroxysmal AF?</p> <p>What is the efficacy of</p>	<p>One post-hoc sub group analysis of the RE-LY trial found that the treatment with the new drug dabigatran was as effective as warfarin on prevention of stroke or systemic embolism in patients with previous stroke or transient ischemic attack and AF.</p> <p><b>Antithrombotic therapy for other at risk sub groups</b></p> <p>The ESTEEM trial concluded that ximelagatran added to aspirin was beneficial in comparison to aspirin for patients who developed AF after a myocardial infatuation.</p> <p><b>Comparison of anticoagulation to antiplatelet therapy (11 studies)</b></p> <p>One Cochrane review and two other systematic reviews have investigated oral anticoagulant treatment compared with antiplatelet therapy on major vascular events in patients with non-valvular AF. Only the Cochrane review specifically indicated that this was for individuals with no history of stroke or TIA. All three</p>	
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<p>anticoagulation therapy versus antiplatelet therapy for stroke prevention in persistent /permanent/paroxysmal AF?</p> <p>What is the efficacy of antiplatelet therapy versus placebo for stroke prevention in persistent permanent/paroxysmal AF?</p> <p><b>Relevant section of guideline</b> (Section, 7,11)</p> <p><b>Recommendations</b> (R25, R26,R52,R53, R54,R55,R56, R57, R58)</p>	<p>reviews concluded that oral anticoagulants (adjusted dose-warfarin and related drugs) reduce stroke, disabling stroke and other major vascular events for those with non-valvular AF by about one third when compared with antiplatelet (aspirin) therapy.</p> <p>In addition seven individual RCTs assessing anticoagulation against antiplatelet therapy have also been identified.</p> <ul style="list-style-type: none"> <li>• Two RCTs concluded warfarin significantly reduced the risk of thromboembolism in comparison to aspirin in patients with AF with and without rheumatic mitral valve disease.</li> <li>• Five studies have looked at the relative efficacy of warfarin and aspirin (or in combination) with patient age as a risk factor. One RCT indicated that warfarin was better tolerated than aspirin in the 80-90 year age range, a conclusion that was supported for the 75+year olds by two further RCTs. However, one RCT indicated that combined therapy was more effective in the &gt; 75years age group. A further RCT assessed low dose warfarin against aspirin and fixed dose</li> </ul>	
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	<p>warfarin in an &gt;75 years population, however this trial was stopped due to safety issues with the fixed dose warfarin. One RCT indicated that patients aged 65-75 would benefit from an aspirin alone a strategy.</p> <p><b>Oral Anticoagulation therapy</b></p> <p>A Cochrane review to characterize the efficacy and safety of oral anticoagulants for the primary prevention of stroke in patients with chronic AF concluded that adjusted-dose warfarin treatment (INRs of two to three) reduces stroke, disabling or fatal stroke, and death for patients with non-valvular AF.</p> <p>One RCT has shown that in patients over 75 years, a low stroke rate is best obtained with low intensity anticoagulation. Analysis of data from the SPORTIF III and V trials indicated that in patients with AF taking warfarin, the risks of death, MI, major bleeding, and stroke are related to INR control.</p>	
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	<p><b>Antiplatelet therapy</b></p> <p>One RCT in Japanese low risk patients found that aspirin was ineffective and was stopped early due to excess mortality in the aspirin group.</p> <p><b>Newer anti thrombotic agents</b></p> <p>A range of new anti-thrombotic agents both licensed and unlicensed in the UK have been assessed since the guideline was published. These have included the following licensed agents;</p> <ul style="list-style-type: none"> <li>• Apixaban was found to be successful at reducing the risk of stroke in comparison to aspirin in patients who vitamin K antagonist therapy is unsuitable in one RCT.</li> <li>• Dabigatran has shown efficacy in various sub groups and settings including; pre and post ECV, post stroke and in AF patients. It has similar efficacy to warfarin and may prove cost-effective dependant on pricing (six RCTs). This agent is currently been appraised by NICE with an expected completion date in late 2011.</li> </ul>	
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	<ul style="list-style-type: none"> <li>• Clopidogrel was indicated to be inferior to oral anticoagulation therapy and resulted in the stopping of one RCT. However a second RCT indicated that although the addition of Clopidogrel to aspirin was not advantageous, Clopidogrel and aspirin may be indicated in patients who cannot tolerate oral anticoagulation therapy.</li> <li>• Irbesartan an angiotensin-receptor blocker was no more effective than placebo in one RCT.</li> <li>• Idraparinux was found to cause significant excess bleeding in comparison to warfarin in one RCT.</li> </ul> <p>The following non-licensed agents have also been identified:</p> <ul style="list-style-type: none"> <li>• Edoxaban showed similar efficacy to warfarin however induces more bleeding in one RCT.</li> <li>• AZD0837 a new oral anticoagulant showed comparable safety, tolerability to warfarin in one RCT.</li> <li>• Ximelagatran a direct thrombin inhibitor has been extensively</li> </ul>	
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	<p>tested in comparison to warfarin in the two large RCTs. Ximelagatran was generally well tolerated in the trial populations, and showed efficacy however but a small proportion (5-6%) developed elevated liver enzyme levels, further development was discontinued in 2006 after it turned out hepatic damage could develop.</p> <p><b>Summary</b></p> <p>The guideline recommends appropriate thromboprophylaxis for all eligible patients with AF(asymptomatic, symptomatic, persistent, permanent and paroxysmal). A stroke risk stratification algorithm with indications for specific thromboprophylaxis options for sub groups of patients with AF is provided in the guideline. In addition the treatment of co-morbidities and attention to bleeding risks is recommended for all patients.</p> <p>New evidence was identified on most effective treatment options for specific sub groups at increased stroke risk. In addition</p>	
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	<p>evidence was identified that contradicts the stroke risk stratification algorithm and indicates that the low risk category treatment option may have safety issues for some populations of AF patients. New agents that are effective for thromboprophylaxis in patients were identified and one has an associated NICE TA in development. TA <a href="#">Dabigatran etexilate for the prevention of stroke or systemic embolism in people with atrial fibrillation</a></p> <p>New evidence that may address a research recommendation (CG36/3) in the guideline relating the combination of oral anticoagulation with antiplatelet therapy for subgroups of patients with AF was also identified.</p>	
<b>Clinical area 9: Referral and monitoring</b>		
<b>Clinical question</b>	<b>Summary of evidence</b>	<b>Relevance to guideline recommendations</b>

<p>Q: Which non-pharmacological treatments benefit patients with AF benefit and which patients should be referred?</p> <p>In patients receiving anticoagulation therapy, is self-system management using near-patient testing devices in primary care as effective as management using hospital lab testing?</p> <p>Previous clinical questions in guideline;</p> <p>In patients receiving anticoagulation therapy, is self-system management using near-patient testing devices in primary care as effective as management</p>	<p>Through the high level RCT search 34 studies relevant to the clinical question were identified.</p> <p><b>Monitoring (two studies)</b></p> <p>A meta-analysis was identified that evaluated the efficacy and safety of self-management of oral anticoagulant therapy for patients on long-term oral anticoagulant therapy. This review indicated that self management of oral anticoagulant therapy appeared to be at least as good and possible better than conventional management in highly selected patients. In addition one RCT assessed the safety and efficacy of oral anticoagulant therapy self-management in elderly patients with major thromboembolic and haemorrhagic complications as primary outcomes compared to routine care. The results suggested that self-management of oral anticoagulation was safe and feasible for elderly patients willing to participate in a structured training</p>	<p><b>Potential new evidence that may change current guideline recommendation(s).</b></p>
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<p>using hospital lab testing?</p> <p>Which patients with AF benefit from referral to specialist services for non-pharmacological treatment or electrophysiological studies?</p> <p><b>Relevant section of guideline</b> (Section 7.0, 8.0, 12.0)</p> <p><b>Recommendations</b> (R27, R29, R30, R31, R59, R66)</p>	<p>programme.</p> <p><b>Referral (32 studies)</b></p> <p><b>Ablation</b></p> <p>29 studies were identified that related to ablation of AF in differing populations or compared medical treatment strategy. However, of note is that in the abstract numerous studies do not always clarify which group of patients (or type of AF) that is under investigation. In other studies a mixed population group may have been used (i.e. paroxysmal and persistent AF) without stating outcomes by AF type. This makes it hard to assess the full impact and efficacy of a treatment in this instance. In other studies the term ablation has been used with no further indication of the site or nature this procedure. Likewise terminology differs in this area with regards to both patient groups and procedures. Many studies did not state if the patients were refractory to ADT in the abstract. The majority of identified studies related to PVI or the surgical treatment of atrial</p>	
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	<p>flutter.</p> <p>However, 11 studies investigating ablation (not specified-pulmonary vein (PV) or surgical treatment for atrial flutter) have been retrieved from the high level RCT search (two meta-analyses, two cost effectiveness, seven RCTs):</p> <ul style="list-style-type: none"><li>• A meta analysis concluded that in selected patients with AF, radiofrequency catheter ablation (RFA) was a relatively effective and well-tolerated procedure to cure AF. A second meta-analysis to determine whether atrioventricular junction ablation in combination with conventional right ventricular pacemaker therapy or cardiac resynchronization was an effective therapy in AF. The review found limited randomized trial data and was unable to make a clear recommendation.</li><li>• An economic evaluation of RFA versus antiarrhythmic drug therapy (ADT) as first-line treatment of symptomatic paroxysmal AF found RFA to be cost neutral two years after the initial procedure compared to ADT. A Markov decision</li></ul>	
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	<p>analysis model compared mitral valve surgery alone to mitral valve surgery plus an ablation (Maze procedure). The model indicated surgery plus ablation was associated with a reduced postoperative AF risk and was likely to be cost-effective.</p> <ul style="list-style-type: none"> <li>• In addition 4 RCTs assessing RFA for patients with AF during cardiac surgery found that left atrial size reduction improved sinus rhythm conversion and was safe and effective.</li> <li>• One RCT indicated that as a first-line strategy, tricuspid annulus-inferior vena cava isthmus ablation offers no advantages over direct current cardioversion for the management of coarse AF.</li> <li>• The long-term effects of atrioventricular junction ablation and pacing (on cardiac function and quality of life) were compared in one RCT for patients with permanent AF and showed a similar decline.</li> <li>• The use of ADT for six weeks after AF ablation compared to no ADT was found in an RCT to be tolerated and reduce the</li> </ul>	
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	<p>incidence of clinically significant atrial arrhythmias and need for CV /hospitalization.</p> <p><b>Ablation for Atrial Flutter</b></p> <p>One RCT compared amiodarone therapy and RFA after only one episode of symptomatic AFL. The RCT concluded that RFA should be considered a first-line therapy even after the first episode of symptomatic AFL as there was a better long-term success rate, the same risk of subsequent AF, and fewer secondary effects.</p> <p><b>Pulmonary Vein Isolation/Ablation (14 studies)</b></p> <p>14 studies relating to PVI have been retrieved from the high level RCT search.</p> <p>Two RCTs comparing PVI to other surgical strategy were identified. Both studies found that modified Cox maze procedure and PVI were similarly effective in restoring sinus or regular rhythm in permanent AF associated with mitral valve disease.</p>	
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	<p>12 studies were identified that have compared PVI to ADT or as adjunctive therapy for PVI.</p> <ul style="list-style-type: none"><li>• Adjunctive hydrocortisone in PVI shortly post ablation was found to offer some clinical benefit on AF recurrence. Whereas another RCT found that continuing ADT in patients who had undergone catheter ablation for AF did not lower the rate of AF recurrences. However adjunctive antiarrhythmic drugs increased the proportion of patients with asymptomatic AF episodes. One RCT established that adjunctive ADT following ablation therapy was superior to ADT alone in preventing atrial arrhythmia recurrences in patients with paroxysmal or persistent AF in whom ADT has already failed.</li><li>• Meta-analysis comparing PVI and medical therapy for the maintenance of sinus rhythm concluded that PVI results in dramatically increased freedom from AF at one year compared to ADT. A Markov model from the US health care perspective for a hypothetical cohort of patients with drug-refractory</li></ul>	
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	<p>paroxysmal AF, treated either with RFA with/without ADT or ADT alone concluded that RFA with/without ADT for symptomatic, drug-refractory paroxysmal AF was reasonably cost-effective compared with ADT therapy alone based on improved quality of life and avoidance of future health care costs.</p> <ul style="list-style-type: none"><li>• One study evaluated safety and efficacy of ablation therapy in comparison to ADT in diabetes mellitus two patients with drug refractory AF. In this patients group cardiac ablation provided significant clinical benefits over ADT.</li><li>• In ADT refractory patients in an RCT, PVI was more successful than ADT (flecainide, sotalol, and amiodarone) for prevention of PAF with few complications.</li><li>• A study comparing PVI or "new" antiarrhythmic drugs alone or in combination demonstrates the superiority of catheter ablation over ADT with regard to maintenance of sinus rhythm and improvement in symptoms, exercise capacity, and quality of life.</li></ul>	
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	<ul style="list-style-type: none"> <li>• PVI maintained long term sinus rhythm in the majority of patients with chronic atrial fibrillation independently of the effects of antiarrhythmic-drug therapy, cardioversion, or both in a further RCT.</li> <li>• Among patients with paroxysmal AF who had not responded to at least one antiarrhythmic drug, the use of catheter ablation compared with ADT resulted in a longer time to treatment failure during the 9-month follow-up period in one RCT.</li> <li>• Catheter ablation maintained sinus rhythm more effectively and improved symptoms and QoL than ADT as a second-line treatment for patients with refractory paroxysmal AF in one RCT.</li> </ul> <p><b>Thrombosis and ablation (three studies)</b></p> <ul style="list-style-type: none"> <li>• One RCT evaluated the need for preablation transesophageal echocardiography for the patients with planned catheter ablation for AF and antithrombotic therapy with oral</li> </ul>	
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	<p>anticoagulation. Atrial thrombi could be resolved partly but not completely in the patients with AF who had not received long-term oral anticoagulation previously.</p> <ul style="list-style-type: none"> <li>• Two studies were identified that related to the new technique of left atrial appendage exclusion/closure in AF patients. One RCT undertook LAA during open mitral valve surgery and demonstrated the safety of and feasibility of the technique. The second RCT assessed the efficacy and safety of percutaneous closure of the LAA for prevention of stroke compared with warfarin treatment in patients with AF. LAA was successful in stroke prevention and could provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular AF.</li> </ul> <p><b>Arrhythmia Surgery (three studies)</b></p> <p>Three studies were identified in the high level search that related</p>	
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	<p>to arrhythmia surgery in patients with AF.</p> <p>A RCT determined the effect of add-on arrhythmia surgery to cardiac surgery. Health-related quality of life in patients with paroxysmal, permanent and persistent AF improved after cardiac surgery regardless of giving add-on surgery or not. In a second RCT a cost analysis was performed from a societal perspective alongside. Concluding that concomitant arrhythmia surgery in AF is not cost-effective after a one-year follow-up compared to regular cardiac surgery. An RCT comparing AF outcomes after 6 months indicated that mitral valve surgery plus biatrial modified radiofrequency Maze procedure using Medtronic Cardioblate System was more effective than mitral valve surgery plus intensive rhythm control strategy.</p> <p><b>Summary</b></p> <p>The guideline recommended the referral for specialist intervention (for example, PVI, pacemaker therapy, arrhythmia surgery) for</p>	
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	<p>patients in whom ADT had failed or was unsuitable. The self monitoring of patients on long term oral anticoagulation therapy was recommended providing the patient a number of criteria relating to training and competency were met.</p> <p>Since the publication of the guideline new evidence relating to the efficacy and application of interventions, including both existing and new surgical procedures in patients with AF refractory to ADT or as a first line treatment for patients with AF has been identified. In addition, further evidence confirming the previous recommendations relating to the monitoring of oral anticoagulation was retrieved</p>	
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**TABLE 2- Summary of articles from the focused search**

<b>Clinical area 1:</b>		
<b>Clinical question</b>	<b>Summary of evidence</b>	<b>Relevance to guideline recommendations</b>
<p>Q: What factors impact on treatment outcomes and should be considered in the risk stratification for oral thromboprophylaxis in patients with atrial fibrillation?</p> <p><b>Relevant section of guideline</b> (Section 11)</p> <p>Recommendations; (R4,</p>	<p>Through the focused search 58 studies relevant to the clinical question were identified.</p> <p><b>Clinical risk factors (18 studies)</b></p> <p><b>Multiple risk factor studies</b> A systematic review ascertained that four clinical features (prior stroke/TIA, advancing age, hypertension, diabetes) are consistent independent risk factors for stroke in AF patients. With a prior stroke/TIA been the most powerful and reliable high risk factor.</p> <p>Two retrospective cohort studies which assessed multiple clinical risk factors were identified. Clinical markers of mortality in patients with AF in one study included; a history of heart failure, age<math>\geq</math>75 years, and CHADS2 score<math>&gt;</math>0. In the second study of Chinese hospitalised AF</p>	<p>Potential new evidence that may change current guideline recommendation(s).</p>

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<p><b>R52, R53, R54, R55, R56, R57, R58)</b></p>	<p>population the specific risk factors for stroke were age &gt; or = 75 years, diabetes, history of hypertension and high systolic blood pressure.</p> <p><b>Singular risk factor studies</b></p> <ul style="list-style-type: none"> <li>• Gender <ul style="list-style-type: none"> <li>○ A systematic review indicated that women with AF have a higher risk of stroke compared with their male counterparts but derive the greatest benefit from anticoagulation.</li> </ul> </li> <li>• Race <ul style="list-style-type: none"> <li>○ Two prospective cohorts were identified. In both the percent of AF patients on warfarin did not differ by race/ethnicity. No difference in regard to the rate of stroke and racial differences in AF patients on warfarin therapy were identified in the first study. Whereas ethnic differences (between non-Hispanic whites and Mexican Americans) were seen to impact on the rate of recurrence stroke in the second study.</li> </ul> </li> <li>• Inflammation markers <ul style="list-style-type: none"> <li>○ C-reactive protein was correlated to stroke risk (as determined</li> </ul> </li> </ul>	
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	<p>using CHADs, SPAF and NICE stratification), and related to stroke risk factors and prognosis in a cross sectional and longitudinal study of patients with AF.</p> <ul style="list-style-type: none"> <li>○ Plasma sCD40L identified patients with AF at high thrombo-embolic risk in a prospective cohort.</li> <li>● Cognitive dysfunction <ul style="list-style-type: none"> <li>○ Cognitive dysfunction in patients with AF was not associated with increased thrombotic risk providing anticoagulation medication was effectively delivered in one RCT.</li> </ul> </li> <li>● Type of AF <ul style="list-style-type: none"> <li>○ Paroxysmal AF had a comparable risk for thrombo-embolic events as persistent and permanent AF in a large prospective cohort. A second prospective cohort indicated that treatment of patients with paroxysmal AF with warfarin improves survival as this group of patients showed increased mortality, which is related to concomitant cardiovascular risks.</li> <li>○ In patients with recurrent AF episodes an observational study indicated that risk stratification for thromboembolic events could</li> </ul> </li> </ul>	
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	<p>be improved by combining CHADS<sub>2</sub> score with AF presence/duration.</p> <ul style="list-style-type: none"> <li>• Hypertension <ul style="list-style-type: none"> <li>○ A post hoc analysis from a RCT indicated that hypertension contributes to increased stroke and systemic embolic events in patients with AF.</li> </ul> </li> <li>• Cardiovascular risks <ul style="list-style-type: none"> <li>○ A systematic review found that evidence that demonstrates patients with AF hospitalized for acute myocardial infarction have serious adverse prognostic implications regarding in-hospital and long-term mortality and increases the risk for ischemic stroke.</li> <li>○ A post-hoc analysis from an RCT indicated that patients with AF with markers of heart failure are at increased risk of thromboembolic events.</li> </ul> </li> <li>• Hyperthyroidism <ul style="list-style-type: none"> <li>○ One case control study found that hyperthyroid patients who present with new-onset AF are at an increased risk of ischemic</li> </ul> </li> </ul>	
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	<p>stroke.</p> <ul style="list-style-type: none"> <li>• Renal function <ul style="list-style-type: none"> <li>○ A cohort study found that decreased renal function was associated with thromboembolic events in patients with AF. Likewise a retrospective observational study showed that chronic kidney disease increases the risk of thromboembolism in AF independently of other risk factors.</li> </ul> </li> </ul> <p><b>Echocardiography risk factors (five studies)</b></p> <p>New evidence relating to the use of echocardiography to identify factors which may aid risk stratification and the decision to administer thromboprophylaxis was found in four studies:</p> <ul style="list-style-type: none"> <li>• An ejection fraction of &lt;40 and left atrial dimension <math>\geq 50</math> mm were independent predictors for the presence of thrombus and dense spontaneous echo contrast in AF patients in patients with low CHADS2 score as indicated by a prospective cohort.</li> <li>• In a retrospective cohort of Chinese hospitalized AF patients the presence of left atrial thrombi as detected by transesophageal</li> </ul>	
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	<p>echocardiography was an independent risk factor for stroke.</p> <ul style="list-style-type: none"> <li>• The presence of left atrial spontaneous echocardiographic contrast and greater than moderate mitral regurgitation were independent predictors of mortality in patients with AF a retrospective cohort study.</li> <li>• A case-control study indicated that atrial fibrillatory rate obtained from surface ECG lead V1 was not a risk marker for stroke in patients with AF.</li> </ul> <p>The following study provided evidence which confirmed the summary statements in the guideline</p> <ul style="list-style-type: none"> <li>• Left ventricular diastolic dysfunction was a significant determinant of ischemic stroke in AF as determined in a cross sectional study.</li> </ul> <p><b>Risk factors for bleeding (11 studies)</b></p> <p>Eleven studies relating to bleeding risks in the patients with AF were identified.</p> <p>A systematic review for risk factors of anticoagulation-related bleeding</p>	
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	<p>complications in patients with AF identified the following predictors; advanced age, uncontrolled hypertension, history of myocardial infarction or ischaemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet agents.</p> <p>Two studies that have developed models for bleeding risk in AF patients have been identified. The first utilised a large retrospective to develop and validated the model which incorporated eight variables; age &gt; or = 70 years; gender; remote bleeding; recent bleeding; alcohol/drug abuse; diabetes; anaemia; and antiplatelet use to produce a final risk score. The second study adapted existing classification schemes which included the following risk factors; hepatic or renal disease, ethanol abuse, malignancy, older (age &gt; 75 years), reduced platelet count or function, hypertension (uncontrolled), anaemia, genetic factors, excessive fall risk, and stroke.</p> <p>Six studies relating to bleeding risk and age were identified.</p>	
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	<ul style="list-style-type: none"> <li>• A prospective cohort indicated that in AF patients older than 75 years with CHADS2 score 1-3 had a low risk of bleeding. However, in the same study, AF patients &gt;85 years with CHADS2 4-6 the risk of bleeding was high.</li> <li>• Three prospective cohort studies indicated no influence of age on major bleeding patterns in patients with AF on anticoagulation medication. One risk factor indentified for major bleeding episodes in those with good anticoagulation control was polypharmacy in patients &gt;75years.</li> <li>• Post-hoc analysis from an RCT indicated that increasing age and additional aspirin use were associated with an increased risk of bleeding in patients treated with anticoagulants.</li> <li>• A cohort study found that rates of hemorrhage derived from younger non-inception cohorts underestimated the bleeding that occurs in practice in AF patients on antithrombotic medication.</li> </ul> <p>There was conflicting evidence relating to bleeding risk and gender. A</p>	
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	<p>post-hoc analysis from a RCT results indicated that women were more prone to anticoagulant-related bleeding and had a higher rate of thrombo-embolism due to frequent interruptions of anticoagulant therapy. Whereas a systematic review indicated that there were no significant sex differences in major bleeding risk from warfarin in patients with AF.</p> <p><b>Stroke risk stratification schemes (Nine studies)</b></p> <p>Four studies were identified that have compared different stroke risk stratification schemes for patients with AF.</p> <ul style="list-style-type: none"><li>• CHADS(2 )and NICE scores were associated with the best predictive accuracy compared to the ACCP algorithm for primary prevention using data from a prospective cohort study on oral anticoagulant therapy. For secondary prevention all models had similar predictive outcomes.</li><li>• One study found that the CHADS(2), SPAF, and Framingham schemes had greater predictive accuracy in a large cohort of AF patients at moderate or high risk of ischemic stroke treated with warfarin or ximelagatran.</li></ul>	
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	<ul style="list-style-type: none"> <li>• One study compared the predictive ability of 15 published stratification schemes for stroke risk in actual clinical practice in the UK. The study concluded that current published risk schemes have modest predictive value for stroke prevention. A new scheme was suggested that may discriminate those at truly low risk and minimize classification of subjects as intermediate /moderate risk.</li> <li>• One study compared five schemes and highlighted that differences in outcomes related to the source of data.</li> </ul> <p>The use of the CHADS2 as a risk stratification strategy has been assessed in five identified studies.</p> <ul style="list-style-type: none"> <li>• In patients with AF and an intermediate risk of stroke (CHADS2 score =1) the prescription of an anticoagulant was independently associated with a decreased risk of death or stroke. Factors independently associated with an increased risk of events were older age, concomitant heart failure, diabetes, lack of prescription of an anticoagulant) and permanent AF.</li> </ul>	
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	<ul style="list-style-type: none"> <li>• One prospective cohort indicated that the CHADS2 score was a useful marker of stroke risk in a Japanese population.</li> <li>• Post-hoc subgroup analysis from a RCT indicated that patients with a CHADS(2)=1 had a low risk of stroke and still derived a statistically significant absolute reduction in stroke with oral anticoagulation therapy.</li> <li>• Gender differences in CHADS2 scores were found in a post-hoc analysis, with CHADS2 score been higher in women than in men. However, in the RCT population women tended to be older, more frequently have heart failure, and hypertension.</li> <li>• In a retrospective cohort study of AF patients with CHADS(2) score 1, warfarin was found to be better at preventing ischemic stroke than aspirin without increasing the incidence of major bleeding complications.</li> </ul> <p><b>Anti-coagulation therapy (18 studies)</b></p> <p>Three systematic reviews and one meta –analysis confirmed that oral</p>	
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	<p>anticoagulants (adjusted dose-warfarin) reduce stroke, disabling stroke and other major vascular events for those with non-valvular AF in comparison to antiplatelet treatment. The 2006 Cochrane review also concluded that 'although not definitively supported by the evidence, aspirin may prove to be useful for stroke prevention in sub-groups with a low risk of stroke, with less risk of hemorrhage than with warfarin'.</p> <p>Five RCT studies investigating the use of new agents which may impact on the current stroke risk stratification scheme were identified.</p> <ul style="list-style-type: none"><li>• Oral anticoagulation therapy with warfarin was superior to clopidogrel plus aspirin for prevention of vascular events in patients with AF and one or more risk factor for stroke.</li><li>• The post-hoc findings from one RCT findings do not support the use of dual-antiplatelet therapy with clopidogrel and aspirin in patients with AF who are asymptomatic for CV risk factors for anti-thrombotic therapy due to increased mortality and death in comparison to aspirin alone.</li><li>• In patients with AF for whom vitamin K-antagonist therapy was</li></ul>	
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	<p>unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage.</p> <ul style="list-style-type: none"> <li>• In patients with AF for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.</li> <li>• For patients with previous stroke or transient ischaemic attack, the effects of dabigatran on stroke or systemic embolism were similar to those of warfarin.</li> </ul> <p>Evidence from three RCTs was identified that conflicts with the current stroke risk stratification algorithm.</p> <ul style="list-style-type: none"> <li>• An RCT supported the use of warfarin therapy for people aged over 75 who have AF in comparison to aspirin.</li> <li>• One RCT indicated that for prevention of stroke in patients with AF, aspirin at 150 to 200 mg per day does not seem to be either effective</li> </ul>	
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	<p>or safe in Japanese patients</p> <ul style="list-style-type: none"> <li>• The &gt;75years with AF had a rate of severe bleeding when receiving anticoagulant therapy than those &lt;75years. Antiplatelet plus moderate-level anticoagulant therapy compared with anticoagulant therapy, significantly reduced vascular events and bleeding mortality in elderly patients.</li> </ul> <p>In addition, there was evidence that supports the current stroke risk stratification algorithm.</p> <ul style="list-style-type: none"> <li>• A meta-analysis concluded that as patients with AF age, the relative efficacy of antiplatelet therapy to prevent ischemic stroke appears to decrease, whereas it does not change for oral coagulation therapy. Because stroke risk increases with age, the absolute benefit of oral coagulation therapy increases as patients get older.</li> <li>• A post hoc sub group analysis from a RCT did not support the use of treatment doses of low molecular weight heparin in any patients with acute ischemic stroke and AF</li> </ul>	
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	<ul style="list-style-type: none"> <li>• Mixed retrospective and prospective cohort study indicated that the net clinical benefit of warfarin therapy is highest among patients with the highest untreated risk for stroke, which included the oldest age category.</li> <li>• One RCT indicated that for patients with AF associated with rheumatic mitral valve disease warfarin was more effective than aspirin in preventing adverse thrombotic events.</li> <li>• One RCT found Aspirin was as effective as warfarin in preventing stroke in patients age 65 to 75 years old without risk factor, and warfarin was more effective than aspirin in preventing stroke in patients (<math>\geq 75</math>y) and all patients with risk factors.</li> </ul> <p><b>Summary</b></p> <p>New agents which may impact on the choice of thromboprophylaxis agent in relation to the current stroke risk stratification algorithm were identified. New evidence that confirmed and conflicted aspects of the stratification with regards to clinical and demographic risk factors was identified. New echocardiography risk factors and bleeding risk factors relevant to</p>	
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	patients with AF was identified. In addition evidence that contradicts the status of current clinical and demographic factors as potential bleeding risks in patients with AF was retrieved.	
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223 clinical trials including, 73 ongoing and 151 recently completed clinical trials (publication dates unknown) were identified focusing on: ablation, ablation in comparison to pharmacological therapy, antiarrhythmic drug therapy for post operative AF, pacing, monitoring, thromboprophylaxis studies and antiarrhythmic treatment were identified.

New evidence was identified that was relevant to three research recommendations in the original guideline. Specifically, the high level search identified numerous RCTs that related to the optimal mode of cardioversion and the use of antiarrhythmic drugs pre-cardioversion. RCT evidence was relating to the clinical and cost effectiveness of the 'pill-in-the-pocket treatment for patients with paroxysmal AF was identified. Evidence from the focus search identified new evidence relating to combined anticoagulation with antiplatelet therapy for any subgroups of patients with AF.

### **Guideline Development Group and National Collaborating Centre perspective**

A questionnaire was distributed to GDG members and the National Collaborating Centre to consult them on the need for an update of the guideline. Three responses were received with respondents highlighting a large amount of relevant new literature derived from numerous clinical trials about the thromboprophylaxis, ablation, cost effectiveness and pharmacological treatment of AF. Multiple ongoing clinical trials for new oral anticoagulants including ARISTOTLE, new data on antiarrhythmic drugs e.g. PALLAS and trials investigation ablation as a first line therapy in comparison to medical therapy.

All respondents indicated that current practice varies from the guidance due to the emergence of new evidence and treatment options for AF including stroke prevention, bleeding risk assessment, new antiarrhythmic drugs, and rhythm

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control therapies (including ablation). GDG members indicated that the NICE algorithm for stroke prevention outdated and recommendations for stroke prevention and bleeding risk assessment urgently requiring updating. In addition, the GDG recognised that guidelines from other sources utilised different stroke risk algorithms which may have more predictive value. It was indicated that clinically this has resulted in substantial modifications to any practices recommended by the current guideline with less emphasis on aspirin, and more emphasis on oral anticoagulation for stroke prevention.

Numerous significant audits of practice /implementation were identified by the GDG since the publication of the current guideline. These include the NHS Improvement Programme, data from the EuroHeart survey, AF Net and comparisons of the value of the NICE stroke algorithm versus other stroke risk schema, local audits have been published. These all indicate that thromboprophylaxis was sub-optimal. With regard to efficacy or safety concerns, the overuse of aspirin for stroke prevention with its associated deleterious effects in older AF patients was highlighted.

The potential for cost savings in relation to prescribing costs and monitoring medical adherence of new drugs introduced since the publication of the guideline was highlighted by the GDG respondents. In addition, the need for thromboembolism prevention was also highlighted as a major source of potential cost savings.

Areas that were noted as difficult to manage and where specific guidance would be helpful included the management of patients with AF presenting with an acute coronary syndrome and/or undergoing coronary stenting and the medical management of AF patients post-ablation.

This feedback contributed towards the development of the clinical questions for the focused searches.

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The majority of respondents felt that there is sufficient variation in current practice supported by adequate evidence at this time to warrant an update of the current guideline.

### **Implementation and post publication feedback**

In total 60 enquiries were received from post-publication feedback, most of which were routine.

An analysis by the NICE implementation team indicated that the guideline has been helpful although the size and complexity of the guideline has made it a challenge to implement. Suggestions were made to split and simplify the guideline to define management of AF patients by service provider, i.e. GP, ambulance staff, emergency room staff, mental health trusts for treatment initiation. Issues regarding the QOF indicator for 'warfarin or equivalent' for Atrial Fibrillation in Primary Care were highlighted with thresholds stated as being too generous for prescribing targets.

One small audit reported showed excellent compliance with NICE guidance for newly diagnosed patients but indicated substantially lower compliance in pre-existing AF patients for both ADT and thromboprophylaxis therapy. In addition, during initial intelligence gathering a report from NHS improvement was identified which highlighted that amongst patients with recognised AF only 46% of those who would benefit from warfarin were not receiving it.

This feedback contributed towards the development of the clinical questions as described above

No new evidence was identified through post publication enquiries or implementation feedback that would indicate a need to update the guideline.

### Relationship to other NICE guidance

The following NICE guidance is related to CG36:

Guidance	Review date
<b>Related NICE guidance not included in CG36</b>	
Technology appraisals TA197 Dronedronone for the treatment of non-permanent atrial fibrillation Issued: August 2010 Review date: March 2013	Review date: March 2013
IPG123 Cryoablation for atrial fibrillation in association with other cardiac surgery Guidance issue date: 25 May 2005	
IPG184 High intensity focused ultrasound ablation of atrial tissue for atrial fibrillation as an associated procedure with other cardiac surgery Guidance issue date: 26 July 2006	
IPG122 Microwave ablation for atrial fibrillation in association with other cardiac surgery Guidance issue date: 25 May 2005	
IPG294 Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation Guidance issue date: 25 March 2009	

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IPG349 Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism  
Guidance issue date:23 June 2010

IPG168 Percutaneous radiofrequency catheter ablation for atrial fibrillation  
Guidance issue date:26 April 2006

IPG121 Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery  
Guidance issue date:25 May 2005

IPG286 Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation  
Guidance issue date:28 January 2009

IP Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation  
Provisional publication date: June 2011

IP Thoracoscopic exclusion of the left atrial appendage in atrial fibrillation (with or without other cardiac surgery) for the prevention of thromboembolism: June 2011

TA95 Arrhythmia - implantable cardioverter defibrillators (ICDs) (review): guidance  
25 January 2006

TA95; and TA120; Cardiac resynchronisation therapy for the treatment of heart failure: Proposal to combine and plan an update to the guidance into the appraisal work

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CG68: Stroke. Issued: July 2008	programme 2010
TA170 Venous thromboembolism - rivaroxaban April 2007	Review update- Oct 2011
CG48 MI: secondary prevention.	Timetabled for update
TA52 Myocardial infarction - thrombolysis	
<b>Related NICE guidance in progress</b>	
TA Atrial fibrillation (stroke prevention) - rivaroxaban	Expected date of issue: TBC
TA Dabigatran etexilate for the prevention of stroke or systemic embolism in people with atrial fibrillation	Expected date of issue: December 2011
Suspended TA Clopidogrel in combination with aspirin for the prevention of vascular events in people with atrial fibrillation	Suspended: Ministers have considered developments since this product was originally referred to NICE, including information received from the manufacturers in relation to this indication. As a result Ministers have now agreed that this topic should be formally un-referred from the NICE work programme.
Suspended TA Atrial fibrillation - idraparinux sodium	Suspended: the regulatory strategy in relation to this product is not finalised
Suspended TA Ximelagatran for the treatment and prevention of stroke and other thromboembolic complications associated with	Suspended: Withdrawn from market due to safety issues

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atrial fibrillation	
Suspended - Vernakalant for the treatment of rapid conversion of recent onset atrial fibrillation = 7 days	Suspended: May 2011 following on from information received from the manufacturer, regarding the timings of the launch of the product in the UK, NICE has decided to suspend this appraisal on its current work programme.
CG Stroke rehabilitation	Publication April 2012

### **Anti-discrimination and equalities considerations**

No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope is inclusive of all adults aged over 18 years with new onset AF, acute AF, atrial flutter, postoperative AF and chronic AF: including paroxysmal (recurrent), persistent and permanent/sustained AF. The guideline covered the co-morbidities that impact upon as well as the identification and diagnosis of AF. Treatment options were considered for all AF subtypes including cardioversion, antithrombotic therapy and monitoring and referral to specialist services.

### **Conclusion**

From the evidence and intelligence identified through the process, it suggests that some areas of the guideline may need updating at this stage, particularly in relation to:

- Pharmacological treatment for AF
- Cardioversion

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- Thromboprophylaxis, including stroke and bleeding risk stratification
- Surgical interventions

### **3. Review recommendation**

The guideline should be considered for an update at this time.

Centre for Clinical Practice  
25 July 2011

## Appendix I

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