Appendix A: Summary of evidence from surveillance

NICE guideline CG180

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Summary of evidence from surveillance

Diagnosis and assessment

| 180-01 | Identification and assessment: presenting symptoms/pulse palpitation |

Subquestion

In patients with diagnosed AF (including those presenting with stroke), what are the frequencies of the presenting symptoms?

Recommendations derived from this question

1.1.1 Perform manual pulse palpation to assess for the presence of an irregular pulse that may indicate underlying atrial fibrillation in people presenting with any of the following:
   - breathlessness/dyspnoea
   - palpitations
   - syncope/dizziness
   - chest discomfort
   - stroke/transient ischaemic attack. [2006]

Surveillance decision

This review question should be updated.

4-year surveillance summary

Blood pressure monitoring

A systematic review¹ (21 studies, n=15,129) assessed the accuracy of different methods for detecting pulse irregularities caused by AF. Compared to 12-lead ECG-diagnosed AF, blood pressure monitors (BPMs); seven interventions) and non-12-lead ECGs (20 interventions) had the greatest accuracy for detecting pulse irregularities attributable to AF.

A systematic review² (6 studies, n=2332) investigated the accuracy of AF detection using the Microlife BPM. Taking 3 sequential readings with at least 2 detecting AF gave the highest diagnostic accuracy. The results indicated that AF detection with routine automated BP measurement was a reliable tool for detecting AF in the elderly, which requires confirmation by ECG. Paroxysmal AF was also detected by routine automated home or
ambulatory BP monitoring. This technology is covered by NICE Medical technologies guidance 13 WatchBP Home A for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension. NICE MTG13 found that WatchBP Home A was cost saving and could provide significant clinical benefits when used for opportunistic AF detection in asymptomatic patients being screened or monitored for hypertension in primary care. WatchBP Home A was particularly beneficial for older patients at higher risk of stroke.

Portable ECG recorders
A phase II diagnostic test accuracy study\(^3\) (n=191) found that ‘MyDiagnostick’, an alternative new screening tool to pulse palpation, had high sensitivity and specificity for the detection of AF. Future research was recommended by the authors to determine the place of the MyDiagnostick in possible screening or case-finding strategies for atrial fibrillation.

A study\(^4\) (n=7173) and secondary analysis\(^5\), also noted by a topic expert, conducted a systematic screening programme using a handheld ECG recorder for intermittent ECG recordings over 2 weeks, among 75- to 76-year-old individuals. The screening programme using this technology identified a significant proportion of participants with untreated AF. Initiation of stroke prophylactic treatment was accepted by the majority of individuals with newly diagnosed AF. Participation in the programme varied according to socioeconomic conditions.

Insertable cardiac monitors for cryptogenic stroke
An RCT\(^6\) (n=441) explored the detection of AF in cryptogenic stroke patients using continuous long-term monitoring via insertable cardiac monitors (ICMs). Three-year monitoring by ICM demonstrated a significantly higher AF detection rate compared with routine care. The majority of patients were then prescribed oral anticoagulation therapy.

A meta-analysis\(^7\) (4 studies n=1149) found that prolonged cardiac monitoring beyond 7 days compared to shorter cardiac monitoring of less than 48 hours duration improved detection of AF and anti-coagulation use after cryptogenic stroke or transient ischemic attack (TIA).

A cost effectiveness study\(^8\) evaluated whether AF detection using continuous long-term monitoring with an ICM is cost-effective for preventing recurrent stroke in patients with cryptogenic stroke, in comparison to the standard of care. The incremental cost-effectiveness ratio, compared to standard of care in the base-case scenario, was below established quality-adjusted life years willingness-to-pay thresholds.

A secondary analysis\(^8\) (n=168) of the CRYSTAL AF trial found that long-term continuous ECG monitoring with ICMs was significantly more effective than any of the simulated intermittent monitoring strategies for identifying AF in patients with previous cryptogenic stroke. The long term strategy involved quarterly monitoring through 24-hour, 48-hour, and 7-day Holters and monthly 24-hour Holters.

An RCT\(^10\) (n=572) found that, among patients with a recent cryptogenic stroke or TIA who were 55 years of age or older, paroxysmal AF was common. Non-invasive ambulatory ECG monitoring for a target of 30 days significantly improved the detection of AF by a factor of more than five and nearly doubled the rate of anticoagulant treatment, as compared with the standard practice of short-duration 24-hour ECG monitoring.

Active case finding
An RCT\(^11\) (n=928) evaluated the usefulness of a programme for early diagnosis of AF in patients from an urban primary care centre. The intervention included:

- initial visit with clinical history, electrocardiogram, and instruction about pulse palpation and warning signs and
- electrocardiogram every 6 months during a 2-year follow-up.

The control group comparator intervention was not described in the abstract. In the intervention group, the early detection of AF within 6 months and the time to first diagnosis of AF was significantly higher compared to the control group.

A Cochrane systematic review\(^12\) (1 study) found that systematic screening and opportunistic screening for AF increased the rate of detection of new cases compared with routine practice. Data were derived from 25 general practices within which cohorts of 200 patients were randomly allocated to opportunistic (pulse and ECG) or systematic screening (postal invitation for ECG). Although these approaches had comparable effects on
the overall AF diagnosis rate, the cost of systematic screening was significantly greater than the cost of opportunistic screening from the perspective of the health service provider. A subgroup analysis found that systematic screening and opportunistic screening were more effective in men than in women. No adverse events associated with screening were reported. Additional research was recommended by the authors to examine the effectiveness of alternative screening strategies and to investigate the effects of the intervention on risk of stroke for screened versus non-screened populations.

A further secondary analysis of the included RCT found that, based on CHADS2 score comparisons, there were no significant differences in the number of new cases of AF, or in stroke risk profiles of patients detected via opportunistic and systematic screenings.

Opportunistic screening was found to be non-inferior.

**Topic expert feedback**

**Case detection**

Topic expert feedback highlighted that the guideline committee did not review the diagnosis of AF at the time of developing CG180. The reason for this was described in the full guideline as being due to the constraints of the guideline process. The diagnosis recommendations were brought forward from the 2006 guideline. This meant that the SAFE study, considered to be important by the topic expert, was not included in the remit of the 2014 development group. The topic expert indicated that this remains a significant oversight in the published guideline. The SAFE study, covering opportunistic and other screening programmes in patients over 65 years and over, is covered by the Cochrane review that is included in the surveillance evidence summary.

Feedback via the development of the NICE Quality Standard on AF indicated that diagnosis was omitted from the quality standard as it was felt that the section of the guideline on diagnosis and assessment should be updated first.

Topic experts highlighted that addressing detection in a guideline review is highly important and will need to incorporate a number of components, including:

- age targeting or targeting individuals with other pathologies predisposing to AF
- the optimal means of detection including new technological developments such as through pulse rhythm checks and with the use of the new handheld ECG monitors
- monitoring for secondary prevention in patients who have already had a stroke.

It was noted that none of these issues were considered in CG180, due to being outside the remit of NICE.

**New ECG technologies**

Topic expert feedback indicated that increasing numbers of ECG recording systems, including those using single lead technology, are available for AF diagnosis and were considered superior to Holter monitoring and 12 lead ECG, as an easier way to diagnosing symptomatic paroxysmal AF.

These range from simple Smart phone devices to specific devices for looking for AF in an at-risk population. Since the 2014 guideline, the STROKESTOP trial from Sweden has been published showing the importance of this simple single lead ECG technology in diagnosing AF in the high risk post stroke population. The study was retrieved by the surveillance literature search and is covered in the evidence summary.

New digital technologies were highlighted by topic experts, to help identify, diagnose and monitor for AF (such as AliveCor Kardia handheld ECG – approved by NICE and part of the NHS Innovation scheme). These were recommended for inclusion in the guideline, although no studies were cited.

**Insertable cardiac monitors**

The CRystal AF study was recommended by a topic expert for consideration relating to implantable loop recorders (ILR) to detect AF in those who have suffered a cryptogenic stroke, and is included in the evidence summary.

**Impact statement**

**Case detection**

Systematic review evidence indicates that case detection is as effective as population screening but at a significantly lower cost. There is therefore a potential impact on the guideline to consider case detection based on clinical suspicion in high risk patients.

However, screening is outside the remit of the guideline, and is within the remit of the National Screening Committee (NSC). The most recent review by the NSC was published prior to CG180 in 2014 and did not recommend
screening. A review of the NSC recommendation is scheduled for 2017 or 2018.

**Portable ECG monitors**

Recommendation 1.1.1 advises performing manual pulse palpation to assess for the presence of an irregular pulse that may indicate underlying atrial fibrillation in people presenting with any of the following: breathlessness/dyspnoea, palpitations, syncope/dizziness, chest discomfort, or stroke/transient ischaemic attack.

New systematic review evidence and topic expert feedback indicates that portable and handheld ECG monitors may have greater accuracy than 12-lead ECGs for detecting pulse irregularities. The new evidence has a potential impact on recommendation 1.1.1 to consider portable ECGs as alternative methods to detect pulse irregularities.

New evidence, including the NICE MedTech innovation briefing 35 AliveCor Heart Monitor and AliveECG app (Kardia Mobile) for detecting atrial fibrillation (August 2015) has highlighted the use of the AliveCor portable ECG recorder. This is included in the NICE atrial fibrillation pathway, but may need to be incorporated into CG180 recommendations.

The diagnostic evidence supporting the use of the MyDiagnostick tool may require further studies to establish its value in case detection.

**Blood pressure monitoring**

New systematic review evidence indicates that BPMs may have greater accuracy than 12-lead ECGs for detecting pulse irregularities. The new evidence has a potential impact on recommendation 1.1.1, which does not recommend BPMs.

New evidence, including NICE MTG13 WatchBP Home A supports the use of routine automated blood pressure measurement for opportunistic case detection of AF during diagnosis and monitoring of hypertension in primary care. The available evidence suggests that the device reliably detects AF and may increase the rate of detection when used in primary care. This would allow prophylactic treatment to be given to reduce the incidence of AF-related stroke. WatchBP Home A should therefore be considered for use in people with suspected hypertension and those being screened or monitored for hypertension, in primary care. In addition to impacting on CG180 recommendations, the technology should also be incorporated into the NICE AF pathway and will be passed onto the NICE Pathways team. NICE Pathways bring together everything NICE has said on a topic in an interactive flowchart.

**Insertable cardiac monitors**

New evidence and topic expert feedback indicates that ICMs, including loop recorders, are a cost-effective diagnostic tool for the prevention of recurrent stroke in patients with cryptogenic stroke. CG180 does not make recommendations for the use of ICMs. There is therefore a potential impact to consider incorporating ICMs into the recommendations in the context of cryptogenic stroke.

New evidence identified that may change current recommendations.
180-02 In patients with suspected AF based on an irregular pulse, how accurate is an ECG in diagnosing AF?

180-03 In patients with suspected intermittent AF, how effective is ambulatory ECG rather than event ECG in diagnosing AF?

Recommendations derived from this question

1.1.2 Perform an electrocardiogram (ECG) in all people, whether symptomatic or not, in whom atrial fibrillation is suspected because an irregular pulse has been detected. [2006]

1.1.3 In people with suspected paroxysmal atrial fibrillation* undetected by standard ECG recording:

- use a 24-hour ambulatory ECG monitor in those with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart
- use an event recorder ECG in those with symptomatic episodes more than 24 hours apart. [2006]

Surveillance decision

These review questions should not be updated.

4-year surveillance summary

12 Lead ECG Interpretation

A systematic review14 (10 studies, n=55,376) compared accuracy of methods for interpreting 12 lead ECGs for diagnosing atrial fibrillation (AF). The results indicated that automated ECG-interpreting software most accurately excluded AF with high specificity, although its sensitivity was similar to all healthcare professionals. Within primary care, the specificity of AF diagnosis from ECG was greater for General practitioners (GPs) than nurses.

Topic expert feedback

12 Lead ECG interpretation

Topic expert feedback indicated that the quality of automated reporting software is variable, and that diagnosis will have to be confirmed by a health professional with appropriate ECG interpretation expertise due to the medico-legal nature of the issue.

Impact statement

12 Lead ECG interpretation

CG180 does not make recommendations on ECG-interpreting software. The new systematic review evidence indicates that the use of automated ECG-interpreting software may enable GPs to accurately interpret 12 lead ECGs and to rule out AF in primary care. However, its sensitivity appears to be similar to interpretation by healthcare professionals and further evidence may therefore be required to establish a definite impact on the guideline. The lack of conclusive evidence was also confirmed by topic expert feedback.

New evidence is unlikely to change guideline recommendations.

* Paroxysmal atrial fibrillation spontaneously terminates within 7 days, usually within 48 hours.
In which patients should echocardiography be performed to identify underlying structural/functional heart disease?

Recommendations derived from this question

1.1.4 Perform transthoracic echocardiography (TTE) in people with atrial fibrillation:

- for whom a baseline echocardiogram is important for long-term management
- for whom a rhythm-control strategy that includes cardioversion (electrical or pharmacological) is being considered
- in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management (for example, choice of antiarrhythmic drug)
- in whom refinement of clinical risk stratification for antithrombotic therapy is needed (see section 1.4 Assessment of stroke and bleeding risks and section 1.5 Interventions to prevent stroke). [2006, amended 2014]

1.1.5 Do not routinely perform TTE solely for the purpose of further stroke risk stratification in people with atrial fibrillation for whom the need to initiate anticoagulation therapy has already been agreed on appropriate clinical criteria (see section 1.4 Assessment of stroke and bleeding risks and section 1.5 Interventions to prevent stroke). [2006, amended 2014]

1.1.6 Perform transoesophageal echocardiography (TOE) in people with atrial fibrillation:

- when TTE demonstrates an abnormality (such as valvular heart disease) that warrants further specific assessment
- in whom TTE is technically difficult and/or of questionable quality and where there is a need to exclude cardiac abnormalities
- for whom TOE-guided cardioversion is being considered. [2006]

Surveillance decision

This review question should not be updated.

4-year surveillance summary

A systematic review and economic evaluation investigated the clinical effectiveness and cost-effectiveness of transthoracic echocardiography (TTE) in all patients who are newly diagnosed with AF. The results indicated that TTE-diagnosed left ventricular dysfunction, increased left atrial diameter and valvular abnormality were significantly associated with an increased risk of stroke, mortality or thromboembolism. Diagnostic accuracy of TTE was found to be high for both specificity and sensitivity, although accuracy for the specific pathologies was not reported in the abstract. The mathematical model predicted that when the CHADS2 tool was used, the addition of TTE in identifying patients with left atrial abnormality appeared to be cost-effective for informing some oral anticoagulant decisions.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

New systematic review evidence indicates that TTE has diagnostic value for identifying underlying structural or functional heart disease, and assessing risk of stroke and bleeding, in patients newly diagnosed with AF. This is consistent with recommendation 1.1.4,
which advises the use of TTE in patients with AF:

- in whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management (for example, choice of antiarrhythmic drug)
- in whom refinement of clinical risk stratification for antithrombotic therapy is needed (see section 1.4 Assessment of stroke and bleeding risks and section 1.5 Interventions to prevent stroke). [2006, amended 2014].

The evidence also indicated that TTE may be cost effective when combined with CHADS2, although further research, as recommended by the authors, may be required to confirm this.

New evidence is unlikely to change guideline recommendations.

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**Personalised package of care and information**

**180-05** What educational and behavioural interventions are clinically and cost effective for aiding the management of anticoagulation therapy, rate and rhythm strategies and symptoms in patients with AF?

**Recommendations derived from this question**

1.2.1 Offer people with atrial fibrillation a personalised package of care. Ensure that the package of care is documented and delivered, and that it covers:

- stroke awareness and measures to prevent stroke
- rate control
- assessment of symptoms for rhythm control
- who to contact for advice if needed
- psychological support if needed
  - up-to-date and comprehensive education and information on:
    - cause, effects and possible complications of atrial fibrillation
    - management of rate and rhythm control
    - anticoagulation
    - practical advice on anticoagulation in line with recommendation 1.3.1 in 'Venous thromboembolic diseases' (NICE clinical guideline 144)
    - support networks (for example, cardiovascular charities). [new 2014]

1.2.2 NICE has produced guidance on the components of good patient experience in adult NHS services. Follow the recommendations in patient experience in adult NHS services (NICE clinical guideline 138). [new 2014]
**Surveillance decision**

This review question should not be updated.

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**4-year surveillance summary**

**Post discharge management**

A topic expert noted an RCT\(^8\) (n=335) which found that the SAFETY intervention, a post-discharge management programme specific to AF, was associated with proportionately more days alive and out of hospital relative to standard management. It did not but not prolonged event-free survival, however. The SAFETY intervention comprised a home visit and Holter monitoring 7-14 days after discharge by a cardiac nurse with prolonged follow-up and multidisciplinary support as needed.

**Nurse led care**

A secondary analysis of an RCT\(^1\) (n=712) found that a nurse-led integrated chronic care approach significantly improved AF-related knowledge at follow-up in the intervention group, compared with the usual care group. However, there were no significant differences in quality of life over time.

Nurse-led care consisted of guidelines-based, software supported care, supervised by cardiologists. Usual care was provided by cardiologists in the regular outpatient setting.

**Topic expert feedback**

**Patient values and preferences**

Topic expert feedback highlighted the need for greater focus on patient values and preferences – citing a recent European Heart Rhythm Association consensus document and a narrative review. However, these publication types were not eligible for inclusion in the surveillance review.

The NICE Medicines Evidence Commentary *Atrial fibrillation: differences among patients and physicians in values and preferences about antithrombotic choice* covered a qualitative study which found a wide range of views among patients and physicians on the acceptable trade-off between a reduction in risk of stroke and an increased risk of bleeding in atrial fibrillation.

**Impact statement**

**Nurse led care**

No evidence on nurse led care to improve patient education was reviewed for CG180. The new RCT evidence indicating that a nurse-led chronic care approach may increase AF related patient knowledge is unlikely to impact on the personalised package of care advised in recommendation 1.2.1, because the outcome did not translate into improved quality of life.

**Post discharge management**

New RCT evidence indicating that the SAFETY intervention may increase survival and out of hospital days is relevant to the personalised package of care advised in recommendation 1.2.1. However, the study was conducted in the Australian healthcare setting and any impact on CG180 is therefore unlikely until further studies validate the findings in the UK setting.

**Patient values and preferences**

Topic expert feedback highlighted the need for greater focus on patient values and preferences but in the absence of eligible new evidence, no impact on CG180 is anticipated. The NICE Medicines Evidence Commentary *Atrial fibrillation: differences among patients and physicians in values and preferences about antithrombotic choice* highlighted the need for clinicians and patients to discuss treatment options, which is consistent with CG180 recommendations to provide a personalised package of care.

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New evidence is unlikely to change guideline recommendations.
Referral for specialised management

180-06 What is the clinical and cost effectiveness of referral to specialist AF services?

Subquestion

Which patients with AF benefit from referral to specialist services for non-pharmacological treatment or electrophysiological studies?

Recommendations derived from this question

1.3.1 Refer people promptly at any stage if treatment fails to control the symptoms of atrial fibrillation and more specialised management is needed. [new 2014]

Surveillance decision

This review question should not be updated.

4-year surveillance summary

No relevant evidence was identified.

Topic expert feedback

Topic experts noted that the NICE approach has been formulated as a ‘3-step’ patient pathway, that has been successfully adopted by local CCGs clinical commissioning groups (CCGs) and academic health science networks (AHSNs) to streamline primary-secondary care pathways for AF management decision-making. It was recommended that any update of the NICE guideline should consider implementing the 3 step decision making pathway to streamline decision making process for AF stroke prevention management pathways. Topic experts noted that the AHSN’s in some areas have or are working on updated referral, service delivery through the AF Association – Detect, Protect, Correct & Perfect projects. The AF Association Healthcare Pioneers Report identifies leading services within the UK, improvements made and best outcomes for the AF patient.

Impact statement

Topic expert feedback highlighted that a 3 step patient pathway has been adopted by local CCGs and AHSNs, and that AHSNs are working on updated referral and service delivery projects. As these points relate to implementation, they are unlikely to impact on the recommendations.

New evidence is unlikely to change guideline recommendations.

† The Guideline Development Group defined ‘promptly’ as no longer than 4 weeks after the final failed treatment or no longer than 4 weeks after recurrence of atrial fibrillation following cardioversion when further specialised management is needed.

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014) NICE guideline CG180

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Assessment of stroke and bleeding risks

180-07 What is the most clinically and cost-effective risk stratification tool for stroke or thromboembolic events in people with AF?

Recommendations derived from this question

Stroke risk

1.5 Do not routinely perform TTE solely for the purpose of further stroke risk stratification in people with atrial fibrillation for whom the need to initiate anticoagulation therapy has already been agreed on appropriate clinical criteria (see section 1.4 Assessment of stroke and bleeding risks and section 1.5 Interventions to prevent stroke). [2006, amended 2014]

1.4.1 Use the CHA2DS2-VASc stroke risk score to assess stroke risk in people with any of the following:
- symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation
- atrial flutter
- a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. [new 2014].

Surveillance decision

This review question should be updated.

4-year surveillance summary

Atrial stroke risk score

A study\(^\text{18}\) (n=60,594) compared predictive ability of CHA\(_2\)DS\(_2\)-VASc and CHADS2 ischemic stroke risk scores with the ATRIA stroke risk score and their implications for anticoagulant treatment in patients with AF. Results indicated that the ATRIA score more accurately identified low-risk patients than the CHA\(_2\)DS\(_2\)-VASc score, which assigned these patients to higher-risk categories.

A meta-analysis\(^\text{19}\) 2016 (6 studies, 363,432) found that based on C-statistics and net reclassification improvement values, the ATRIA score performed better than the CHA\(_2\)DS\(_2\)-VASc score for stroke risk prediction. In contrast, the CHA\(_2\)DS\(_2\)-VASc score was superior to the ATRIA score for identifying low risk AF patients.

Asian populations

A topic expert noted two cohort studies\(^\text{20,21}\) which investigated whether the age threshold for an increased stroke risk for patients with AF may be different for people from an Asian origin. The first\(^\text{20}\) (n=186,570) found that for Taiwanese patients 50 to 64 years of age, the annual stroke risk exceeded the threshold for OAC use for stroke prevention. The annual risk of ischemic stroke for AF patients under 50 years of age was lower than the threshold. However, applicability to the UK population was questionable. The second study\(^\text{21}\) (n=225,866) found that the modified version mCHA\(_2\)DS\(_2\)-VASc score performed better than the original CHA\(_2\)DS\(_2\)-VASc in people from an Asian origin, and could further identify AF patients who may derive a positive net clinical benefit from oral anticoagulation.

Tropinin T

A secondary analysis\(^\text{22}\) (n=14,897) of an RCT found that in patients with AF the level of high-sensitivity troponin T was independently associated with an increased risk of stroke, cardiac death, and major bleeding and improved risk stratification beyond the CHA\(_2\)DS\(_2\)-VASc risk score.

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)

NICE guideline CG180
**ABC stroke score**

Another validation study\(^2^3\) (n=8356) found that the ABC-stroke score was well calibrated and consistently performed better than both the CHA\(_2\)DS\(_2\)-VASC and ATRIA stroke scores.

**CHA\(_2\)DS\(_2\)-VASC score**

A systematic review\(^2^4\) (10 studies) assessed the risk of ischemic stroke for patients with AF and CHA\(_2\)DS\(_2\)-VASC score of 0, 1, or 2 not treated with oral anticoagulation. For CHA\(_2\)DS\(_2\)-VASC score of 1, the annual risk of ischemic stroke met the theoretical threshold for using non-vitamin K antagonist oral anticoagulants (NOACs) but was below the threshold for warfarin. It should be noted that there was high heterogeneity between studies and the sample sizes of studies were not reported in the abstract.

A systematic review\(^2^5\) (12 studies n=unreported) compared CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASC, in terms of their predictive risk evaluation, in patients with AF who were and were not taking anticoagulants. Patients with CHA\(_2\)DS\(_2\)-VASC scores greater than 2 had a greater risk of stroke and thromboembolism than patients with CHA\(_2\)DS\(_2\)-VASC scores <2, independent of anticoagulation therapy. The results for CHADS\(_2\) were not reported in the abstract, nor were the sample sizes of included studies.

**Composite risk scores**

A secondary analysis\(^2^6\) of an RCT developed two novel composite risk-prediction scores for stroke, thromboembolism or bleeding. The scores were validated externally (n=441) in a ‘real-world’ cohort of outpatients with AF receiving anticoagulation treatment. Both composite scores 1 and 2 demonstrated numerically higher discriminatory performance than CHADS\(_2\), CHA\(_2\)DS\(_2\)-VASC, and HAS-BLED but these were non-significant. The CHADS\(_2\), CHA\(_2\)DS\(_2\)-VASC, and HAS-BLED scores were considered to have greater practicality and a more personalised balancing of risks.

**SAME-TT2R2 score**

A validation study\(^2^7\) (n=1089) found that in AF patients receiving vitamin K antagonist (VKA) therapy, the SAME- TT2R2 score was able to identify the patients who were less likely to achieve good outcomes of time in therapeutic range, major bleeding events and stroke or transient ischaemic attack.

**Risk following percutaneous coronary intervention (PCI)**

An observational study\(^2^8\) (n=929) assessed whether CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASC and HAS-BLED scores are useful in predicting outcome of AF patients after PCI. A high CHA\(_2\)DS\(_2\)-VASC score was found to be superior in predicting thrombotic outcomes after PCI in a high risk AF population. High modified HAS-BLED score was not predictive of bleeding events.

**QStroke and QBleed**

Topic experts noted two validation studies, which preceded the 4 year surveillance search period but were not covered in the evidence review for CG180. They are therefore included in this summary. The first study\(^2^9\) (n=15,371 derivation cohort, n=7689 validation cohort with AF) developed and validated the QStroke risk algorithm to estimate risk of stroke or transient ischaemic attack in patients without prior stroke or transient ischaemic attack at baseline. It compared QStroke with CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASC scores in patients with AF. QStroke had some improved performance on all measures of discrimination compared with CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASC.

The second study\(^3^0\) (n=39,679 derivation cohort, n=12,560 validation cohort with AF) developed and validated the QBleed algorithm for estimating the absolute risk of upper gastrointestinal and intracranial bleed for patients with and without anticoagulation aged 21-99 years in primary care. The final QBleed algorithms incorporated 21 variables. The algorithms provided were found to be valid in calculating absolute risk of gastrointestinal and intracranial bleed in patients with and without anticoagulation.

For both QStroke and QBleed scores, the authors recommended further research to evaluate the clinical outcomes and cost effectiveness of using these algorithms in primary care.

**Topic expert feedback**

QStroke and QBleed

A topic expert highlighted QStroke and QBleed as stoke and bleeding risk-estimating tools in people with AF. The stated advantages of QStroke and QBleed over CHA\(_2\)DS\(_2\)-VASC and HASBLED were that they give an actual absolute risk of bleed, unlike the risk estimators.
recommended in CG180, and over a longer period than was possible for the AF patient decision aid, which was derived from a Scandinavian cohort for 1 year only. This was considered by the expert to be crucial for patient-centred shared decision-making. In addition, QStroke and QBleed are derived from a UK patient population with a much larger population size than in the validation studies for CHA2DS2-VASc and HASBLED. The cited references are included in the evidence summary.

CHADS2-VASc

Topic expert feedback highlighted a study that found that in an Asian AF cohort, the modified mCHADS2-VASc score performed better than the CHA2DS2-VASc in stroke risk stratification. The study was also retrieved by the surveillance literature search. The results indicated that mCHADS2-VASc would further identify AF patients who may derive a positive net clinical benefit from oral anticoagulation.

A further study found that the age threshold (65 years) used in the CHA2DS2-VASc system for initiating oral anticoagulants might be lower in Taiwanese AF patients than in non-Asians, indicating that a threshold of 50 years may be more appropriate. The study was also retrieved by the surveillance literature search.

However, the populations of both these studies were not fully representative of the UK population, which limits the impact of the results.

CHADS2-VASc risk factor components

Topic experts noted that new information has been published on the degree of risk among patients with a single risk factor. There was stated to be varying importance amongst the individual CHADS2-VASc risk factor components, with age being the most important.

The revised European Society of Cardiology Guideline on AF was also cited for relevance. This was highlighted as particularly interesting in that it was considered to effectively discount female gender when there is only one other risk factor.

If it was thought appropriate to make a similar change to CG180, this would represent a significant simplification and removal of a point which often causes confusion at present. However, topic experts also noted that the updated ESC guidelines still recommend CHADS2-VASc score for estimating stroke risk along with an individualised weighing of risk as well as patient preferences to inform the decision to anticoagulate.

Topic expert feedback stated that there is much more data on high risk associated even with 1 stroke risk factor, and the positive net clinical benefit of oral anticoagulants in these patients. One cited study found that, in a community-based cohort of unselected AF patients with 1 non-gender related stroke risk factor (i.e., CHADS2-VASc 1 in males or 2 in females), OAC use as indicated according to the guidelines was associated with a positive net clinical benefit for the prevention of stroke and thromboembolic events.

The topic expert also advised caution in interpreting some studies that suggest low event rates with CHADS2-VASc score 1, due to what the expert felt was flawed methodology with ‘conditioning on the future’ approach. This approach excludes all patients at baseline for whom oral anticoagulant treatment is initiated during follow-up. It was considered to underestimate event rates. A cohort study cited that compared the differing methodological approaches. It recommended that a censored approach be taken, which allows for inclusion of observation time and thromboembolic events before a treatment initiation decision. The study was not retrieved by the surveillance literature search.

Topic experts noted that various other stroke and bleeding risk stratification tools have been published – however, they have focused on complicated multivariate scores or those adding in biomarkers, leading to loss of practicality and extra cost. Many biomarkers in some proposed risk scores are also predictive of stroke, MI, bleeding and death, which could lead to non-specialists being confused about which endpoint is of concern.

The NICE guideline approach was stated as remaining very simple, easy and practical for the majority of clinicians looking after AF patients, i.e. focus on initial identification of low risk patients, following which stroke prevention (i.e. with oral anticoagulants) can be offered to those with ≥1 stroke risk factors.
Impact statement

The guideline recommends (1.4.1) the use of CHA₂DS₂VASc stroke risk score to assess stroke risk in AF, atrial flutter, or a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm. The collective new evidence and topic expert feedback indicates that other risk scores including Atria, ABC, and QStroke may perform more accurately than CHA₂DS₂VASc and should be considered for inclusion in the guideline. However, new evidence did not support the use of novel composite risk scores in place of CHA₂DS₂VASc.

The review of these tools should take into account the following factors as indicated by new evidence and topic expert feedback:

- The complexity of the tools, including the potential simplification of CHA₂DS₂VASc to focus on a single risk factor, with age being the most important.
- The implementation challenge of changing recommended risk calculators.
- Potential added value of Tropinin T with CHA₂DS₂VASc.
- New evidence supporting the use of the Atria score in enabling reclassification of stroke risk to prevent overuse of anticoagulants in very low stroke risk patients with AF.
- The need for a censored methodology approach be taken, which allows for inclusion of observation time and thromboembolic events before a treatment initiation decision.
- Sample size and setting of the validation studies. In particular, QStroke, was validated in a large UK sample.
- Further validation that may be necessary for certain clinical prediction tools, such as SAMe-TT2R2, to help decision making by clinicians between warfarin and NOACs.
- Appropriate risk assessment for specific sub-groups, such as
  - patients who have undergone PCI. Evidence was consistent with recommendation 1.4.1 to use CHA₂DS₂VASc
  - people of Asian family origin, with new evidence indicating possible differing thresholds depending on family origin, and that a modified version of CHA₂DS₂VASc may be more useful for people from Asian family origin.

New evidence identified that may change current recommendations.

180-08 What is the clinical and cost effectiveness of HAS-BLED compared to other tools in assessing bleeding risk in people with AF?

Subquestion

In people with AF what are the risks of long-term oral anticoagulation administration as thromboprophylaxis?

In patients with AF, what are the risk factors associated with stroke/TIA and thromboembolism?

Bleeding risk

1.4.2 Use the HAS-BLED score to assess the risk of bleeding in people who are starting or have started anticoagulation. Offer modification and monitoring of the following risk factors:

- uncontrolled hypertension
- poor control of international normalised ratio (INR) ('labile INRs')
• concurrent medication, for example concomitant use of aspirin or a non-steroidal anti-inflammatory drug (NSAID)
• harmful alcohol consumption. [new 2014]

1.4.3 When discussing the benefits and risks of anticoagulation, explain to the person that:
• for most people the benefit of anticoagulation outweighs the bleeding risk
• for people with an increased risk of bleeding the benefit of anticoagulation may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important. [new 2014]

1.4.4 Do not withhold anticoagulation solely because the person is at risk of having a fall. [new 2014]

**Surveillance decision**
This question should be updated.

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**4-year surveillance summary**

**ABC bleeding score**
A secondary analysis33 of 2 RCTs validated a new biomarker based risk score, for major bleeding among patients with AF. The ABC-bleeding score, using age, history of bleeding, and three biomarkers (haemoglobin, cTn-hs, and GDF-15 or cystatin C/CKD-EPI) was internally (n=14,537) and externally (n=8468) validated and calibrated in large cohorts of patients with AF receiving anticoagulation therapy. The ABC-bleeding score yielded a higher c-index than HAS-BLED and ORBIT.

**Orbit bleeding score**
A validation study34 (2015) (n=7411) found that the five-element ORBIT bleeding risk score had better ability to predict major bleeding in AF patients when compared with HAS-BLED and ATRIA risk scores. This score and its more complex 12 element version both had similar discrimination, but markedly better calibration when compared with the HAS-BLED and ATRIA scores in an external validation population from the ROCKET-AF trial.

**HAS-BLED versus ATRIA and HEMORR2HAGES**
A systematic review35 (6 studies, n=unreported) found that HAS-BLED had higher sensitivity than both HEMORR2HAGES and ATRIA scores for assessing bleeding risk in AF patients. However, none of the high risk categories of these major bleeding risk scores had high sensitivity.

A systematic review36 (11 studies, n=unreported) compared the diagnostic accuracy between the HAS-BLED score and the HEMORR2 HAGES, ATRIA, CHADS2, or CHA2DS2-VASc scores in anticoagulated patients with AF. The HAS-BLED score performed better than the HEMORR2 HAGES and ATRIA bleeding scores, and was also superior to the CHADS2 and CHA2DS2-VASc stroke scores for bleeding prediction.

A study37 (13,559) compared how well the stroke risk scores CHADS2 and CHA2DS2-VASc scores and 2 haemorrhage risk scores (the ATRIA bleeding score and the HAS-BLED score) predicted major haemorrhage on and off warfarin in adults with AF. The ATRIA bleeding score had the highest predictive ability of all the scores in patients on and off warfarin.

A study38 (n=1157) compared HAS-BLED, ATRIA and HEMORR2HAGES scores in AF patients over 80 years old who were using a vitamin-K antagonist. Results showed a statistically significant association for all models with major bleeding, but discriminatory abilities were poor based on c-statistic, without clear superiority for any of the three scores.

An observational study39 (n=210,299) investigated the value of a recalibration of the HAS-BLED score to account for two points, one point each for stroke and bleeding, from a haemorrhagic stroke. Recalibration of the "S"
component in the HAS-BLED score (counting two points for a haemorrhagic stroke) resulted in an increase in the C-statistics, NRI, and integrated discrimination improvement.

An observational study \(^{25}\) (n=787) investigated the association of bleeding scores with outcomes of AF-associated strokes, defined as symptomatic intracranial haemorrhage (sICH), favourable outcome (modified Rankin Scale [mRS] 0-2) or death. HAS-BLED was found to have an independent predictive value on the occurrence of sICH regardless of the treatment (thrombolysis or conservative therapy). The CHA\(_2\)DS\(_2\)VASc score was inversely related to the favourable outcome.

An observational study \(^{26}\) (n=929) assessed whether CHADS2 and CHA\(_2\)DS\(_2\)VASc and HAS-BLED scores are useful in predicting outcome of AF patients after PCI. A high CHA\(_2\)DS\(_2\)VASc score was found to be superior in predicting thrombotic outcomes after PCI in a high risk AF population. High mHAS-BLED score was not predictive of bleeding events.

**Topic expert feedback**

Topic experts noted that there was considerable debate about the use of the HASBLED score to assess the risk of intervention for stroke prevention during the development of the CG180.

Subsequent clinical education experience has indicated that the recommendation 1.4.2 has not been well implemented and in some areas seems to be obstructing intervention. Topic experts stated uncertainty of how useful HAS-BLED is, referring to recent ESC guidelines on AF, which lists bleeding risk factors that are considered to be far more inclusive than HAS-BLED. Consequently it was felt that HASBLEDs position in the guideline should be reviewed.

However, additional topic expert feedback stated the value of HASBLED, as a simple score for bleeding risk assessment which also focuses on identification of high risk patients for review and follow-up, and which highlights the potentially reversible bleeding risk factors. Some newer bleeding risk scores were considered by the topic expert to perform sub-optimally, compared to HASBLED, in warfarin users – and warfarin still is widely used. Two post-hoc analyses \(^{41,42}\) (n=3551 and (n=3551) were cited. In both studies, HAS-BLED was found to categorise major bleeding events in low-risk and high-risk patients appropriately. The predictive value of ORBIT, ATRIA and HEMORR2HAGES was inferior, but improved when TTR was added.

Topic experts further noted that the ESC guidelines do not express a preference in terms of bleeding risk assessment tools but refer to use of HASBLED, ORBIT or ABC tool and advise that a high bleeding risk score should generally not result in withholding anticoagulation. The ESC guidelines recommend that bleeding risk factors should be identified and treatable factors corrected, which concur with NICE recommendation 1.4.2.

Substantially more validation and application of the SAME-TT2R2 score was recommended by a topic expert, to help decision making by clinicians between warfarin and NOACs. If there is a high score, these patients were considered to be less likely to achieve good TTR so can be reviewed more regularly and INR checks, or an NOAC could be administered. Two references were provided but were ineligible because they did not meet the publication type inclusion criteria for the surveillance review.

**QStroke and QBlead**

A topic expert highlighted QStroke and QBlead as stoke and bleeding risk-estimating tools in people with AF. The stated advantages of QStroke and QBlead over CHA\(_2\)DS\(_2\)VASc and HAS-BLED were that they give an actual absolute risk of bleed, unlike the risk estimators recommended in CG180, and over a longer period than was possible for the AF patient decision aid, derived from a Scandinavian cohort for 1 year only. This was considered by the expert to be crucial for patient-centred shared decision-making. In addition, QStroke and QBlead are derived from a UK patient population with a much larger population size than in the validation studies for CHA\(_2\)DS\(_2\)VASc and HASBLED. The cited studies are summarised in the evidence summary for question 180-07.

**Impact statement**

The guideline advises (1.4.2) using the HAS-BLED score to assess the risk of bleeding in people who are starting or have started anticoagulation, with modification and monitoring for several risk factors.
New evidence and topic expert feedback indicates that HAS-BLED may not be superior to other bleeding risk scores, including Atria, ABC, and QBleed. There is therefore a potential impact on recommendation 1.4.2 to review the different risk scores, taking into account the following factors emerging from the collective evidence and topic expert feedback:

- The complexity of the tools, including the potential recalibration of HAS-BLED counting two points for a hemorrhagic stroke.
- The implementation challenge of changing recommended risk calculators.
- Sample size and setting of the validation studies. In particular, QBleed, was validated in a large UK sample.
- Appropriate risk assessment for specific subgroups, such as patients who have undergone PCI, for whom new evidence indicated that a modified version of HAS-BLED (omitting labile INR and liver function) was not predictive of major bleeding events.
- People over 80 years old, for whom new evidence indicated no superiority of any single risk tool. Models may need to incorporate elderly-specific risk factors for more accurate assessment.
- The predictive value of bleeding risk tools for stroke related outcomes. New evidence indicates that HAS-BLED may have value in predicting symptomatic intracranial haemorrhage in AF related stroke.

New evidence identified that may change current recommendations.

Interventions to prevent stroke

180-09 What is the most clinical and cost-effective antithrombotic therapy for stroke prevention in people with AF?

Subquestion

What is the efficacy of anticoagulation therapy versus placebo for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f) asymptomatic AF?

What is the efficacy of anticoagulation therapy versus antiplatelet therapy for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke?

What is the efficacy of antiplatelet therapy versus placebo for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f) asymptomatic AF?

Recommendations derived from this question

1.5.1 Do not offer stroke prevention therapy to people aged under 65 years with atrial fibrillation and no risk factors other than their sex (that is, very low risk of stroke equating to a CHA2DS2-VASc score of 0 for men or 1 for women). [new 2014].

Anticoagulation

Anticoagulation may be with apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist.

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014) NICE guideline CG180
1.5.2 Consider anticoagulation for men with a CHA2DS2-VASc score of 1. Take the bleeding risk into account. [new 2014]

1.5.3 Offer anticoagulation to people with a CHA2DS2-VASc score of 2 or above, taking bleeding risk into account. [new 2014]

1.5.4 Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences. [new 2014]

Apixaban

1.5.5 Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with 1 or more risk factors such as:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- symptomatic heart failure.

[This recommendation is from Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation (NICE technology appraisal guidance 275).] [2013]

1.5.6 The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of international normalised ratio (INR) control.

[Dabigatran etexilate]

1.5.7 Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:

- previous stroke, transient ischaemic attack or systemic embolism
- left ventricular ejection fraction below 40%
- symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- age 75 years or older
- age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

[This recommendation is from Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (NICE technology appraisal guidance 249).] [2012]

1.5.8 The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran etexilate should be considered in light of their level of international normalised ratio (INR) control.

[Rivaroxaban]

1.5.9 Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:
• congestive heart failure
• hypertension
• age 75 years or older
• diabetes mellitus
• prior stroke or transient ischaemic attack.

[This recommendation is from Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (NICE technology appraisal guidance 256).] [2012]

1.5.10 The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control. [This recommendation is from Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (NICE technology appraisal guidance 256).] [2012]

1.5.15 Do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation. [new 2014]

Review of people with atrial fibrillation

1.5.16 For people who are not taking an anticoagulant, review stroke risk when they reach age 65 or if they develop any of the following at any age:
• diabetes
• heart failure
• peripheral arterial disease
• coronary heart disease
• stroke, transient ischaemic attack or systemic thromboembolism. [new 2014]

1.5.17 For people who are not taking an anticoagulant because of bleeding risk or other factors, review stroke and bleeding risks annually, and ensure that all reviews and decisions are documented. [new 2014]

1.5.18 For people who are taking an anticoagulant, review the need for anticoagulation and the quality of anticoagulation at least annually, or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk. [new 2014]

Surveillance decision

This review question should be updated.

4-year surveillance summary

Perioperative anticoagulation

An RCT\textsuperscript{43} (n=2124) found that among patients with AF undergoing intracoronary stenting, administration of either rivaroxaban 15 mg daily plus P2Y12 inhibitor monotherapy or 2.5 mg rivaroxaban twice daily plus dual antiplatelet therapy (DAPT) reduced risk of all-cause mortality or recurrent hospitalisation for adverse events compared with standard-of-care VKA plus DAPT.

An RCT\textsuperscript{44} (n=1884) found that in patients with AF who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was non-inferior to perioperative bridging with low-molecular-weight heparin for the prevention of stroke.
of arterial thromboembolism and decreased the risk of major bleeding.

**Darexaban**

A phase II dose finding RCT\textsuperscript{45} (n=1297) found that in patients with non-valvular AF, a lower bleeding rate was observed with 120 mg daily darexaban compared with warfarin with a reduction in plasma D-dimer as a marker for haemostasis. It should be noted that limited effectiveness data was presented in the abstract.

**Warfarin versus antiplatelets**

A systematic review\textsuperscript{46} (9 studies, n=unreported) found that compared with antiplatelet drugs, warfarin treatment significantly reduced the risk of stroke, systemic embolism events, ischemic stroke events, stroke-related disability or death events. Warfarin did not increase the incidence of all-cause mortality, intracranial haemorrhage events, or major haemorrhage events.

A systematic review\textsuperscript{47} (3 studies, n=unreported) found that compared to low-intensity anticoagulation, aspirin alone did not reduce the incidence of ischemic stroke or systemic embolism, major bleeding or vascular death. The use of aspirin was associated with a significant increase in all-cause mortality.

A systematic review\textsuperscript{48} (2016) (15 studies, 5 AF, n=2982) found that the use of VKAs was associated with an increased risk of major bleeding when compared to aspirin alone. However, in patients achieving a good time in therapeutic range, the risk of major bleeding was similar.

A systematic review\textsuperscript{49} (8 studies, n=4363) found that warfarin was more effective than aspirin in preventing embolisms in patients with AF, as the risk of bleeding was not increased. There was no significant difference in the overall stroke rate between the groups, or in the rate of haemorrhage/major bleeding.

**Non-vitamin K antagonist oral anticoagulants (NOACs)**

30 systematic reviews\textsuperscript{50-79} were identified evaluating the use of multiple NOACs in patients with AF.

The recommendations in this area have been incorporated into the guideline from the technology appraisals:

TA249: [Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation](#). (March 2012).

TA256: [Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation](#). (May 2012)

Further evidence in this area is covered by the technology appraisal TA355: [Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation](#) (September 2015).

This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

**Apixaban**

A total of 3 systematic reviews\textsuperscript{80-82}, 1 RCT\textsuperscript{83}, 19 secondary analyses of RCTs\textsuperscript{84-102} and 1 cost effectiveness analysis\textsuperscript{103} were identified evaluating the use of apixaban in patients with AF. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA275: [Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation](#) (February 2013). This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

**Dabigatran**

One RCT\textsuperscript{104} 5 secondary analyses of RCTs\textsuperscript{105-109} and 3 systematic reviews\textsuperscript{110-112} were identified evaluating the use of dabigatran in patients with AF. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA249: [Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation](#) (March 2012). This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

**Rivaroxaban**

2 RCTs\textsuperscript{113,114}, 17 secondary analyses of RCTs\textsuperscript{115-131} and 3 systematic reviews\textsuperscript{132-134} were identified evaluating the use of rivaroxaban in patients with AF. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA256: [Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation](#) (May 2012). This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.
**Edoxaban**

Two RCTs\(^{135,136}\), 14 secondary analyses of RCTs\(^{137-150}\), 1 systematic review\(^{151}\) and 1 cost effectiveness study\(^{152}\) were identified evaluating the use of edoxaban in patients with AF. The recommendations in this area are covered by the technology appraisal TA355: *Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation* (September 2015).

This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

**Topic expert feedback**

**Assessment of the respective roles of warfarin and NOACs in anticoagulation**

Topic expert feedback noted a perceived shortcoming of CG180 in not making any comparative assessment of warfarin and NOACs. The reason for this was that the roles of individual NOACs had already been addressed or were being addressed by NICE’s technology appraisals, which precluded any further assessment in CG180. Consequently CG180 only considered ‘generic anticoagulation’ which could have been with either warfarin or NOAC, with no indication of the types of situation where one or other might be preferable. This lack of contextual guidance was highlighted further by the fact that CG180 was published alongside an initiative from the NICE Implementation Collaborative (NIC) to encourage NOAC uptake. The guideline consequently received conflicting feedback for both favouring NOACs over warfarin and for failing to address the greater safety of NOACs.

The NIC statement advises that key groups in whom NOACs should especially be considered include patients who cannot take VKAs, those who cannot be stabilised on VKAs with poor time in therapeutic range (e.g., below 65%) despite adequate adherence, and those taking aspirin for stroke prevention.

As a consequence, there are inevitable inconsistencies in relation to CG180 and the individual STAs in relation to which patients are eligible for which type of anticoagulant. For example, men or women aged 65 to 74 as a single risk factor are eligible for anticoagulation in CG180, but do not fulfil criteria for NOAC eligibility in the individual STAs and hence, if adhering strictly to the recommendations, would only be eligible for warfarin.

The main issue noted by topic experts was that, although CG180 was a significant step forward in simplifying the algorithm for generic anticoagulation, it does nothing to help patients or doctors in choice of anticoagulant. The decision as to whether or not to address this issue was considered to be the most important for any update to CG180.

Topic expert feedback also highlighted the following MHRA safety alerts:

- **New oral anticoagulants apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto): Risk of serious haemorrhage—clarified contraindications apply to all 3 medicines**
- **Dabigatran (Pradaxa): risk of serious haemorrhage**
- **Dabigatran (Pradaxa): contraindicated in patients with prosthetic heart valve(s) requiring anti-coagulant treatment**
- **Reversal of the anticoagulant effect of dabigatran: idarucizumab**
- **Warfarin and head injury**

A Coroner’s report asked NICE to consider whether existing guidance given to patients on warfarin needs to be revised in relation to the need to seek medical attention in the event of a head injury. Expert advice indicated that the guideline should cross refer to the NICE guideline head injury CG176 recommendation 1.4.12:

For patients (adults and children) who have sustained a head injury with no other...
indications for a CT head scan and who are having warfarin treatment, perform a CT head scan within 8 hours of the injury. A provisional written radiology report should be made available within 1 hour of the scan being performed.

**Dual antiplatelet and anticoagulation therapy**

Topic experts noted that the course of action in the context of AF and an indication for dual antiplatelet and anticoagulation therapy is a problem which is frequently encountered in clinical practice. This includes people who have had a myocardial infarction and who also have AF. This issue is only briefly considered in the full version of the guideline, because most of the applicable studies had already been considered in NICE’s guideline on myocardial infarction. However, topic experts stressed that, given the importance of this issue, evidence and specific recommendations on the indication for dual antiplatelet and anticoagulation therapy in patients with AF should be considered in an update to CG180.

**Edoxaban**

Topic expert feedback highlighted that since the publication of NICE guideline CG180, a further NOAC has been released, Edoxaban which, although having a Technical Appraisal from NICE TA355, is not included in the guideline.

Since publication further data has also been published on the effectiveness of the NOACs clearly showing them to have lower incidence of intracerebral bleeds in real population and together with the instability of warfarin should be examined as to where they sit in the pathway.

A topic expert highlighted a potential inequality in the use of antplatelets vs NOACs in very elderly patients, because fewer older adults receive anticoagulation.

**Apixaban**

A topic expert cited a secondary analysis of an RCT relating to apixaban, indicating that this might strengthen the recommendation. The recommendations in this area have been incorporated into the guideline from the technology appraisal TA275: *Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation*. (February 2013). This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

Topic experts noted that new evidence indicates the superiority of non-VKAs in both efficacy and safety and may warrant a full review of cost-analysis in comparison with VKAs.

Direct oral anticoagulants were considered by topic experts to be associated with a lower risk of intracranial haemorrhage and should be recommended over warfarin. A meta-analysis and a secondary analysis of an RCT were cited and are included in the evidence summary. A further cited study was ineligible for inclusion as it did not meet the inclusion criteria for the review question. The recommendations in this area have been incorporated into the guideline from multiple technology appraisals (see evidence summary). This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

**Cost-effectiveness**

Topic experts noted that the costs of the NOACs have been significantly reduced since the cost analysis was under taken for the guideline. The cost of warfarin has climbed with inflation.

Topic expert feedback indicated that the recommended approach of NICE guideline CG180 (also in the 2012 ESC guidelines) has been found to translate to better outcomes if it is adhered to, and modelling analysis also shows healthcare cost benefits. A clinical and economic modelling study was cited which modelled the effect of the increasing use of edoxaban in preference to warfarin in a European AF population. The model predicted a substantial reduction in the human and economic burden of AF up to the year 2050.

**Impact statement**

**Warfarin and head injury**

In the light of safety concerns about the use of warfarin in patients with AF who experience a head injury, expert advice indicated that the guideline should cross refer to the NICE guideline on head injury recommendation 1.4.12:

For patients (adults and children) who have sustained a head injury with no other indications for a CT head scan and who are having warfarin treatment, perform a CT head scan within 8 hours of the injury. A provisional written radiology report should be made available within 1 hour of the scan being performed.
NOACs; Edoxaban
Since the publication of NICE guideline CG180, a further anticoagulant has been released, edoxaban which, although being covered by NICE technology appraisal TA355: Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation (September 2015), is not included in the guideline. The recommendations from the technology appraisal may need to be incorporated into CG180 section 1.5 Interventions to prevent stroke: anticoagulation.

Dual antiplatelet and anticoagulation therapy
Topic expert feedback indicated the need to consider the indication for dual antiplatelet and anticoagulation therapy in patients with AF should be considered in an update to CG180. This includes the subgroup of patients who have had a myocardial infarction. Evidence was not considered for this issue in the surveillance review due to indirectness to the existing review questions, but may need to be considered in an update of CG180. A cross referral to NICE’s guideline on myocardial infarction (recommendations 1.3.22 to 1.3.29) should be considered in the context of AF and an indication for dual antiplatelet therapy and anticoagulation.

Choice of anticoagulants
Topic expert feedback highlighted that the costs of NOACs have been significantly reduced since the cost analysis was undertaken for the guideline. The cost of warfarin has climbed with inflation. However the existing economic model has demonstrated the superior cost effectiveness of NOACs and therefore there is unlikely to be an impact on the health economic modelling undertaken for CG180.

Additionally, topic expert feedback highlighted the need to contextualise the NICE technology appraisals incorporated into CG180 for NOACs, to aid decision making for the choice of anticoagulant, and switching between warfarin and anticoagulants, in specific patient groups. However, the highly diverse range of factors informing the choice of anticoagulant are beyond the scope of the guideline. NICE implementation teams will explore methods and tools to aid treatment choices. Expert feedback indicated that in using the recommendations, clinicians should consider all the possible options, including the advantages and disadvantages of each agent as appropriate to the individual person’s clinical circumstances, needs, values and preferences.

Perioperative anticoagulation
The guideline does not make specific recommendations about perioperative anticoagulation in patients with AF undergoing cardiothoracic surgery.

The new RCT evidence indicates that rivaroxaban in combination with P2Y12 inhibitor or with antiplatelet therapy may reduce the risk of all-cause mortality or recurrent hospitalisation. Despite the large sample size of the trial, further studies and a systematic review of interventions for perioperative anticoagulation may be needed to substantiate the findings of the RCT.

New RCT evidence indicates that in patients with AF who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation may be non-inferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and may decrease the risk of major bleeding. Despite the large sample size of the trial, further studies and a systematic review may be needed to substantiate the findings.

Darexaban
The new RCT evidence indicates that darexaban may achieve a lower bleeding rate in AF patients compared with warfarin with a reduction in plasma D-dimer as a marker for haemostasis. However, the findings may need to be validated by further research, before a clear impact on the guideline can be established. It should also be noted that darexaban is also unlicensed for this indication and its development was terminated in 2011.

Warfarin versus antiplatelets
The new systematic review evidence indicating superiority of warfarin over aspirin in reducing stroke and all-cause mortality is consistent with the evidence reviewed for CG180 and recommendation 1.5.15 which advises against the use of aspirin monotherapy solely for stroke prevention for people with AF.

New evidence identified that may change current recommendations.
Subquestion

In patients receiving anticoagulation therapy, is self-management using near-patient testing devices in primary care as effective as management using hospital lab testing?

When should a cardioverted patient be followed up after cardioversion?

Recommendations derived from this question

Assessing anticoagulation control with vitamin K antagonists

1.5.11 Calculate the person's time in therapeutic range (TTR) at each visit. When calculating TTR:
- use a validated method of measurement such as the Rosendaal method for computer-assisted dosing or proportion of tests in range for manual dosing
- exclude measurements taken during the first 6 weeks of treatment
- calculate TTR over a maintenance period of at least 6 months. [new 2014]

1.5.12 Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:
- 2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months
- 2 INR values less than 1.5 within the past 6 months
- TTR less than 65%. [new 2014]

1.5.13 When reassessing anticoagulation, take into account and if possible address the following factors that may contribute to poor anticoagulation control:
- cognitive function
- adherence to prescribed therapy
- illness
- interacting drug therapy
- lifestyle factors including diet and alcohol consumption. [new 2014]

1.5.14 If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person. [new 2014]

Self-monitoring and self-management of vitamin K antagonists

NICE has developed diagnostics guidance on Self-monitoring coagulation status in people on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease: point-of-care coagulometers (the CoaguChek XS system and the INRatio2 PT/INR monitor).
4-year surveillance summary

A systematic review\(^{153}\) (26 studies, n=8763) investigated the clinical effectiveness and cost-effectiveness of point-of-care coagulometers (CoaguChek system, INRatio2 PT/INR monitor and ProTime Microcoagulation system) for the self-monitoring of coagulation status in people receiving long-term VKA therapy, compared with standard clinic monitoring. Results showed that self-monitoring was significantly better than standard monitoring in preventing thromboembolic events, especially for people with artificial heart valves. Self-monitoring, and in particular self-management, of anticoagulation status appeared cost-effective when pooled estimates of clinical effectiveness were applied. This is consistent with NICE diagnostics guidance 14 Self-monitoring coagulation status in people on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease: point-of-care coagulometers (the CoaguChek XS system and the INRatio2 PT/INR monitor) (September 2014), which found coagulometers to be cost effective for patients receiving vitamin K antagonist therapy. However, the INRatio2 PT/INR monitor has been withdrawn from the market and is not currently available to the NHS.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

New systematic review evidence supports the use of point of care coagulometers for the self-monitoring of coagulation status in people receiving long-term VKA therapy, compared with standard clinic monitoring. This is consistent with NICE diagnostics guidance 14 Self-monitoring coagulation status in people on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease: point-of-care coagulometers (the CoaguChek XS system and the INRatio2 PT/INR monitor) (September 2014). CG180 makes a general cross referral to DG14, and there is unlikely to be any impact.

New evidence is unlikely to change guideline recommendations.

**180-011** What is the clinical and cost effectiveness of left atrial appendage occlusion (LAAO) compared to anti-thrombotic therapy in the prevention of stroke in people with AF?

**Recommendations derived from this question**

**Left atrial appendage occlusion**

1.5.19 Consider left atrial appendage occlusion (LAAO) if anticoagulation is contraindicated or not tolerated and discuss the benefits and risks of LAAO with the person. For more information see [Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism](https://www.nice.org.uk/guidance/dg14) (NICE interventional procedure guidance 349). [new 2014]

1.5.20 Do not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated. [new 2014]

**Surveillance decision**

This review question should be updated.
4-year surveillance summary

Two systematic reviews\textsuperscript{154,155} (17 studies, n=1107 and 7 studies, n=3653) and 2 RCTs\textsuperscript{156,157} (n=51 and n=707) found that in patients with nonvalvular AF, left atrial appendage occlusion (LAAO) was non-inferior to oral anticoagulation without LAAO with comparable efficacy and safety.

Watchman device

A systematic review\textsuperscript{158} (7 studies, n=73,978) evaluated the Watchman LAAO device versus NOACs and warfarin. No difference was seen between the Watchman device and warfarin for efficacy end points; however, the Watchman device had more complications than warfarin. No results data were reported in the abstract for Watchman device versus NOACs.

A systematic review\textsuperscript{159} (3 studies, n=1114) found that LAAO prevented more strokes and reduced mortality in comparison with warfarin among patients with AF. Only one of the studies covered surgical LAAO and this had a small sample size, however. The pooled evidence supporting percutaneous LAAO with the Watchman device was stronger.

A systematic review\textsuperscript{160} of RCTs and observational studies (38 studies n=3585) evaluated the efficacy and safety of transcatheter LAAO in patients with nonvalvular AF, including Watchman and several other devices; Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO), Amplatzer Cardiac Plug device (ACP), non-dedicated Amplatzer occluders (NDAs), Amulet, and WaveCrest. The pooled data demonstrated that transcatheter LAAO was effective and safe in the patients with nonvalvular AF who were not suitable for lifelong antithrombotic therapy. No specific device was shown to be superior to the others, however.

LAAO combined with ablation

An RCT\textsuperscript{161} (n=173) found that in patients with longstanding persistent AF, empirical electrical isolation of the LAA combined with extensive ablation versus extensive ablation alone improved long-term recurrence from atrial arrhythmias without increasing complications.

Topic expert feedback

Cost effectiveness of LAAO

Topic expert feedback indicated that, although CG180 provided for the use of LAAO in situations where other forms of anticoagulation were contraindicated, there was no formal cost efficacy assessment as part of CG180. Over the last few years, provision has been made for a limited number of patients to undergo LAAO through NHS England’s Commissioning through Evaluation scheme. This finished in November 2016 and there is no longer a funding source for this procedure. A clearer identification on guideline review of patients in whom the procedure is thought to be cost effective was considered to be important. No cost effectiveness evidence was cited or retrieved in the literature search, however.

Watchman device

Topic experts noted that further data had been published on the Watchman left atrial appendage occlusion device showing a very impressive safety profile at 3 years which was unavailable to the development group and may change the positioning within the treatment algorithm. No references were cited, however.

Impact statement

New systematic review and RCT evidence indicates that LAAO is non-inferior to oral anticoagulation without LAAO, with comparable efficacy and safety. New evidence and topic expert feedback also indicates that LAAO with the Watchman device is a non-inferior alternative to warfarin for stroke prevention in patients with AF, but cautious use is essential given safety concerns over complications. The comparable efficacy between the Watchman device, NOACs and other LAAO devices was not clearly demonstrated in the new evidence.

CG180 recommends 1.5.19 that LAAO should be considered if anticoagulation is contraindicated or not tolerated, and to discuss the benefits and risks of LAAO with the person. It also advises (1.5.20) against LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated. The new evidence is largely consistent with current recommendations, which also cross refer to NICE interventional procedure guidance 349 Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. This recommends the use of LAAO provided that normal arrangements are in place for clinical governance, consent and audit. However, this guidance may need to be updated with the new evidence supporting the Watchman device, and potentially other devices, as appropriate technologies for the procedure. A comparative review, including cost effectiveness, between the different...
devices may therefore be necessary, and an update of IPG349 should be considered. Further expert feedback highlighted that surgical closure should be considered as an alternative intervention, using a thoracoscopic technique with an Atriclip that is always occlusive.

**LAAO combined with ablation**

New RCT evidence suggests that electrical isolation of the LAA combined with extensive ablation versus extensive ablation alone improved long-term recurrence from atrial arrhythmias without increasing complications in patients with longstanding persistent AF. However, as the evidence came from a single RCT without a large sample size, further studies may be required to substantiate the findings before this could be considered for the guideline.

*New evidence identified that may change current recommendations.*

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**Rate and rhythm control**

<table>
<thead>
<tr>
<th>180-012</th>
<th>What is the clinical and cost effectiveness of rhythm control (excluding ablation) compared to rate control in the treatment of AF in reducing stroke or improving prognosis?</th>
</tr>
</thead>
</table>

**Subquestion**

In which patients with persistent AF does rate control result in improved mortality/morbidity/quality of life over rhythm control?

**Recommendations derived from this question**

*When to offer rate or rhythm control*

1.6.1 Offer rate control as the first-line strategy to people with atrial fibrillation, except in people:

- whose atrial fibrillation has a reversible cause
- who have heart failure thought to be primarily caused by atrial fibrillation
- with new-onset atrial fibrillation
- with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm

for whom a rhythm control strategy would be more suitable based on clinical judgement. [new 2014]

**Surveillance decision**

No new information was identified at any surveillance review.

This review question should not be updated.
Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014) NICE guideline CG180

180-013 What is the clinical and cost effectiveness of using different rate control drug strategies in the pharmacological management of atrial fibrillation?

Subquestion
In patients with permanent AF, what is the efficacy of rate-limiting calcium antagonists compared with digoxin in rate control?
In patients with permanent AF, what is the efficacy of beta-blockers compared with digoxin in rate control?
In patients with permanent AF, what is the efficacy of beta-blockers compared with rate-limiting calcium antagonists in rate control?
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?
In patients with permanent AF, what is the efficacy of beta-blockers in combination with digoxin compared with beta-blocker monotherapy in rate control?
In patients with paroxysmal AF, is amiodarone or sotalol better than beta-blockers in reducing the frequency of paroxysms?

Recommendations derived from this question

1.6.2 Offer either a standard beta blocker (that is, a beta blocker other than sotalol) or a rate limiting calcium channel blocker as initial monotherapy to people with atrial fibrillation who need drug treatment as part of a rate control strategy. Base the choice of drug on the person's symptoms, heart rate, comorbidities and preferences when considering drug treatment. [new 2014]

1.6.3 Consider digoxin monotherapy for people with non-paroxysmal atrial fibrillation only if they are sedentary (do no or very little physical exercise). [new 2014]

1.6.4 If monotherapy does not control symptoms, and if continuing symptoms are thought to be due to poor ventricular rate control, consider combination therapy with any 2 of the following:

- a beta blocker
- diltiazem
- digoxin. [new 2014]

1.6.5 Do not offer amiodarone for long term rate control. [new 2014]

Surveillance decision

This review question should be updated.

4-year surveillance summary

**Landiolol**
A secondary analysis\(^{162}\) (n=200) of an RCT found that landiolol was more useful in controlling rapid heart rate, regardless of patient characteristics, as compared with digoxin in AF patients complicated with LV dysfunction.

**Digoxin**
The NICE Medicines Evidence Commentary Atrial fibrillation and chronic heart failure:

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014) NICE guideline CG180
systematic review suggests digoxin is not associated with increased mortality

found that, based on a large systematic review, the association between digoxin use and increased mortality reported in observational studies was no longer statistically significant when RCTs were added to the analysis. However, for the secondary outcome of hospital admissions, a statistically significant reduction was observed with digoxin in all study types.

Topic expert feedback
Topic expert feedback indicated that there is some debate over the value of beta-blockers in AF patients with heart failure, with regard to prognosis. An individual patient data meta-analysis163 (11 studies, n=18,254) was cited, which found that in patients with concomitant heart failure and AF, beta-blocker therapy did not result in a significant reduction in all-cause mortality versus placebo. The lack of efficacy for the primary outcome was noted in all subgroups of AF, including age, sex, left ventricular ejection fraction, heart rate, and baseline medical therapy.

New evidence and topic expert feedback indicates that in patients with concomitant heart failure and AF, beta-blocker therapy may not reduce all-cause mortality in all patient groups, including AF, and may reduce hospital admission. However, the lack of RCT data available in people who have AF without heart failure is consistent with the limited strength of the recommendations for using digoxin in CG180. Results from further RCTs, which are currently underway in people with AF (RATE-AF) and heart failure (DIGIT-HF), may help to inform the future use of digoxin.

Impact statement
New evidence and topic expert feedback indicates that in patients with concomitant heart failure and AF, beta-blocker therapy may not reduce all-cause mortality. Recommendation 1.6.2 advises that the choice of drug, either a beta blocker or calcium channel blocker, should be based on the person's symptoms, heart rate, comorbidities and preferences when considering drug treatment. The new evidence is broadly consistent with basing the choice on comorbidities, but the recommendation may need to be revised to omit beta blockers as an option for initial monotherapy in patients with comorbid AF and heart failure. The new evidence is stronger than the single trial reviewed by the guideline committee relating to beta-blockers in this sub-population. There is therefore a potential impact on CG180 to amend the recommendation.

Landiolol
New evidence suggests that landiolol may be more effective than digoxin in controlling rapid heart rate in AF. This is consistent with recommendation 1.6.2 which advises a standard beta blocker or a rate-limiting calcium-channel blocker as initial monotherapy to people with AF who need drug treatment as part of a rate control strategy. However, landiolol is not licensed for use in the UK and its UK development status is unknown. The new evidence is therefore unlikely to have any impact.

Digoxin
The NICE Medicines Evidence Commentary Atrial fibrillation and chronic heart failure: systematic review suggests digoxin is not associated with increased mortality covered systematic review evidence which suggests that digoxin may not increase all-cause mortality across all patient groups, including AF, and may reduce hospital admission. However, the lack of RCT data available in people who have AF without heart failure is consistent with the limited strength of the recommendations for using digoxin in CG180. Results from further RCTs, which are currently underway in people with AF (RATE-AF) and heart failure (DIGIT-HF), may help to inform the future use of digoxin.

New evidence identified that may change current recommendations.
Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)
NICE guideline CG180

180-014 What is the most clinical and cost-effective means of (excluding ablation) restoring sinus rhythm (a) pharmacological cardioversion, (b) electrical cardioversion or (c) electrical cardioversion combined with antiarrhythmic drugs?

Subquestion
Does electrical conversion versus pharmacological conversion affect rates of thromboembolism, quality of life, exercise capacity, failure rates?
In patients with persistent AF, is amiodarone better than a) flecainide or b) propafenone for use in cardioversion?
In patients with AF is amiodarone better than sotalol for use in cardioversion?
What is the safety and efficacy of the adjunctive administration of antiarrhythmic drugs for use in electrical cardioversion in comparison to electrical cardioversion without adjunctive antiarrhythmic drugs?
Is a conventional anticoagulation strategy for elective cardioversion as effective as a transoesophageal echocardiogram plus anticoagulation?

Recommendations derived from this question

Rhythm control
1.6.6 Consider pharmacological and/or electrical rhythm control for people with atrial fibrillation whose symptoms continue after heart rate has been controlled or for whom a rate-control strategy has not been successful. [new 2014]

Cardioversion
1.6.7 For people having cardioversion for atrial fibrillation that has persisted for longer than 48 hours, offer electrical (rather than pharmacological) cardioversion. [new 2014]
1.6.8 Consider amiodarone therapy starting 4 weeks before and continuing for up to 12 months after electrical cardioversion to maintain sinus rhythm, and discuss the benefits and risks of amiodarone with the person. [new 2014]
1.6.9 For people with atrial fibrillation of greater than 48 hours' duration, in whom elective cardioversion is indicated:
- both transoesophageal echocardiography (TOE)-guided cardioversion and conventional cardioversion should be considered equally effective
- a TOE-guided cardioversion strategy should be considered:
  - where experienced staff and appropriate facilities are available and
  - where a minimal period of precardioversion anticoagulation is indicated due to the person's choice or bleeding risks. [2006]

Surveillance decision
This review question should not be updated.

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)
NICE guideline CG180
**4-year surveillance summary**

**Vanoxerine**
An RCT\(^\text{164}\) (n=104) found that oral vanoxerine converted AF and atrial flutter to sinus rhythm at a significantly higher rate than placebo, was well tolerated, and caused no ventricular proarrhythmia. Single oral doses of vanoxerine 200, 300, and 400 mg were all more effective than placebo within 24 hours, and the 300 and 400mg doses were more effective within 4 hours.

**Transoesophageal echocardiography (TEE)-guided early direct current cardioversion (DCC)**
An RCT\(^\text{165}\) (n=126) examined whether transoesophageal echocardiography (TEE)-guided early direct current cardioversion (DCC), compared with the conventional approach of DCC after 3 weeks of anticoagulation with dabigatran-etztilat, reduces the recurrence of AF. TEE-guided early DCC in patients with persistent AF for less than 60 days resulted in a significant reduction of AF recurrence, but not for AF lasting longer than 60 days.

An RCT\(^\text{166}\) (n=261) found that in patients undergoing electric cardioversion for persistent AF, magnesium infusion did not increase the rate of successful cardioversion.

**Topic expert feedback**
No topic expert feedback was relevant to this evidence.

**Impact statement**

**Vanoxerine**
New evidence suggests that vanoxerine may be effective in cardioversion of AF and atrial flutter to sinus rhythm, but as the evidence was derived from a single small RCT, it is unlikely to impact on the guideline until further evidence becomes available to substantiate the findings. Vanoxerine is also not licensed in the UK.

**TEE-guided early DCC**
No new evidence was reviewed relating to TEE-guided early DCC for CG180. The original 2006 guideline CG36 stated that the theoretical advantage of early cardioversion being more likely to be successful was not supported by the clinical trial data at that time. However, it was considered that TOE-guided cardioversion should be an available treatment, as some patients would prefer the option of not being on prolonged anticoagulation. The recommendation 1.6.9 was carried over to CG180, to consider offering a TOE-guided cardioversion strategy where a minimal period of pre-cardioversion anticoagulation is indicated due to the person's choice or bleeding risks.

The new RCT evidence suggests that TEE-guided early DCC in patients with persistent AF for less than 60 days may reduce AF recurrence, but not for AF lasting longer than 60 days. This is consistent with recommendation 1.6.9.

**Intravenous Magnesium**
New RCT evidence does not support the use of magnesium infusion in electric cardioversion for persistent AF. This is consistent with CG180 which does not recommend the use of magnesium for this indication.

New evidence is unlikely to change guideline recommendations.
Subquestion
In patients with AF, is flecainide or propafenone better than beta-blockers in maintaining sinus rhythm post cardioversion?
In patients with AF, is amiodarone or sotalol better than beta-blockers in maintaining sinus rhythm post cardioversion?
In patients with AF, is flecainide/propafenone better than amiodarone or sotalol in maintaining sinus rhythm post cardioversion?
In which patients should pill-in-the-pocket therapy be recommended?

Recommendations derived from this question
Drug treatment for long-term rhythm control
1.6.10 Assess the need for drug treatment for long-term rhythm control, taking into account the person's preferences, associated comorbidities, risks of treatment and likelihood of recurrence of atrial fibrillation. [new 2014]
1.6.11 If drug treatment for long-term rhythm control is needed, consider a standard beta-blocker (that is, a beta-blocker other than sotalol) as first-line treatment unless there are contraindications. [new 2014]
1.6.12 If beta-blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account. [new 2014]
1.6.13 Dronedarone is recommended as an option for the maintenance of sinus rhythm after successful cardioversion in people with paroxysmal or persistent atrial fibrillation:
- whose atrial fibrillation is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option and after alternative options have been considered and
- who have at least 1 of the following cardiovascular risk factors:
  - hypertension requiring drugs of at least 2 different classes
  - diabetes mellitus
  - previous transient ischaemic attack, stroke or systemic embolism
  - left atrial diameter of 50 mm or greater or
  - age 70 years or older and
  - who do not have left ventricular systolic dysfunction and
  - who do not have a history of, or current, heart failure.
  [This recommendation is from Dronedarone for the treatment of non-permanent atrial fibrillation (NICE technology appraisal guidance 197).] [2010, amended 2012]
1.6.14 People who do not meet the criteria in recommendation 1.6.13 who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop. [This recommendation is from Dronedarone for the treatment]
Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)

NICE guideline CG180

1.6.15 Consider amiodarone for people with left ventricular impairment or heart failure. [new 2014]

1.6.16 Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with known ischaemic or structural heart disease. [new 2014].

1.6.17 Where people have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a 'no drug treatment' strategy or a 'pill-in-the-pocket' strategy‡ should be considered and discussed with the person. [2006]

1.6.18 In people with paroxysmal atrial fibrillation, a 'pill-in-the-pocket' strategy should be considered for those who:

- have no history of left ventricular dysfunction, or valvular or ischaemic heart disease and
- have a history of infrequent symptomatic episodes of paroxysmal atrial fibrillation and
- have a systolic blood pressure greater than 100 mmHg and a resting heart rate above 70 bpm and are able to understand how to, and when to, take the medication. [2006]

**Surveillance decision**

This review question should not be updated.

**4-year surveillance summary**

**Combination therapy**

An RCT¹⁶⁷ (n=173) found that flecainide-metoprolol combination therapy, versus flecainide only or metoprolol only, improved effectiveness of rhythm control in persistent symptomatic AF. Combination therapy significantly reduced recurrences and improved quality of life at 1-year follow-up.

An RCT¹⁶⁸ (n=134) found that AF burden was significantly reduced by moderate dose ranolazine plus reduced dose dronedarone, with good tolerance and safety. The comparators were ranolazine alone or dronedarone alone.

An updated version of a Cochrane systematic review¹⁶⁹ (59 studies, including 2 new studies, n=21,305), that was considered in CG180, aimed to determine in patients who have recovered sinus rhythm after having AF, the effects of long-term treatment with AADs on death, stroke, embolism, drug adverse effects and recurrence of AF. The comparators were no treatment, placebo, or drugs for rate control. The findings in the updated review were unchanged, with several class IA (disopyramide, quinidine), IC (flecainide, propafenone) and III (amiodarone, dofetilide, dronedarone, sotalol) drugs significantly reduced recurrence of AF. Metoprolol also significantly reduced AF recurrences. However, compared with controls, class IA drugs quinidine, disopyramide and sotalol were associated with increased all-cause mortality. Other antiarrhythmics did not seem to modify mortality.

**Ranolazine**

A systematic review¹⁷⁰ (8 studies, n=unreported) found that ranolazine significantly reduced the incidence of AF compared to the control group in various clinical settings as following cardiac surgery, in acute coronary syndromes, and post electrical cardioversion of AF, compared to unspecified control groups. A higher conversion rate of AF

‡ A 'pill-in-the-pocket' strategy is defined as the person managing paroxysmal atrial fibrillation themselves by taking antiarrhythmic drugs only when an episode of atrial fibrillation starts.

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)

NICE guideline CG180
from the combined use of ranolazine and amiodarone compared to amiodarone alone was also detected, with conversion time significantly shorter in RN plus amiodarone compared to amiodarone group.

An RCT\textsuperscript{171} (n=241) found that no dose of ranolazine significantly prolonged time to AF recurrence among patients with persistent AF (7 days to 6 months), compared to placebo. However, the reduction in overall AF recurrence in the combined 500-mg and 750-mg groups was of borderline significance compared to the placebo group and significant compared to 375-mg group. Ranolazine was reported to be well tolerated with acceptable safety.

\textit{Digoxin}

A total of 5 systematic reviews\textsuperscript{172,173,174,175,176} and 3 secondary analyses or RCTs\textsuperscript{131,177,178} found that digoxin use was associated with a significantly increased risk for all-cause mortality in patients with AF, regardless of concomitant heart failure.

The NICE Medicines Evidence Commentary \textit{Atrial fibrillation and chronic heart failure: systematic review suggests digoxin is not associated with increased mortality} found that, based on a large systematic review, the association between digoxin use and increased mortality reported in observational studies was no longer statistically significant when RCTs were added to the analysis. However, for the secondary outcome of hospital admissions, a statistically significant reduction was observed with digoxin in all study types.

A secondary analysis\textsuperscript{179} (n=614) of an RCT found that digoxin was not associated with cardiovascular morbidity and mortality in patients with permanent AF.

\textit{Digoxin in combination with dronedarone}

A systematic review\textsuperscript{180} and a secondary analysis of an RCT\textsuperscript{177} evaluated evidence on the cardiovascular safety of dronedarone.

The recommendations in this area have been incorporated into the guideline from the technology appraisal TA197: \textit{Dronedarone for the treatment of non-permanent atrial fibrillation} (February 2013). This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

\textbf{Topic expert feedback}

No topic expert feedback was relevant to this evidence.

\textbf{Impact statement}

\textit{Digoxin}

New systematic review and RCT evidence indicates that digoxin may increase all-cause and cardiovascular mortalities in patients with AF, independent of concomitant therapies. However, the NICE Medicines Evidence Commentary \textit{Atrial fibrillation and chronic heart failure: systematic review suggests digoxin is not associated with increased mortality} covered systematic review evidence which suggests that digoxin may not increase all-cause mortality across all patient groups, including AF, and may actually reduce hospital admission. The conflicting evidence is limited by the lack of RCT data available in people who have AF without heart failure, and is consistent with the limited strength of the recommendations for using digoxin in CG180. Digoxin is advised as a ‘consider’ recommendation (1.6.3 and 1.6.4) as monotherapy in specific circumstances and in combination therapy if monotherapy with a beta-blocker or calcium channel blocker does not control symptoms. Results from further RCTs, which are currently underway in people with AF (RATE-AF) and heart failure (DIGIT-HF), may help to inform the future use of digoxin.

\textit{Combination therapies}

New RCT evidence suggests that the following combination therapies may be effective in improving rhythm control in persistent AF:

- Flecainide and metoprolol
- Ranolazine and dronedarone

CG180 does not recommend specific drug combinations for long term rhythm control. Since the new evidence was derived from single small RCTs, no impact on the guideline is anticipated. Ranolazine is also unlicensed for this indication, which further limits its impact.

\textit{AAD monotherapies}

Updated systematic review evidence reinforces the findings that in patients who have recovered sinus rhythm after having AF, the following AADs may reduce recurrence of AF:

- class IA (disopyramide, quinidine),
• class IC (flecainide, propafenone)
• class III (amiodarone, dofetilide, dronedarone, sotalol)

Metoprolol also significantly reduced AF recurrences. However, compared with controls, quinidine, disopyramide and sotalol may be associated with increased all-cause mortality. This is consistent with CG180, which recommends beta-blockers other than sotalol (recommendation 1.6.11), and does not recommend either quinidine or disopyramide. Other AADs were not found to increase mortality, but their possible benefits on other clinically relevant outcomes (stroke, embolism, heart failure) were not clear. The evidence, which informed recommendations 1.6.10-1.6.16 in CG180, remains consistent with CG180 as the updated findings remain unchanged.

**Ranolazine**

New systematic review evidence suggests that ranolazine, as monotherapy and in combination with amiodarone, may reduce the incidence of AF post electrical cardioversion. However, unknown sample sizes of included studies, that cover multiple potentially heterogeneous settings, limit the impact, and further studies may be needed to verify the findings.

New evidence indicates that 500-mg and 750-mg of ranolazine may be the superior dose in patients with persistent AF, although this was derived from a single dose finding study and further studies may be needed to confirm its optimum dose and safety. Therefore, no impact on the guideline is anticipated.

Ranolazine is also unlicensed for this indication, which further limits its impact.

New evidence is unlikely to change guideline recommendations.

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**180-016 What is the clinical and cost effectiveness of catheter ablation compared to non-ablation therapies in people with atrial fibrillation?**

**Recommendations derived from this question**

**Left atrial ablation and a pace and ablate strategy**

**Left atrial ablation**

1.6.19 If drug treatment has failed to control symptoms of atrial fibrillation or is unsuitable:

- offer left atrial catheter ablation to people with paroxysmal atrial fibrillation
- consider left atrial catheter or surgical ablation for people with persistent atrial fibrillation
- discuss the risks and benefits with the person

§ For more information on left atrial catheter ablation see Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation (NICE interventional procedure guidance 427), Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation (NICE interventional procedure guidance 399) and Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation (NICE interventional procedure guidance 294). For more information on left atrial surgical ablation without thoracotomy see Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation (NICE interventional procedure guidance 286).

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)

NICE guideline CG180

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1.6.20 Consider left atrial surgical ablation at the same time as other cardiothoracic surgery for people with symptomatic atrial fibrillation** [new 2014]

**Surveillance decision**
This review question should be updated.

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### 4-year surveillance summary

#### Radiofrequency ablation

NICE has published medical technology innovation briefings on:

- **MIB61** ThermoCool SmartTouch catheter for percutaneous radiofrequency ablation in atrial fibrillation (March 2016)
- **MIB60** TactiCath Quartz catheter for percutaneous radiofrequency ablation in atrial fibrillation (March 2016)

The innovation briefings identified limited RCT and observational study evidence in support of both types of catheters.

A systematic review[^181] (162 studies, n=28,836) found that for the effect of rhythm-control therapies in reducing AF recurrence, strength of evidence was high favouring pulmonary vein isolation versus antiarrhythmic medications in younger patients with paroxysmal AF and mild structural heart disease. Pharmacologic rate- and rhythm-control strategies had comparable efficacy across outcomes in primarily older patients with mild AF symptoms. Results also showed that the surgical maze procedure (including pulmonary vein isolation) done during other cardiac surgery was superior to other cardiac surgery alone. The author recommended future research to address uncertainties related to subgroups of interest and the effect of different therapies on long-term clinical outcomes.

#### Cryoballoon Ablation

An RCT[^182] (n=245) found that cryoballoon based pulmonary vein ablation for early recurrence of AF resulted in long term freedom from AF compared to medical therapy.

#### Pulmonary vein isolation versus single tip Wide area catheter ablation

An RCT[^183] (n=120) found that multielectrode pulmonary vein isolation versus single tip wide area catheter ablation for paroxysmal AF had similar rates of single-procedure acute pulmonary vein isolation without serious adverse events in the first 30 days. Multielectrode-phased radiofrequency ablation had slightly lower long-term arrhythmia freedom, but showed marked and significantly shorter procedure, fluoroscopy, and radiofrequency energy times.

An RCT[^184] (n=188) found that in patients with paroxysmal AF, pulmonary vein catheter ablation was equivalent in efficacy to wide-area circumferential ablation. The primary outcome was freedom from symptomatic or documented AF off medications for 7 days at 12 months post-procedure. Pulmonary vein catheter ablation also reduced procedural and fluoroscopy times, but raised the risk of thrombo-embolic and pulmonary stenosis complications.

#### Left ventricular dysfunction

A systematic review[^185] (26 studies, n=1838) found that catheter ablation of AF in patients with impaired left ventricular systolic function reduced AF recurrence when performed early in the natural history of AF and heart failure. Comparator interventions were not detailed in the abstract, however.

A systematic review[^186] (6 studies, n=324) found that catheter ablation of AF significantly improved left ventricular ejection fraction (LVEF), functional capacity, and quality of life.

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[^181]: For more information on left atrial surgical ablation at the same time as other cardiothoracic surgery see High-intensity focused ultrasound for atrial fibrillation in association with other cardiac surgery (NICE interventional procedure guidance 184), Cryoablation for atrial fibrillation in association with other cardiac surgery (NICE interventional procedure guidance 123), Microwave ablation for atrial fibrillation in association with other cardiac surgery (NICE interventional procedure guidance 122) and Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery (NICE interventional procedure guidance 121).

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014) NICE guideline CG180
compared with rate control in patients with systolic LV dysfunction.

A systematic review\textsuperscript{187} (9 studies, n=unreported) found that compared with antiarrhythmic drugs, management of AF with catheter ablation showed superior efficacy in the short term that was maintained over the longer term, for the primary outcome of no recurrence of AF. For the secondary outcome of major adverse events, there was no significant difference, but a trend towards lower incidence in the pooled catheter ablation group.

A systematic review\textsuperscript{188} (3 studies, n=143) found that catheter ablation resulted in improved LVEF, cardiac function, exercise capacity, and QOL for persistent AF patients with heart failure compared with the medical rate control strategy.

**Complications**

A systematic review\textsuperscript{189} (192 studies, n=83,236) found that catheter ablation of AF had a low incidence of periprocedural complications. The acute complication rate decreased significantly between 2007 and 2012. There were no significant associations among procedure duration, ablation time or ablation strategy, and acute complication rate.

A systematic review\textsuperscript{190} (13 studies, 1097 patients) found that in AF patients undergoing catheter ablation, there were similar rates of ischemic stroke or transient ischemic attack and death compared to those receiving or AAD therapy.

A systematic review\textsuperscript{191} (3 studies, n=491) found that radiofrequency catheter ablation was more effective in reducing AF recurrence than medical therapy as first-line treatment of paroxysmal AF in relatively young and otherwise healthy patients. It did cause more severe adverse effects but the statistical significance of these was not reported in the abstract.

A systematic review\textsuperscript{192} (11 studies, n=1481) found that catheter ablation led to significantly lower recurrence of atrial tachyarrhythmia compared to antiarrhythmic drug therapy in drug naive, resistant, and intolerant patients with AF. However, there was a significantly higher incidence of major adverse events in the CA group when compared with those in the antiarrhythmic drug therapy group. The outcomes measured were recurrence of atrial tachyarrhythmia and the incidence of adverse events.

An RCT\textsuperscript{193} (n=146) found that catheter ablation was superior to medical therapy for the maintenance of sinus rhythm in patients with persistent AF at 12-month follow-up. The primary outcome at 12-month follow-up was defined as any episode of AF or atrial flutter lasting more than 24 hours that occurred after a 3-month blanking period.

A systematic review\textsuperscript{194} (46 studies, n=3819) found that for patients with persistent AF, catheter ablation achieved significantly greater freedom from recurrent AF compared with medical therapy. The most efficacious strategy was combining isolation of the pulmonary veins with limited linear ablation within the left atrium.

**Quality of life (QOL)**

A systematic review\textsuperscript{195} (18 studies) investigated the qualitative and quantitative effects of radiofrequency catheter ablation (RFCA) on the QOL in AF patients. RFCA was associated with a significant increase in both the physical and mental component summary scores of the short form-36. Patients without AF recurrence after RFCA had a better improvement in the PCS and MCS than patients who had AF recurrence.

An RCT\textsuperscript{196} (n=294) found that both AAD and RFA as first-line treatment resulted in substantial improvement of HRQoL and symptom burden in patients with paroxysmal AF. Patients receiving RFCA showed greater improvement in physical scales (SF-36) and the EQ-visual analogue scale.

An RCT\textsuperscript{197} (n=127) found that among patients with paroxysmal AF without previous antiarrhythmic drug treatment, radiofrequency catheter ablation compared with antiarrhythmic drugs resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 years. QOL was moderately impaired at baseline in both groups and improved at the 1 year follow-up. However, improvement was not significantly different among groups.

A post hoc analysis\textsuperscript{198} (n=245) of an RCT found that at 5 years, the occurrence and burden of any AF and symptomatic AF were significantly lower in patients receiving RFCA than those receiving AAD as first-line treatment for paroxysmal AF. Improved QoL scores
observed after 2 years persisted after 5 years without between-group differences.

A secondary analysis\(^{199}\) \((n=294)\) of an RCT found that in the treatment of antarrhythmic therapy naive patients with paroxysmal AF, the long-term efficacy of RFCA was superior to AAD therapy. The primary end points were AF burden in 7-day Holter recordings at 3, 6, 12, 18, and 24 months and cumulative AF burden in all recordings.

A systematic review\(^{200}\) \((11\) studies \(n=1763)\) found that catheter ablation significantly reduced AF recurrence and improved QoL when compared with AAD therapy. However, the incidence rates of all-cause mortality and stroke/TIA were comparable between catheter ablation and AAD therapy.

**Persistent or long-standing AF**

A Cochrane systematic review\(^{201}\) \((3\) RCTs, \(n=261)\) examined the efficacy and safety of ablation (catheter and surgical) in people with persistent or long-standing persistent AF compared to antarrhythmic drugs. Results indicated a superiority of RFCA to antarrhythmic drugs in achieving freedom from atrial arrhythmias, reducing the need for cardioversion, and reducing cardiac-related hospitalisations. There was uncertainty surrounding the effect of RFCA with significant bradycardia (or need for a pacemaker), periprocedural complications, and other safety outcomes.

An RCT\(^{202}\) \((n=210)\) found that catheter ablation of persistent or long-standing persistent AF with the phased radiofrequency ablation system was effective with greater reduction of AF compared with medical management.

An RCT\(^{203}\) \((n=203)\) found that catheter ablation of AF was superior to amiodarone in achieving freedom from AF recurrence at long-term follow-up over 24 months, and reduced unplanned hospitalisation and mortality, in patients with heart failure and persistent AF.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

**Radiofrequency catheter ablation**

The collective new evidence indicates that radiofrequency catheter ablation in particular, and possibly cryoballoon ablation, may be more effective than AAD management in reducing AF in both paroxysmal and persistent AF. The evidence also suggests that the acute complication rate of catheter ablation may have decreased over time and could be comparable to that of medical therapy.

CG180 advises \((1.6.19)\) that left atrial catheter ablation should be offered to people with paroxysmal AF, and considered for people with persistent AF, if drug treatment has failed to control symptoms of AF or is unsuitable. The guideline committee found that left atrial catheter ablation was found to be more clinically effective than medical therapies at improving quality of life in paroxysmal AF and reducing recurrence of AF in paroxysmal and persistent AF patients. It was unclear at the time of guideline development whether there was a difference between left atrial catheter ablation and medical therapies in reducing mortality, stroke, hospitalisation for heart failure and embolic complications in AF patients. However, the new evidence indicates that the incidence rates of all-cause mortality and stroke may be comparable between catheter ablation and AAD therapy, and there is therefore a potential impact on the recommendation, to consider left atrial catheter ablation as first line treatment in paroxysmal AF. Specific technologies are included in the NICE medical technology innovation briefings on:

MIB61 [ThermoCool SmartTouch catheter for percutaneous radiofrequency ablation in atrial fibrillation](March 2016)

MIB60 [TactiCath Quartz catheter for percutaneous radiofrequency ablation in atrial fibrillation](March 2016)

The evidence for both of these interventions is based on small RCTs and observational studies and may require further larger studies to verify their effectiveness.

Topic experts noted that the review should also include a comparison between surgical and catheter ablation, and cryoablation as an alternative to radiofrequency ablation.

Topic expert feedback further highlighted that there is increasing evidence for a staged hybrid approach for people with long standing persistent AF, which is the subject of ongoing trials [CASA AF, CEASE AF](https://www.nice.org.uk/guidance/cga187) and [DEEP](https://www.nice.org.uk/guidance/cga187). These will be monitored by the surveillance team.
New evidence indicates that pulmonary vein catheter ablation may be equivalent to wide-area circumferential ablation in achieving freedom from recurrent AF for up to 12 months, but there remains a degree of uncertainty relating to complications. The evidence is based on small RCTs and is unlikely to impact until further larger studies verify the findings.

**Pulmonary vein isolation versus single tip wide area catheter ablation**

For persistent AF, periprocedural complications and other safety outcomes appear to be more uncertain based on new systematic review evidence, which included a small number of trials of moderate to low quality evidence. More evidence of safety may be required to establish a definite impact on recommendation 1.6.19. The advice to discuss the risks and benefits with the person, and for the approach to be guided by personal preference and the skills and experience available, remains important.

**New evidence identified that may change current recommendations.**

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**180-017 What is the clinical and cost effectiveness of surgical ablation compared to non-ablation therapies in people with AF?**

**Recommendations derived from this question**

*Left atrial ablation and a pace and ablate strategy*

**Left atrial ablation**

1.6.19 If drug treatment has failed to control symptoms of atrial fibrillation or is unsuitable:

- offer left atrial catheter ablation to people with paroxysmal atrial fibrillation
- consider left atrial catheter or surgical ablation for people with persistent atrial fibrillation
- discuss the risks and benefits with the person††[new 2014]

1.6.20 Consider left atrial surgical ablation at the same time as other cardiothoracic surgery for people with symptomatic atrial fibrillation‡‡[new 2014]

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**Surveillance decision**

This review question should not be updated.

†† For more information on left atrial catheter ablation see Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation (NICE interventional procedure guidance 427), Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation (NICE interventional procedure guidance 399) and Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation (NICE interventional procedure guidance 294). For more information on left atrial surgical ablation without thoracotomy see Thorascopic epicardial radiofrequency ablation for atrial fibrillation (NICE interventional procedure guidance 286).

‡‡ For more information on left atrial surgical ablation at the same time as other cardiothoracic surgery see High-intensity focused ultrasound for atrial fibrillation in association with other cardiac surgery (NICE interventional procedure guidance 184), Cryoablation for atrial fibrillation in association with other cardiac surgery (NICE interventional procedure guidance 123), Microwave ablation for atrial fibrillation in association with other cardiac surgery (NICE interventional procedure guidance 122) and Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery (NICE interventional procedure guidance 121).

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)  
NICE guideline CG180
4-year surveillance summary

Persistent or long standing persistent AF

A Cochrane systematic review\(^\text{201}\) (3 RCTs, n=261) examined the efficacy and safety of ablation (catheter and surgical) in people with persistent or long-standing persistent AF compared to antiarrhythmic drugs. None of the 3 included studies covered surgical ablation, however.

Concomitant ablation and surgery

A systematic review\(^\text{204}\) (16 studies, n=unreported) found that concomitant surgical ablation and cardiac surgery was safe and effective at restoring sinus rhythm, compared to no ablative treatment. Higher prevalence of sinus rhythm in the surgical ablation group was evident at post-12 month follow-up. There were no significant differences between surgical ablation versus no ablation in terms of mortality, pacemaker implantations, and neurological events.

A systematic review\(^\text{181}\) (162 studies, n=28,836) found that for the effect of rhythm-control therapies in reducing AF recurrence, strength of evidence was high favouring pulmonary vein isolation versus antiarrhythmic medications in younger patients with paroxysmal AF and mild structural heart disease. Pharmacological rate- and rhythm-control strategies had comparable efficacy across outcomes in primarily older patients with mild AF symptoms. Results also showed that the surgical maze procedure (including pulmonary vein isolation) done during other cardiac surgery was superior to other cardiac surgery alone. The author recommended future research to address uncertainties related to subgroups of interest and the effect of different therapies on long-term clinical outcomes.

An RCT\(^\text{205}\) (n=210) found that radiofrequency ablation concurring with valvular surgery resulted in higher sinus rhythm restoration rate when compared with medical anti-arrhythmic drug therapy in low-medium risk rheumatic heart disease.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Persistent or long standing persistent AF

No new evidence was identified relating to surgical ablation versus AADs and therefore there no impact on the guideline is anticipated.

Concomitant ablation and surgery

The new evidence indicates that concomitant surgical ablation and cardiac surgery is safe and effective at restoring sinus rhythm, compared to no ablative treatment. This is consistent with recommendation 1.6.20 to consider left atrial surgical ablation at the same time as other cardiothoracic surgery for people with symptomatic AF.

New evidence is unlikely to change guideline recommendations.
Recommendations derived from this question

**Left atrial ablation and a pace and ablate strategy**

**Left atrial ablation**

1.6.19 If drug treatment has failed to control symptoms of atrial fibrillation or is unsuitable:

- offer left atrial catheter ablation to people with paroxysmal atrial fibrillation
- consider left atrial catheter or surgical ablation for people with persistent atrial fibrillation
- discuss the risks and benefits with the person[0][new 2014]

1.6.20 Consider left atrial surgical ablation at the same time as other cardiothoracic surgery for people with symptomatic atrial fibrillation[***][new 2014]

**Surveillance decision**

This review question should not be updated.

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**4-year surveillance summary**

**ThermoCool SmartTouch catheter for percutaneous radiofrequency ablation in atrial fibrillation** (March 2016) MIB61

**TactiCath Quartz catheter for percutaneous radiofrequency ablation in atrial fibrillation** (March 2016) MIB60

A systematic review[006] (8 studies, n=unreported) found that freedom from AF/arrhythmias was significantly higher in surgical ablation versus catheter ablation at 12-month off-AAD and on-AAD. This difference was maintained in paroxysmal and persistent AF subgroups. The surgical ablation cohort had a significantly lower requirement for repeat ablations compared with the catheter ablation cohort. However, major complications were significantly higher in the surgical ablation group, driven by pleural effusion and pneumothorax.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

New evidence indicates that surgical ablation may reduce recurrence of AF, with lower requirement for repeat ablations compared with

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[***] For more information on left atrial catheter ablation see [Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation](NICE interventional procedure guidance 427), [Percutaneous endoscopic catheter laser balloon pulmonary vein isolation for atrial fibrillation](NICE interventional procedure guidance 399) and [Percutaneous (non-thoracoscopic) epicardial catheter radiofrequency ablation for atrial fibrillation](NICE interventional procedure guidance 294). For more information on left atrial surgical ablation without thoracotomy see [Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation](NICE interventional procedure guidance 286).

For more information on left atrial surgical ablation at the same time as other cardiothoracic surgery see [High-intensity focused ultrasound for atrial fibrillation in association with other cardiac surgery](NICE interventional procedure guidance 184), [Cryoablation for atrial fibrillation in association with other cardiac surgery](NICE interventional procedure guidance 123), [Microwave ablation for atrial fibrillation in association with other cardiac surgery](NICE interventional procedure guidance 122) and [Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery](NICE interventional procedure guidance 121).

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014) NICE guideline CG180
catheter ablation. However, major complications were more common in the surgical group.

CG180 recommends offering left atrial catheter ablation in preference to surgical ablation in the first line ablation management of patients with paroxysmal AF. The GDG considered that in view of the reasonable success rates for left atrial catheter ablation in the management of paroxysmal AF, the relative lack of data on stand-alone surgical ablation and the more invasive nature of surgical ablation, that it was reasonable to recommend that catheter ablation should be offered in preference to surgical ablation in the first line ablation management of patients with paroxysmal AF.

In the case of patients with persistent AF, as success rates (restoring and maintaining sinus rhythm) for left atrial catheter ablation are lower, the GDG thought it reasonable to consider both surgical and catheter ablation as options. The GDG recommended that the decision regarding which approach is used should be informed by patient preference and the skills and experience available.

The new evidence is consistent with these recommendations, in view of the higher risk of complications identified with surgical ablation, and therefore no impact is anticipated.

New evidence is unlikely to change guideline recommendations.

**180-019**  
**What is the clinical and cost effectiveness of atrioventricular node ablation and pacing compared to usual care in the treatment of AF?**

**Recommendations derived from this question**

**Pace and ablate strategy**

1.6.21 Consider pacing and atrioventricular node ablation for people with permanent atrial fibrillation with symptoms or left ventricular dysfunction thought to be caused by high ventricular rates. [new 2014]

1.6.22 When considering pacing and atrioventricular node ablation, reassess symptoms and the consequent need for ablation after pacing has been carried out and drug treatment further optimised. [new 2014]

1.6.23 Consider left atrial catheter ablation before pacing and atrioventricular node ablation for people with paroxysmal atrial fibrillation or heart failure caused by non-permanent (paroxysmal or persistent) atrial fibrillation. [new 2014]

**Surveillance decision**

No new information was identified at any surveillance review. This review question should not be updated.

**Management for people presenting acutely with atrial fibrillation**

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)  
NICE guideline CG180
What is the clinical and cost effectiveness of using different rate control drug strategies in the pharmacological management of atrial fibrillation?

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

Subquestion

In haemodynamically unstable patients presenting with acute AF, what is the best treatment strategy (ECV, PCV or acute (iv) rate control)?

At the diagnosis of AF does immediate anticoagulation (comparison is absence of immediate Tx or later, delayed Tx) result in reduced rates of morbidity and mortality, without increasing pt anxiety, while still being cost effective?

Recommendations derived from this question

Rate and rhythm control

1.7.1 Carry out emergency electrical cardioversion, without delaying to achieve anticoagulation, in people with life-threatening haemodynamic instability caused by new-onset atrial fibrillation. [new 2014]

1.7.2 In people with atrial fibrillation presenting acutely without life-threatening haemodynamic instability, offer rate or rhythm control if the onset of the arrhythmia is less than 48 hours, and start rate control if it is more than 48 hours or is uncertain. [new 2014]

1.7.3 Consider either pharmacological or electrical cardioversion depending on clinical circumstances and resources in people with new-onset atrial fibrillation who will be treated with a rhythm control strategy. [new 2014]

1.7.4 If pharmacological cardioversion has been agreed on clinical and resource grounds for new-onset atrial fibrillation, offer:

- A choice of flecainide or amiodarone to people with no evidence of structural or ischaemic heart disease or
- amiodarone to people with evidence of structural heart disease. [new 2014]

1.7.5 In people with atrial fibrillation in whom the duration of the arrhythmia is greater than 48 hours or uncertain and considered for long-term rhythm control, delay cardioversion until they have been maintained on therapeutic anticoagulation for a minimum of 3 weeks. During this period offer rate control as appropriate. [2006, amended 2014]

1.7.6 Do not offer magnesium or a calcium-channel blocker for pharmacological cardioversion. [new 2014]

Surveillance decision

This review question should not be updated.

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)
NICE guideline CG180
4-year surveillance summary

The NICE MedTech innovation briefing 7 *The hTEE system for transoesophageal echocardiographic monitoring of haemodynamic instability* (August 2014) found 3 studies on this intervention in patients with haemodynamic instability. However, none reported patient outcome measures.

**Ranolazine in combination with amiodarone**

An RCT207 (n=121) found that the addition of ranolazine to amiodarone was safe and well tolerated, and it demonstrated efficacy superior to amiodarone alone for conversion of recent-onset AF.

**Vernakalant**

Two RCTs208,209 were identified evaluating the use of vernakalant in converting recent-onset AF to sinus rhythm. However, guidance on vernakalant was the subject of a suspended technology appraisal [ID454] *Atrial fibrillation - vernakalant*. This information will be passed onto the TA team for consideration when the topic undergoes the review proposal process.

**Statins following cardioversion**

A systematic review210 Yan (5 studies, n=524) found that statin agents, especially atorvastatin or rosuvastatin, were beneficial in lowering the frequency of AF recurrence after electrical cardioversion, compared to no statin treatment (placebo or conventional medical therapy). The preventative effect was significant for the complete 12 month follow up.

**Topic expert feedback**

Topic experts noted that vernakalant is relevant to the management of acute onset AF but was not considered in CG180 as it was not licensed in the UK at that time and is still not licensed for use in the UK.

**Intravenous magnesium**

Topic expert highlighted the need for evidence assessment on safety and effectiveness to inform a recommendation on intravenous magnesium for treatment of acute AF, based on its apparent routine use in clinical practice. No references were cited.

Impact statement

**hTEE system**

The NICE MedTech innovation briefing 7 *The hTEE system for transoesophageal echocardiographic monitoring of haemodynamic instability* (August 2014) found 3 studies, (1 observational study, 1 case series and 1 case report) on the hTEE system in patients with haemodynamic instability. However, none reported patient outcome measures and evidence on clinical effectiveness is currently lacking. There is unlikely to be any impact on the guideline until further research is conducted to establish its effectiveness.

**Vernakalant**

New evidence was identified and topic expert feedback received relating to vernakalant. However, guidance on vernakalant was the subject of a suspended technology appraisal - [ID454] *Atrial fibrillation - vernakalant*. This information will be passed onto the TA team for consideration if the topic appraisal process resumes. Vernakalant is unlicensed for use in the UK.

**Ranolazine in combination with amiodarone**

New evidence suggests that the addition of ranolazine to amiodarone may be safe and well tolerated, and could be superior to amiodarone alone for conversion of recent-onset AF. However, the evidence is from a single small trial and ranolazine is unlicensed for this indication. Any impact on CG180 is therefore unlikely until further studies validate these findings. Ranolazine is also unlicensed for this indication, which further limits its impact.

**Statins following cardioversion**

New evidence indicates that statin agents, especially atorvastatin or rosuvastatin, are beneficial in lowering the frequency of AF recurrence after electrical cardioversion. However, the evidence is based on small studies and any impact on CG180 is therefore unlikely until further studies validate these findings.

New evidence is unlikely to change guideline recommendations.
Subquestion

At the diagnosis of AF does immediate anticoagulation (comparison is absence of immediate Tx or later, delayed Tx) result in reduced rates of morbidity and mortality, without increasing pt anxiety, while still being cost effective?

Recommendations derived from this question

Anticoagulation

1.7.7 In people with new-onset atrial fibrillation who are receiving no, or subtherapeutic, anticoagulation therapy:

- in the absence of contraindications, offer heparin at initial presentation
- continue heparin until a full assessment has been made and appropriate antithrombotic therapy has been started, based on risk stratification (see section 1.4 Assessment of stroke and bleeding risks and section 1.5 Interventions to prevent stroke). [2006, amended 2014]

1.7.8 In people with a confirmed diagnosis of atrial fibrillation of recent onset (less than 48 hours since onset), offer oral anticoagulation if:

- stable sinus rhythm is not successfully restored within the same 48-hour period following onset of atrial fibrillation or
- there are factors indicating a high risk of atrial fibrillation recurrence††† or
- it is recommended in section 1.4 Assessment of stroke and bleeding risks and section 1.5 Interventions to prevent stroke. [2006, amended 2014]

1.7.9 In people with new-onset atrial fibrillation where there is uncertainty over the precise time since onset, offer oral anticoagulation as for persistent atrial fibrillation (see section section 1.4 Assessment of stroke and bleeding risks and section 1.5 Interventions to prevent stroke). [2006, amended 2014]

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

††† Factors indicating a high risk of atrial fibrillation recurrence include: a history of failed attempts at cardioversion; structural heart disease (mitral valve disease, left ventricular dysfunction or an enlarged left atrium); a prolonged history of atrial fibrillation (more than 12 months); previous recurrences of atrial fibrillation.

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)
NICE guideline CG180
Initial management of stroke and atrial fibrillation

180-023 Initial management of stroke and atrial fibrillation

Recommendations derived from this question

1.8.1 For guidance on the initial management of stroke and atrial fibrillation see recommendation 1.4.3.1 in 'Stroke' (NICE clinical guideline 68). [new 2014].

Surveillance decision

No new information was identified at any surveillance review.
This review question should not be updated.

Prevention and management of postoperative atrial fibrillation

180-024 Is the perioperative administration of antiarrhythmic drugs effective prophylaxis for post-operative AF?

Recommendations derived from this question

1.9.1 In people undergoing cardiothoracic surgery:
- reduce the risk of postoperative atrial fibrillation by offering 1 of the following:
  - amiodarone
  - a standard beta-blocker (that is, a beta-blocker other than sotalol)
  - a rate-limiting calcium antagonist
- do not offer digoxin. [2006, amended 2014]

1.9.2 In people undergoing cardiothoracic surgery on pre-existing beta-blocker therapy, continue this treatment unless contraindications develop (such as postoperative bradycardia or hypotension). [2006, amended 2014]

Surveillance decision

This review question should not be updated.

4-year surveillance summary

Anti-arrhythmics
An RCT\textsuperscript{211} (n=251) compared preoperative administration of amiodarone and metoprolol in preventing postoperative AF (POAF) after coronary artery bypass grafting (CABG). Results indicated that amiodarone and metoprolol had similar effects in prevention of AF after cardiac surgery. No significant difference was observed between the groups in

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)
NICE guideline CG180
terms of intensive care unit and hospital stay. However, the authors recommended larger-scale studies to substantiate the findings.

An RCT\(^{212}\) (n=150) evaluated whether amiodarone hydrogel is superior to corticosteroid hydrogel or placebo, in patients with CABG to prevent POAF. The incidence of POAF was significantly less in the amiodarone hydrogel group than in the control groups, but there was significantly more bradycardia in the amiodarone hydrogel group.

**Beta blockers**

An RCT\(^{213}\) (n=200) found that nebivolol was non-inferior to metoprolol in preventing POAF in cardiac surgery patients.

A systematic review \(^{214}\) (4 studies n=601) evaluated the effect of carvedilol versus metoprolol on the incidence of POAF in patients undergoing CABG. Compared with metoprolol, carvedilol significantly reduced the incidence of POAF.

A systematic review including direct and network meta-analyses\(^{215}\) (6 studies, n=unreported) found that treatment with beta-blockers was associated with a significant reduction in the incidence of POAF compared with placebo/control following CABG. Insufficient evidence was available to show that one beta-blocker treatment was more effective than the others were.

Two systematic reviews\(^{216,217}\) (9 studies, n=807 and 6 studies, n=560) found that perioperative landiolol administration reduced POAF after cardiac surgery, compared to control group (saline administration, no drug administration, or other treatment). Landiolol was reported to be well tolerated, with no significant adverse effects.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

**Anti-arrhythmics**

New evidence indicates that preoperative administration of combination amiodarone and metoprolol may have similar effects in prevention of AF after cardiac surgery. However the evidence is from a single small trial, and any impact on CG180 is unlikely until further studies validate these findings.

New evidence indicates that amiodarone hydrogel is superior to corticosteroid hydrogel in patients with CABG, to prevent POAF. However the evidence is from a single small trial, and any impact on CG180 is unlikely until further studies validate these findings.

**Beta blockers**

New evidence indicates that treatment with beta-blockers reduces the incidence of POAF following CABG and other cardiac surgery. This included new evidence supporting the use of landiolol, but which did not compare its performance to other beta blockers. Insufficient evidence is available to show that one beta-blocker treatment is more effective than the others.

This is consistent with recommendation 1.9.1, which advises reducing the risk of POAF by offering a standard beta blocker as one possible option. This could include any licensed beta blocker with the exception of sotalol. It should be noted that landiolol is not yet licensed for use in the UK.

New evidence is unlikely to change guideline recommendations.
180-025 What is the best treatment strategy (rate or rhythm control or no treatment) for patients with postoperative AF?

Recommendations derived from this question

1.9.3 Unless contraindicated, offer a rhythm-control strategy as the initial management option for the treatment of postoperative atrial fibrillation following cardiothoracic surgery. [2006, amended 2014]

1.9.4 Unless contraindicated, manage postoperative atrial fibrillation following non-cardiothoracic surgery as for new-onset atrial fibrillation with any other precipitant. [2006, amended 2014]

1.9.5 In the prophylaxis and management of postoperative atrial fibrillation, use appropriate antithrombotic therapy and correct identifiable precipitants (such as electrolyte imbalance or hypoxia). [2006, amended 2014]

Surveillance decision

This review question should be updated.

4-year surveillance summary

An RCT\(^2\)\(^1\)\(^8\) (n=2109) found that strategies for rate control versus rhythm control to treat POAF were associated with equal numbers of days of hospitalisation, similar complication rates, and similarly low rates of persistent AF 60 days after onset. Neither treatment strategy showed a net clinical advantage over the other.

An RCT\(^2\)\(^1\)\(^9\) (n=1016) found that combined low dose aspirin and warfarin therapy in patients with POAF following mechanical heart valve replacement significantly decreased thromboembolic events as compared with warfarin therapy alone. This combined treatment was not associated with an increase in the risk of major bleeding or mortality.

Topic expert feedback

Topic experts noted that in the management of POAF rhythm control may have no advantage over rate control and that the guideline recommendation should be changed. An RCT was cited and is included in the evidence summary.

Impact statement

*Treatment of POAF*

New evidence and topic expert feedback indicates that strategies for rate control and rhythm control achieved similar outcomes in treating POAF and that neither treatment strategy showed a net clinical advantage over the other. Rate control for symptomatic/fast ventricular response was advised on clinical grounds, together with appropriate anticoagulation. There is a potential impact on recommendation 1.9.3 to review the advice to offer a rhythm-control strategy as the initial management option for the treatment of POAF following cardiothoracic surgery, unless contraindicated.

New evidence supports combined low dose aspirin and warfarin therapy in patients with POAF following mechanical heart valve replacement. This is consistent with the guideline recommendation (1.9.5) to use appropriate antithrombotic therapy in the management of POAF.

New evidence identified that may change current recommendations.
Areas not currently covered in the guideline

NQ – 01 Other interventions to prevent postoperative atrial fibrillation

This question was not addressed by the guideline.
New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

Surveillance decision
This question should be added.

4-year surveillance summary

Levosimendan
An RCT\textsuperscript{220} (n=100) investigate whether the use of levosimendan versus placebo could reduce the frequency of AF after CABG in patients with poor left ventricle function. The occurrence of AF was significantly lower in the levosimendan group than the placebo group. The duration of AF in the levosimendan group was significantly shorter than that in the control group.

Antioxidants
A systematic review\textsuperscript{221} (23 studies n=4278) sought to determine the impact of antioxidants (N-acetylcysteine [NAC], polyunsaturated fatty acids [PUFAs] and vitamins) on incidence of POAF and duration of length of hospital stay in patients undergoing cardiac surgery. Pooled effects estimates on POAF showed a significant reduction after either NAC, PUFA or vitamin C treatment. Hospital length of stay was not reduced after NAC therapy but decreased with PUFA and vitamin C.

A systematic review\textsuperscript{222} (10 studies n=1026) evaluated whether NAC could prevent POAF after cardiac surgery. Prophylactic NAC reduced the incidence of POAF and all-cause mortality compared with controls, but did not reduce the stay in intensive care unit (ICU) and overall stay in hospital. The authors recommended larger studies to further evaluate the outcomes.

A systematic review\textsuperscript{223} (8 studies, n=2687) found that treatment with PUFA had no effect on the incidence of POAF in patients undergoing cardiac surgery compared to placebo. Subgroup analyses showed the quality of the studies, the ratio of EPA/DHA, accompanied with diabetes might impact the effect of PUFA on POAF.

A systematic review\textsuperscript{224} (11 studies n=3137) found that the use of PUFA alone did not reduce the incidence of POAF compared with the control. However, combination therapy with PUFA and vitamins C and E reduced the incidence of POAF. Subgroup analysis indicated that a 1:2 ratio of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) was effective in preventing POAF.

A systematic review\textsuperscript{225} (9 studies, n=1037) found that cardiac surgery patients who received vitamin C as prophylaxis, had a significantly lower incidence of POAF versus placebo.

An RCT\textsuperscript{226} (n=105) did not find any significant improvement in the incidence or time of occurrence of POAF in CABG patients receiving ascorbic acid. There was also no difference in the other observed postoperative complications. The control group comparison intervention was not reported in the abstract.

An RCT\textsuperscript{227} (n=170) found that vitamin C significantly reduced the incidence of POAF after CABG surgery, compared to placebo. Length of hospital stay was also significantly reduced.

Steroids
A systematic review\textsuperscript{228} (45 studies, n=unreported) examined the protective effects of corticosteroids on clinical outcomes following CABG. Steroid prophylaxis significantly reduced the incidence of POAF and length of hospital stay, but slightly increased the length
of ventilation time. However, no significant impact on the incidence of infection was observed compared with the placebo.

An RCT\textsuperscript{229} (n=340) found that prophylactic short-term use of steroids both intraoperatively and postoperatively proved to be safe and effective in reducing the incidence of POAF in patients undergoing CABG alone or combined with valve surgery. The comparator intervention received by control group was not reported in the abstract. No statistical significant difference in the rate of postoperative complications including mediastinitis as well superficial wound infections was observed between the two groups.

A systematic review\textsuperscript{230} (42 studies n=7621) found that glucocorticoid prophylaxis in cardiac surgery significantly lowered participants’ risk of developing POAF, and reduced length of ICU stay. It did not increase all-cause infection or mortality. The control group comparison was not reported in the abstract, however.

An RCT\textsuperscript{231} (n=4494) found that intraoperative administration of dexamethasone had no protective effect on the occurrence of any or new-onset AF after cardiac surgery, compared to placebo. AF was defined by the occurrence of any reported AF within 30 days after surgery.

**Biatrial pacing**

An RCT\textsuperscript{232} (n = 148) assessed the value of postoperative overdrive biatrial pacing in the prevention of POAF in patients without a history of AF undergoing aortic valve replacement or CABG. Biatrial pacing reduced the late POAF incidence in patients with aortic cross-clamp time longer than 50 minutes.

**Statins**

A Cochrane systematic review\textsuperscript{233} (23 studies n=3292) examined the effectiveness of preoperative statin therapy in patients undergoing cardiac surgery versus no preoperative statin therapy or placebo. However, this review has been withdrawn for updating.

A systematic review\textsuperscript{234} (11 trials, n=1105) found that short-term statin pretreatment reduced the risk of POAF among patients undergoing cardiac surgery, compared to placebo or control medication. The effect was consistent across subgroups.

A systematic review\textsuperscript{235} (18 studies n=9952) found that atorvastatin was associated with a decreased risk of POAF. However, subgroup analyses showed that in the primary prevention subgroup, atorvastatin reduced the risk of new-onset POAF in patients after coronary surgery, but had no beneficial effect in patients without coronary surgery; in the secondary prevention subgroup, atorvastatin had no beneficial effect on AF recurrence in patients with electrical cardioversion. Further research was recommended by the authors.

A systematic review\textsuperscript{236} (20 studies n=4338) found that among the patients who underwent cardiac surgery, perioperative statin therapy was significantly associated with a decreased risk of POAF, particularly in the subgroup of patients who used atorvastatin and those who underwent isolated CABG. Perioperative statin use significantly decreased the length of hospital stay but not ICU stay.

**Magnesium**

An RCT\textsuperscript{237} (n=120) found that magnesium administration via cardioplegic solution during aortic cross-clamping at doses of 80 and 100 mg/kg significantly reduced the occurrence of AF after CABG compared to the dose of 60 mg/kg. There was a lower rate of AF incidence and shorter length of ICU stay in patients receiving 100 mg/kg of magnesium.

An RCT\textsuperscript{238} (n=363) found that high-dose intraoperative magnesium therapy did not decrease the incidence of new-onset POAF after cardiac surgery versus placebo. The total dose was 100mg/kg split into two boluses of 50mg/kg.

**Ranolazine**

A systematic review\textsuperscript{239} (8 studies, n=unreported) found that ranolazine significantly reduced the incidence of AF compared to the control group in various clinical settings as following cardiac surgery, in acute coronary syndromes, and post electrical cardioversion of AF, compared to unspecified control groups. A higher conversion rate of AF from the combined use of ranolazine and amiodarone compared to amiodarone alone was also detected, with conversion time significantly shorter in ranolazine plus amiodarone compared to amiodarone group.

An RCT\textsuperscript{240} (n=102) found that oral ranolazine 375 mg twice daily for 3 days prior to CABG surgery significantly lowered incidence of POAF compared with the control group receiving usual care.

**Adjuvant surgery: pericardiotomy**

A systematic review\textsuperscript{241} (10 studies n=1648) found that posterior pericardiotomy significantly...
improved the prevention of POAF in adult patients after CABG. Sensitivity analyses by methodological quality and surgical technique yields similar results.

Adjuvant surgery: bilateral pulmonary vein radiofrequency ablation
An RCT\textsuperscript{241} (n=175) found that adjuvant intraoperative bilateral pulmonary vein radiofrequency ablation did not decrease the incidence of postoperative AF in patients undergoing CABG, but did increase the mean length of stay in the hospital.

Colchicine
An RCT\textsuperscript{242} (n=360) found that perioperative use of oral colchicine did not reduce POAF compared to placebo in patients undergoing cardiac surgery. It also increased the risk of gastrointestinal adverse effects.

A systematic review\textsuperscript{243} (3 studies n=916) found that perioperative colchicine therapy reduced incidence of POAF within 12 months after cardiac surgery, compared to placebo. Colchicine therapy was associated with increased incidence of gastrointestinal intolerance but not with early treatment discontinuation.

An RCT\textsuperscript{244} (n=360) found that colchicine administered preoperatively to patients undergoing cardiac surgery and continued until hospital discharge did not significantly reduce the incidence of early POAF, compared to no colchicine. Diarrhoea was the most common adverse effect of colchicine leading to its discontinuation in more than half of the patients with this adverse effect.

Carperitide
An RCT\textsuperscript{245} (n=668) found that perioperative carperitide infusion reduced the occurrence of POAF in CABG patients, compared to placebo. Carperitide, the human atrial natriuretic peptide, was administered from the initiation of cardiopulmonary bypass.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Levosimendan
New evidence suggests that levosimendan could reduce the frequency of AF after CABG in patients with poor left ventricle function. However, the evidence is from a single small trial and levosimendan is unlicensed for this indication. Any impact on CG180 is therefore unlikely until further studies validate these findings.

Antioxidants
New systematic review evidence relating to antioxidants in the prevention of POAF in patients undergoing cardiac surgery indicates that:

- NAC may be effective in preventing POAF, but not in reducing length of ICU or hospital length of stay. As the new evidence is based on small studies, any impact on CG180 is unlikely until further larger studies substantiate these findings.

- the evidence relating the PUFA is conflicting, alone or in combination with other antioxidants, and is therefore unlikely to impact on the guideline

- the evidence relating the vitamin C is conflicting, alone or in combination with other antioxidants, and is therefore unlikely to impact on the guideline

CG180 does not make recommendations for the use of antioxidants in the prevention of POAF. Topic experts noted that antioxidants are not used in practice for preventing POAF. As the new evidence is based on small studies and antioxidants are unlicensed for this indication, any impact on CG180 is unlikely until further larger studies substantiate these findings.

Steroids
New evidence relating to the use of steroids indicates that the following may be effective in the prevention of POAF following cardiac surgery:

- methylprednisolone combined with hydrocortisone
- unspecified corticosteroids
- unspecified glucocorticoids

New evidence indicates that dexamethasone is not effective in preventing POAF following cardiac surgery.

Topic expert feedback highlighted that perioperative steroids are not used in practice for POAF due to safety concerns of adverse effects, such as hyperglycaemia, immunosuppression, impaired wound healing, and increased gastrointestinal complications. Due to the risks of adverse effects, and the limited reporting of these in the identified studies, there is unlikely to be any impact on the guideline.
Statins
New systematic review evidence indicates that perioperative statin therapy, particularly atorvastatin, may decrease the risk of POAF in patients undergoing cardiac surgery. The evidence appears to be strongest in patients undergoing isolated CABG. Topic expert feedback noted that statins are used in most patients undergoing cardiac surgery and that their anti-inflammatory effects are considered to be beneficial for preventing POAF and the inflammatory responses to cardiopulmonary bypass. CG180 does not make recommendations on the use of statins, and there is therefore a potential need to include the new question in an update of CG180. Expert feedback also advised a cross referral from CG180 to the NICE clinical guideline 181 Cardiovascular disease: risk assessment and reduction, including lipid modification (July 2014), to assess cardiovascular risk as advised in CG181, prior to discussing with patients the use of statins for the prevention of POAF.

Magnesium
New evidence for the use of magnesium in the prevention of POAF in cardiac surgery was conflicting, and combined with topic expert opinion that magnesium is not considered beneficial in practice, indicates that there is unlikely to be any impact on the guideline.

Ranolazine
New systematic review evidence suggests that ranolazine, as monotherapy and in combination with amiodarone, may reduce the incidence of AF post electrical cardioversion. However, unknown sample sizes of included studies, covering multiple potentially heterogeneous settings, limit the impact, and further studies may be needed to verify the findings. Ranolazine is also unlicensed in the UK for this indication.

Colchicine
New evidence is inconclusive for the effectiveness of colchicine in reducing the frequency of AF after CABG in patients with poor left ventricle function. The evidence does indicate the risk of significant gastrointestinal adverse effects, however. Any impact on CG180 is unlikely until more conclusive evidence is available.

Carperitide
New evidence suggests that perioperative carperitide infusion may reduce the occurrence of POAF in CABG patients. However, the evidence is from a single trial and any impact on CG180 is unlikely until further studies substantiate these findings. Carperitide is also unlicensed for this indication in the UK.

Adjuvant pericardiectomy
New evidence on adjuvant surgery indicates that pericardiectomy may be effective in the prevention of POAF following CABG. However there is unlikely to be an impact on the guideline until further research becomes available to confirm the safety of the procedure.

Adjuvant bilateral pulmonary vein radiofrequency ablation
New evidence does not support the use of bilateral pulmonary vein radiofrequency ablation as adjuvant surgery for the prevention of POAF following CABG, as it does not appear to decrease POAF following CABG.

New evidence identified that may impact on the guideline.
This question was not addressed by the guideline. New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

**Surveillance decision**

This question should be added.

### 4-year surveillance summary

**Antiarrhythmic drugs (AADs) Post ablation for maintaining long term sinus rhythm**

Two systematic reviews [246, 247] (6 studies, n=2667 and 6 studies, n=814) and 3 RCTs [248-250] (n=112, n=212, n=2038) found that the use of AADs following catheter ablation significantly reduced the incidence of early recurrent atrial tachyarrhythmias within 3 months, but did not prevent late recurrence of AF beyond 3 months of ablation, compared to unspecified controlled groups. Two of the RCTs [248, 249] found that periprocedural continuous amiodarone prevented early recurrence of AF.

**Impact statement**

**Antiarrhythmic drugs (AADs) Post ablation**

New evidence indicates that the use of AADs following catheter ablation may reduce the incidence of early recurrent atrial tachyarrhythmias within 3 months, but did not prevent late recurrence of AF beyond 3 months of ablation. CG180 (recommendation 1.6.5) advises against the use of amiodarone for long term rate control but does not make specific recommendations relating to AADs post ablation. There is a potential impact to consider a new recommendation for the short term use of AADs following ablation.

**New evidence identified that may impact on the guideline.**

### Research recommendations

**Prioritised research recommendations**

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE’s research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision will be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014) NICE guideline CG180
• New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  – The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.

• New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  – The research recommendation will be retained because there is evidence of research activity in this area.

• New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  – The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.

• Ongoing research relevant to the research recommendation was found.
  – The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.

• No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  – The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

• The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  – The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

• The new research recommendation was made during a recent update of the guideline.
  – The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
RR – 01 What is the clinical and cost effectiveness of cognitive behavioural therapy (CBT) compared with usual care for people with newly diagnosed atrial fibrillation?

Ongoing research relevant to the research recommendation was found.
The Internet-based Cognitive Behavior Therapy for Atrial Fibrillation pilot study, was expected to complete recruitment in 2017.

**Surveillance decision**
The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.

RR – 02 What is the comparative effectiveness of the 3 main drug classes used for rate control (beta-blockers, calcium-channel blockers and digoxin) in people aged 75 and over with atrial fibrillation in controlling symptoms, improving quality of life and reducing morbidity and mortality?

Ongoing research relevant to the research recommendation was found.
The RATE-AF trial, comparing digoxin with beta-blockers in people aged over 60, is expected to complete final data collection in 2018.

**Surveillance decision**
The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.

RR – 03 What is the effect of case volume on complications and outcomes after left atrial catheter ablation?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

**Surveillance decision**
The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.

RR – 04 Do people with atrial fibrillation whose anticoagulant control is poor, or is predicted to be poor, with warfarin benefit from changing to one of the non-vitamin K antagonists (non-VKA) oral anticoagulants?

New evidence relating to non-VKA antagonists compared to warfarin was identified. However, the recommendations in this area have been incorporated into the guideline from the technology appraisals:

TA275: Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation. (February 2013).
TA249: Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. (March 2012).
TA355: Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation (September 2015).
New evidence was not summarised. The NICE technology appraisals team has been informed about all evidence identified by cumulative surveillance reviews.

**Surveillance decision**

The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.

**RR – 05  Can routine data from UK primary care databases clarify stroke risk in people with atrial fibrillation according to baseline risk factors and treatment?**

New evidence was found on the QStroke risk tool and an update of the review question is planned.

**Surveillance decision**

This research recommendation will be considered again at the next surveillance point unless a new research recommendation is made as part of the update process.
Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)

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References


27. Poli D, Antonucci E, Testa S et al. (2014) A prospective validation of the SAME-TT2R 2 score: how to identify atrial fibrillation patients who will have good anticoagulation control on warfarin. Internal and emergency medicine 9:443-447.


Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)

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Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)


100. Ng KH, Shestakovska O, Connolly SJ et al. (2016) Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial. Age & Ageing 45:77-83.


147. Ruff CT, Giugliano RP, Braunwald E et al. (2016) Cardiovascular Biomarker Score and Clinical Outcomes in Patients With Atrial Fibrillation: A Subanalysis of the ENGAGE AF-TIMI 48 Randomized Clinical Trial. JAMA Cardiology 5:5.


Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)

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Appendix A: summary of evidence from 4-year surveillance of Atrial fibrillation: management (2014)

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