National Institute for Health and Care Excellence

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Atrial fibrillation: diagnosis and management

Evidence review H: Discontinuing anticoagulation in people whose atrial fibrillation has resolved

NICE guideline NG196

Intervention evidence review

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Developed by the National Guideline Centre, Royal College of Physicians

Disclaimer

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1.1 Review question: What is the clinical and cost-effectiveness of discontinuing anticoagulation in people whose atrial fibrillation has resolved?

1.2 Introduction

As part of Atrial Fibrillation (AF) treatment, some people will undergo an ablation or have cardiac surgery. The aim of these procedures is to stop AF and reduce and/or eliminate AF symptoms such as palpitations, dizziness and breathlessness. If the procedure is successful, the result means the AF is deemed resolved. What this means for the person with AF is that they no longer have detectable atrial fibrillation. The AF is classed as resolved when there is no longer have any evidence of any form of atrial fibrillation (usually this is confirmed by ECG or a period of monitoring). For those who had experienced symptoms, after the procedure, AF is seen as resolved if the person reports that they no longer experience any symptoms. This section will examine the clinical and cost effectiveness of discontinuing anticoagulation in people whose atrial fibrillation has resolved. This specifically relates to people who had a clinical reason/ indication for anticoagulation in terms of stroke risk (i.e. CHADVASC score ≥2) and are not low risk of stroke.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People aged over 18, with all of the following: • a previous diagnosis of AF • using OACs, at least until study inception • experiencing current 'resolution' of AF 'Resolution' is that defined by the clinician.
Intervention	Discontinuation of anticoagulants
Comparison	Continuation of anticoagulants at previous dose
Outcomes	Critical • health-related quality of life • mortality • stroke or thromboembolic complications • major bleeding • recurrent atrial fibrillation • Exacerbation of heart failure.
Study design	Randomised controlled trials, SRs of RCTs, and prospective/retrospective cohort studies (with adjustment for stroke risk and risk of bleeding).

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[42] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

A search was initially conducted for randomised trials comparing outcomes between discontinuation and continuation of anticoagulants in people with resolved atrial fibrillation. No randomised trials were identified that matched the protocol for this review. Observational studies in the form of retrospective or prospective cohorts with adjustment for stroke and bleeding risk were therefore considered due to the absence of randomised trials, as pre-specified in the protocol for this review.

One observational study, a retrospective cohort study that compared outcomes between people switching from warfarin to aspirin (discontinuation of anticoagulants) and those continuing warfarin anticoagulation following ablation-induced resolution of atrial fibrillation, was included in the review;[74]thisissummarised in Table 2 below. Stroke and bleeding risk were not adjusted for in this study; however, the stroke and bleeding risks were similar at baseline for the two groups. Evidence from this study is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Uhm 2014[74] Retrospective cohort N=608	Discontinuation of anticoagulants: switching warfarin to aspirin(n=296). At 3 months post-successful ablation, switched from warfarin to 100 mg aspirin. If a recurrence occurred following initiation of this intervention, warfarin was restarted. Continuation of anticoagulants: continuation of warfarin anticoagulation(n=312). At 3 months post-successful ablation, warfarin anticoagulation continued.	People aged 18 years and over with AF resolved by catheter ablation, using warfarin prior to ablation. Does not explicitly state non-valvular AF but no mention of any concomitant valve disease. Predominantly (>75% in each group) paroxysmal AF. AF resolution: If no recurrence of AF at 3 months following ablation, determined by Holter monitoring, ablation successful and included in the study.	Stroke or thromboembolic complications (stroke and transient ischaemic attack) Major bleeding Recurrent atrial fibrillation Mean follow-up duration of 18±12.2 months	Does not specify the dose of warfarin prior to successful resolution by ablation (does not state that it was changed/altered, so have not rated down for indirectness). Mean CHADSVASc score: 1.45±1.34 (discontinuation) and 1.55±1.36 (continuation) Mean HAS-BLED score: 1.37±0.83 (discontinuation) and 1.45±1.02 (continuation) Although mean CHADVASc scores similar between groups, lower proportion in discontinuation group with previous stroke/TIA compared with continuation group (7.1% vs. 14.5%). Time in therapeutic range of INR was 44.2% across the follow-up – low and could contribute to the lack of differences observed between the two groups for outcomes?

See appendix Dfor full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Discontinuation versus continuation of oral anticoagulants in people with AF resolved by ablation

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with continuation of anticoagulants (at previous dose)	Risk difference with Discontinuation of anticoagulants (95% CI)
Stroke	578 (1 study) 18±12.2 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.17 (0.07 to 18.98)	Moderate	
				3 per 1000	1 more per 1000 (from 3 fewer to 51 more)
Transient ischaemic attack	578 (1 study) 18±12.2 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.16 (0.01 to 2.53)	Moderate	
				6 per 1000	10 fewer per 1000 (from 20 fewer to 0 more)[c]
Major bleeding	578 (1 study) 18±12.2 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.17 (0.16 to 8.43)	Moderate	
				6 per 1000	1 more per 1000 (from 5 fewer to 42 more)
Recurrence of atrial fibrillation	608 (1 study) 18±12.2 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.85 (0.54 to 1.35)	Moderate	
				119 per 1000	18 fewer per 1000 (from 55 fewer to 42 more)

[a]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[b]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c]Zero events in one arm (intervention group) so absolute value calculated manually from risk difference

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6.3 Unit costs

Table 4: UK costs of anticoagulants

Drug	Daily dose	Cost – per day	Cost – per year
Apixaban tablet	2.5-5mg twice daily	£1.90	£693.50
Dabigatran capsule	110-150mg twice daily	£1.70	£620.50
Edoxaban tablet	60mg once daily	£1.75	£638.75
Rivaroxaban tablet	20mg once daily	£1.80	£657.00
Warfarin tablet	5mg daily(a)	£0.02	£5.74

Sources: Dosing and unit costs from BNFonline[9], accessed January 2020, with exception of unit cost for warfarin: eMIT[12], accessed January 2020.

(a) Assumed here to be an average daily dose of 5mg. Initially 5–10 mg, to be taken on day 1; subsequent doses dependent on the prothrombin time, reported as INR (international normalised ratio), a lower induction dose can be given over 3–4 weeks in patients who do not require rapid anticoagulation, elderly patients to be given a lower induction dose; maintenance 3–9 mg daily, to be taken at the same time each day.

For warfarin there is also the cost of monitoring. In the previous update of the guideline (CG180), the annual cost of warfarin monitoring (anticoagulation clinic) was reported in the costing template and inflated to 2017/2018 costs (using OECD Purchasing Power Parities):[47]£251a year.[41]

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

All outcomes listed in the protocol for this review, which comprised health-related quality of life, mortality, stroke or thromboembolic complications, major bleeding, recurrent atrial fibrillation and exacerbation of heart failure, were considered by the committee to be critical for decision-making. No additional important outcomes were specified in the protocol.

In this review, no clinical evidence was identified for the following critical outcomes: health-related quality of life, mortality and exacerbation of heart failure.

1.7.1.2 The quality of the evidence

The quality of the evidence for all outcomes included in this review was of very low quality according to GRADE analysis. One of the main reasons for this was the fact that all evidence was obtained from only one study that was observational in design as it was a retrospective cohort study. These study designs have inherent issues with selection bias as assignment to

different intervention groups has not been performed randomly and is likely to be based on one or more patient characteristics, meaning the participants within each group are more likely to differ in terms of their characteristics and prognosis. These differences between the groups may contribute to any differences observed in the effectiveness of the different treatments and lead to inappropriate conclusions being made. The committee considered the risk of bleeding and risk of stroke to be important confounders for this review, and for this reason only observational studies that had adjusted for or were similar at baseline for these two factors were included in this review.

Issues with blinding, incomplete outcome data and outcome reporting bias, which are components of the risk of bias assessment alongside selection bias, were also present for some of the outcomes in this review.

In addition to risk of bias, the presence of imprecision in all of the outcomes included in this review also contributed to the very low quality rating that was obtained.

1.7.1.3 Benefits and harms

The evidence included in this review was obtained from a single retrospective cohort study. There was some evidence based on point estimates for two outcomes (transient ischaemic attack and recurrence of atrial fibrillation) of a clinical benefit of discontinuing warfarin (switching to aspirin) compared to continuing warfarin; however, uncertainty surrounding the point estimates made it difficult to determine a clear benefit of either one of the interventions. The point estimates for the stroke and major bleeding outcomes suggested a slight clinical benefit of continuation of warfarin compared to discontinuation (switching to aspirin), though the absolute values suggested that only 1 more per 1000 would experience each of these events in the discontinuation group compared with the continuation group, which may represent no clinically important difference between the two groups. Substantial uncertainty around the point estimate was also observed for the stroke and major bleeding outcomes, which meant the committee could not be sure of the true effect.

Overall, the committee agreed that the uncertainty in the evidence for all outcomes was too high to come to any firm conclusions based on the evidence presented. The committee agreed that further research is required into the use of anticoagulation following successful resolution of AF following ablation or cardiac surgery, and made research recommendations in this area.

In addition, the committee noted that a paper was identified during the scoping phase which reported on a cohort of patients who were recorded as ‘resolved atrial fibrillation’ on GP registers. These patients had not undergone either ablation or cardiac surgery. The committee noted that paroxysmal atrial fibrillation could easily be missed, and it did not consider that any patient who had not undergone either ablation or cardiac surgery should be considered to have resolved atrial fibrillation. It was noted that the paper actually reported a much higher incidence of stroke or transient ischaemic attack in the resolved atrial fibrillation group compared with the controls without atrial fibrillation. This strongly suggests that atrial fibrillation is continuing in many of those classified as having resolved atrial fibrillation in the study. Based on this, the committee made a consensus-based recommendation that anticoagulation should only be stopped in people with a diagnosis of atrial fibrillation based on a risk assessment that includes the person’s CHA2DS2-VASc and ORBIT scores, even if they now appear to be in sinus rhythm and atrial fibrillation is not detected. This recommendation would also include people where an attempt to resolve their atrial fibrillation has been made, for example by ablation or cardioversion, as there was insufficient evidence available to inform different recommendations.

1.7.2 Cost effectiveness and resource use

No relevant health economic analyses were identified for this review; therefore unit costs were presented to aid committee consideration of cost effectiveness. The unit costs of anticoagulants were presented alongside the cost of monitoring for warfarin. There was insufficient clinical evidence and no health economic evidence to support a recommendation concerning the discontinuation of anticoagulation following successful resolution of atrial fibrillation. The committee were concerned about the potential harms of discontinuing anticoagulants based solely on the absence of AF. As a result they agreed to make a consensus recommendation not to discontinue anticoagulants unless based on a risk assessment that includes the person's CHA2DS2-VASc and ORBIT scores, whether or not their atrial fibrillation is still detectable, as well as consideration of patient preferences. This is considered current practice and so it is anticipated that there will be no impact on NHS resources.

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: Discontinuation of anticoagulants following resolution of AF

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Clinical and cost effectiveness of discontinuing anticoagulation in people whose atrial fibrillation has resolved
2.	Review question	What is the clinical and cost effectiveness of discontinuing anticoagulation in people whose atrial fibrillation has resolved?
3.	Objective	To identify the effects of discontinuation of anticoagulant therapy after resolution of AF (spontaneous or after ablation) in this population
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikos Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Atrial Fibrillation
6.	Population	Inclusion: People aged over 18, with all of the following: • a previous diagnosis of AF • using OACs, at least until study inception • experiencing current ‘resolution’ of AF. ‘Resolution’ is that defined by the clinician Exclusion: Severe valve disease
7.	Intervention/Exposu	Discontinuation of anticoagulants

ID	Field	Content
	re/Test	
8.	Comparator/Reference standard/Confounding factors	Continuation of anticoagulants at previous dose
9.	Types of study to be included	Systematic reviews Randomised controlled trials, SRs of RCTs, and prospective/retrospective cohort studies (with adjustment for stroke risk and risk of bleeding).
10.	Other exclusion criteria	Non-English language studies. AF secondary to Cardiothoracic surgery is excluded from this question - it will be dealt with separately in Q9 because it is a different population that may respond differently. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	health-related quality of life mortality stroke or thromboembolic complications major bleeding recurrent atrial fibrillation Exacerbation of heart failure. Longest follow up point always used
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).

ID	Field	Content
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	Stratification Analyses will be stratified to the following 4 categories of patients: people with resolution of non-post-surgical AF, versus people with resolution of post-surgical AF, versus people with resolution after ablation, versus people with resolution after cardioversion Sub-grouping If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: OAC used (VKA vs DOAC) CHADSVASC score (threshold of >4) Type of AF (persistent AF < 1 year/persistent AF> 1 year/intermittent AF) Existence of HF (yes/No)

ID	Field	Content		
		For stratum 'people with resolution of post-surgical AF' only: cardiac v non-cardiac surgery		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain Mark Perry Nicole Downes		

ID	Field	Content	
		Sophia Kemmis Betty Elizabeth Pearton	
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Atrial Fibrillation, anticoagulants, discontinuation	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated from NICE guideline CG180, the search will be run from October 2013, which was the cut-off date for the searches. For questions being updated from the NICE guideline CG36 and for new questions, the search will be run from 2003.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.[42] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

	Setting: • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The search strategy will be added here after rerun searches have been conducted.

This literature search strategy was used for the following reviews:

- **What is the clinical and cost effectiveness of discontinuing anticoagulation in people whose atrial fibrillation has resolved?**

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[42]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 10 September 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 10 September 2020	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020Issue 9of 12 CENTRAL to 2020Issue 9of 12	None
Epistemonikos (Epistemonikos Foundation)	Inception – 10 September 2020	Systematic review studies

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.

13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	Anticoagulants/
26.	Anticoagulat*.ti,ab.
27.	Warfarin/
28.	Dabigatran/
29.	Rivaroxaban/
30.	(warfarin or apixaban or dabigatran or rivaroxaban or edoxaban).ti,ab.
31.	Coumarins/
32.	(coumarins or coumadin*).ti,ab.
33.	Antithrombins/ or Factor Xa Inhibitors/
34.	(factor xa adj2 (antagonist* or inhibit*)).ti,ab.
35.	xabans.ti,ab.
36.	(vitamin k adj2 antagonist*).ti,ab.
37.	direct antithrombin*.ti,ab.
38.	direct thrombin* inhibit*.ti,ab.
39.	or/25-38
40.	24 and 39
41.	randomized controlled trial.pt.
42.	controlled clinical trial.pt.
43.	randomi#ed.ab.
44.	placebo.ab.
45.	randomly.ab.
46.	clinical trials as topic.sh.
47.	trial.ti.
48.	or/41-47
49.	Meta-Analysis/
50.	Meta-Analysis as Topic/
51.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
52.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
53.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
54.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55.	(search* adj4 literature).ab.
56.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or

	psycinfo or cinahl or science citation index or bids or cancerlit).ab.
57.	cochrane.jw.
58.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
59.	or/49-58
60.	Epidemiologic studies/
61.	Observational study/
62.	exp Cohort studies/
63.	(cohort adj (study or studies or analys* or data)).ti,ab.
64.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
65.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
66.	Controlled Before-After Studies/
67.	Historically Controlled Study/
68.	Interrupted Time Series Analysis/
69.	(before adj2 after adj2 (study or studies or data)).ti,ab.
70.	exp case control study/
71.	case control*.ti,ab.
72.	Cross-sectional studies/
73.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
74.	or/63-76
75.	40 and (48 or 59 or 74)

Embase (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language

23.	*Anticoagulant agent/
24.	Anticoagulat*.ti,ab.
25.	*Warfarin/
26.	*Apixaban/
27.	*Dabigatran/
28.	*Rivaroxaban/
29.	*Edoxaban/
30.	(warfarin or apixaban or dabigatran or rivaroxaban or edoxaban).ti,ab.
31.	*Coumarin derivative/
32.	(coumarins or coumadin*).ti,ab.
33.	*Antithrombin/ or *Blood clotting factor 10a inhibitor/
34.	(factor xa adj2 (antagonist* or inhibit*)).ti,ab.
35.	xabans.ti,ab.
36.	(vitamin k adj2 antagonist*).ti,ab.
37.	direct antithrombin*.ti,ab.
38.	direct thrombin* inhibit*.ti,ab.
39.	or/23-38
40.	22 and 39
41.	random*.ti,ab.
42.	factorial*.ti,ab.
43.	(crossover* or cross over*).ti,ab.
44.	((doubl* or singl*) adj blind*).ti,ab.
45.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
46.	crossover procedure/
47.	single blind procedure/
48.	randomized controlled trial/
49.	double blind procedure/
50.	or/41-49
51.	systematic review/
52.	Meta-Analysis/
53.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
54.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
55.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
56.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
57.	(search* adj4 literature).ab.
58.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
59.	cochrane.jw.
60.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
61.	or/51-60
62.	Clinical study/
63.	Observational study/
64.	family study/
65.	longitudinal study/

66.	retrospective study/
67.	prospective study/
68.	cohort analysis/
69.	follow-up/
70.	cohort*.ti,ab.
71.	69 and 70
72.	(cohort adj (study or studies or analys* or data)).ti,ab.
73.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
74.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
75.	(before adj2 after adj2 (study or studies or data)).ti,ab.
76.	exp case control study/
77.	case control*.ti,ab.
78.	cross-sectional study/
79.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
80.	or/65-71,74-82
81.	40 and (50 or 61 or 80)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Atrial Fibrillation] explode all trees
#2.	((atrial or atria or atrium or auricular) near/3 fibrillat*):ti,ab
#3.	AF:ti,ab
#4.	#1 or #2 or #3
#5.	MeSH descriptor: [Anticoagulants] this term only
#6.	Anticoagulant*:ti,ab
#7.	MeSH descriptor: [Warfarin] this term only
#8.	MeSH descriptor: [Dabigatran] this term only
#9.	MeSH descriptor: [Rivaroxaban] this term only
#10.	(warfarin or apixaban or dabigatran or rivaroxaban or edoxaban):ti,ab
#11.	MeSH descriptor: [Coumarins] this term only
#12.	(coumarins or coumadin*):ti,ab
#13.	MeSH descriptor: [Antithrombins] this term only
#14.	MeSH descriptor: [Factor Xa Inhibitors] this term only
#15.	(factor xa near/2 (antagonist* or inhibit*)):ti,ab
#16.	xabans:ti,ab
#17.	(vitamin k near/ antagonist*)ti,ab
#18.	direct antithrombin*:ti,ab
#19.	direct thrombin* inhibit*:ti,ab
#20.	(or #5-#19)
#21.	#4 and #20

Epistemonikos search terms

1.	(title:(atrial fibrillation OR "AF") OR abstract:(atrial fibrillation OR "AF")) OR (title:(atria fibrillat* OR atrium fibrillat* OR auricular fibrillat*) OR abstract:(atria fibrillat* OR atrium fibrillat* OR auricular fibrillat*))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the Atrial Fibrillation population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA- this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run on Medline and Embase.

Table 8: Database date parameters and filters used

Database	Datessearched	Search filter used
Medline	2003– 10 September 2020	Exclusions Health economics studies
Embase	2003– 10 September 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	NHSEED - 2003 to March 2015 HTA - 2003to 31 March2018	None

Medline (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/

29.	exp Economics, medical/
30.	Economics, nursing/
31.	economics, pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41

Embase (Ovid) search terms

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/

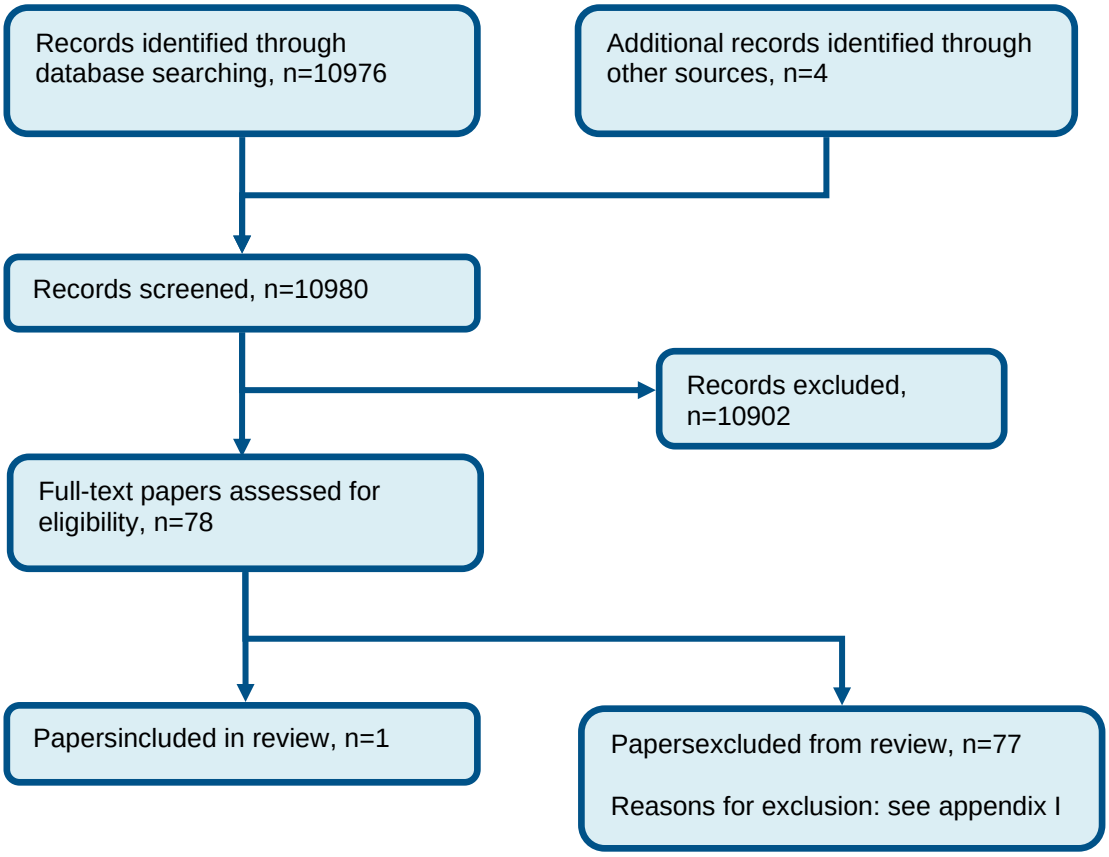
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic*or pharmaco?economic*).ti.
32.	(price*or pricing*).ti,ab.
33.	(cost*adj2 (effectiv*or utilit*or benefit*or minimi*or unit*or estimat*or variable*)).ab.
34.	(financ*or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES
#2.	(((atrial or atria or atrium or auricular) adj3 fibrillat*))
#3.	(AF)
#4.	(#1 or #2 or #3)

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of discontinuation of anticoagulants following resolution of AF



Appendix D: Clinical evidence tables

Study	Uhm 2014[74]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=608)
Countries and setting	Conducted in South Korea; Setting: Outpatient basis
Line of therapy	Unclear
Duration of study	Follow up (post intervention): Mean follow-up post-successful ablation, 18 months.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Holter monitoring - electrocardiography. Presence of a left atrial thrombus was excluded by transesophageal echocardiography.
Stratum	people with resolution of AF after ablation:
Subgroup analysis within study	Post-hoc subgroup analysis: Gives results separately for those with a CHA2DS2VASc score ≥ 2. Not extracted in this way as not specified as a stratum within our protocol.
Inclusion criteria	Patients that underwent catheter ablation for AF with success at 3 months post-ablation based on Holter monitoring (defined as no recurrence of AF at 3 months post-ablation based on absence of AF/atrial tachycardia episodes ≥30 sec in duration); resistance to or intolerance of antiarrhythmic drugs.
Exclusion criteria	Permanent AF refractory to electrical cardioversion; left atrium size >55 mm as measured by echocardiogram; critical coronary artery stenosis (>75% of luminal diameter); severe rheumatic mitral valvular disease; prior radiofrequency catheter ablation of AF
Recruitment/selection of patients	All those underwent successful AF ablation between March 2009 and December 2011 at two centres and that matched inclusion criteria.
Age, gender and ethnicity	Age - Mean (SD): Aspirin, 56.9 (11.7) years; warfarin, 57.6 (10.1) years. Gender (M:F): Aspirin, 230/66; warfarin, 238/74. Ethnicity: Not reported.
Further population details	1. CHADSVASC score: <4 (Mean CHADSVASC score in both groups below 4 (aspirin, 1.45±1.34; warfarin, 1.55±1.36)). 2. Existence of Heart Failure: No HF (or LVEF >=35%) (Heart failure in 4.1% and 2.6% of aspirin and warfarin groups, respectively. Mean ejection fraction in both groups >35% (aspirin, 63.1±8.7; warfarin, 61.8±8.6%).). 3. Type of AF: paroxysmal (Paroxysmal in over 75% of each group (aspirin, 75.7%; warfarin, 75.3%). Persistent in some others but full details not given.).
Extra comments	Predominantly paroxysmal AF (>75% in each group). CHADVASC scores (aspirin, 1.45±1.34; warfarin, 1.55±1.36) and

	HAS-BLED scores (aspirin, 1.37±0.83; warfarin, 1.45±1.02) similar between the groups at baseline. Prior aspirin use (aspirin, 21.3%; warfarin, 26.6%). Comorbidities: hypertension (aspirin, 53.4%; warfarin, 53.2%); diabetes (aspirin, 13.9%; warfarin, 16.0%); previous stroke/TIA (aspirin, 7.1%; warfarin, 14.5%); chronic kidney disease (aspirin, 1.0%; warfarin, 1.3%).
Indirectness of population	No indirectness: Appears to be non-valvular AF, although this is not explicitly stated. No mentions of any concomitant valve disease and mentions non-valvular AF in discussion section.
Interventions	(n=296) Intervention 1: Discontinuation of anticoagulants. Switching warfarin to aspirin. Once no recurrence of AF at 3 months had been confirmed by Holter monitoring (successful ablation), warfarin was switched to 100 mg aspirin. Warfarin restarted according to CHADVASC score if recurrence of AF occurred after the three months post-ablation time-point. Duration Unclear. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: By switching to aspirin, they are discontinuing anticoagulants, just replacing with antiplatelet. Further details: 1. OAC type: VKA (Warfarin for all patients.). (n=312) Intervention 2: Continuation of anticoagulants - Continuation of anticoagulants (at previous dose). Warfarin anticoagulation continued after no recurrence of AF at 3 months had been confirmed by Holter monitoring (successful ablation). No details of the dose given so cannot be sure whether same dose employed as when in AF, but does not state that anticoagulation dose was reduced. Duration Unclear. Concurrent medication/care: Not reported. Indirectness: No indirectness; Indirectness comment: Does not explicitly state dose was the same as before resolution, but does not state that it was reduced or altered. Further details: 1. OAC type: Not applicable
Funding	Academic or government funding (Grants from Korea Health 21 R&D Project, Ministry of Health and Welfare, and Basic Science Research Program of the National Research Foundation of Korea under the Ministry of Education, Science and Technology of the Republic of Korea)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DISCONTINUATION OF ANTICOAGULANTS (SWITCH TO ASPIRIN) versus CONTINUATION OF ANTICOAGULANTS (AT PREVIOUS DOSE)

Protocol outcome 1: Stroke or thromboembolic complications at longest follow up
- Actual outcome for people with resolution of AF after ablation: Transient ischaemic attack at During 18±12.2 months follow-up; Group 1: 0/266, Group 2: 2/312; Comments: TIA was defined as a transient episode of neurologic dysfunction confirmed by a neurologist without brain lesion in imaging studies, with spontaneous symptomatic recovery within 24 hours. In those with events, all were in sinus rhythm at the time of event.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Selection bias not included when generating all-domain risk as already accounted for in GRADE.; Indirectness of outcome: No indirectness; Baseline details: Comparable for age, gender, paroxysmal AF, CHADVASC and HASBLED scores, LA diameter, ejection fraction, prior aspirin use,

hypertension, chronic kidney disease. Difs. for proportion with previous stroke/TIA (7.1% vs. 14.5%) and proportion with concomitant heart failure (4.1% vs. 2.6%); Key confounders: Stroke risk, bleeding risk; Blinding details: Double the proportion with a previous stroke/TIA in warfarin group compared with aspirin group - may have been monitored more closely/treated different if caregivers aware.; Group 1 Number missing: 30, Reason: Warfarin restarted if recurrence of AF occurred. Unclear how many of these suffered stroke before AF recurrence and therefore the type of analysis authors used unclear. Authors reported events with no. originally in each group as denominator, not altered for switching. Reported that none of those with AF recurrence experienced stroke, TIA or major bleeding - adjusted denominator for this group appropriately.; Group 2 Number missing: 0
- Actual outcome for people with resolution of AF after ablation: Stroke at During 18±12.2 months follow-up; Group 1: 1/266, Group 2: 1/312; Comments: Stroke was defined as symptomatic ischemic cerebral infarction with apparent brain lesion in imaging studies.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Selection bias not included when generating all-domain risk as already accounted for in GRADE.; Indirectness of outcome: No indirectness; Baseline details: Comparable for age, gender, paroxysmal AF, CHADVASC and HASBLED scores, LA diameter, ejection fraction, prior aspirin use, hypertension, chronic kidney disease. Difs. for proportion with previous stroke/TIA (7.1% vs. 14.5%) and proportion with concomitant heart failure (4.1% vs. 2.6%); Key confounders: Stroke risk, bleeding risk; Blinding details: Double the proportion with a previous stroke/TIA in warfarin group compared with aspirin group - may have been monitored more closely/treated different if caregivers aware.; Group 1 Number missing: 30, Reason: Warfarin restarted if recurrence of AF occurred. Unclear how many of these suffered stroke before AF recurrence and therefore the type of analysis authors used unclear. Authors reported events with no. originally in each group as denominator, not altered for switching. Reported that none of those with AF recurrence experienced stroke, TIA or major bleeding - adjusted denominator for this group appropriately.; Group 2 Number missing: 0

Protocol outcome 2: Major bleeding at longest follow up
- Actual outcome for people with resolution of AF after ablation: Major bleeding at During 18±12.2 months follow-up; Group 1: 2/266, Group 2: 2/312; Comments: Major bleeding events defined as any type of haemorrhage requiring blood transfusion or intervention, and bleeding with reduction of hemoglobin levels by ≥4.0 g/dL. Events in the study included n=1 for each of pseudoaneurysm rupture and epistaxis (aspirin group) and n=1 for each of intramuscular haematoma and gingival bleeding (warfarin group). In those with events, all were in sinus rhythm at time of event.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Selection bias not included when generating all-domain risk as already accounted for in GRADE.; Indirectness of outcome: No indirectness; Baseline details: Comparable for age, gender, paroxysmal AF, CHADVASC and HASBLED scores, LA diameter, ejection fraction, prior aspirin use, hypertension, chronic kidney disease. Difs. for proportion with previous stroke/TIA (7.1% vs. 14.5%) and proportion with concomitant heart failure (4.1% vs. 2.6%); Key confounders: Stroke risk, bleeding risk; Blinding details: Double the proportion with a previous stroke/TIA in warfarin group compared with aspirin group - may have been monitored more closely/treated different if caregivers aware.; Group 1 Number missing: 30, Reason: Warfarin restarted if recurrence of AF occurred. Unclear how many of these suffered stroke before AF recurrence and therefore the type of analysis authors used unclear. Authors reported events with no. originally in each group as denominator, not altered for switching. Reported that none of those with AF recurrence experienced stroke, TIA or major bleeding - adjusted denominator for this group appropriately.; Group 2 Number missing: 0

Protocol outcome 3: recurrent atrial fibrillation at longest follow up
- Actual outcome for people with resolution of AF after ablation: Recurrence of AF after 3 months post-ablation. at During 18±12.2 months follow-up; Group 1: 30/296, Group 2: 37/312; Comments: Recurrence defined as any episode of AF or atrial tachycardia of at least 30 sec in duration as determined by Holter monitoring. Note

following recurrence patients were restarted or maintained on warfarin. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Selection bias not included when generating all-domain risk as already accounted for in GRADE.; Indirectness of outcome: No indirectness; Baseline details: Comparable for age, gender, paroxysmal AF, CHADVASC and HASBLED scores, LA diameter, ejection fraction, prior aspirin use, hypertension, chronic kidney disease. Difs. for proportion with previous stroke/TIA (7.1% vs. 14.5%) and proportion with concomitant heart failure (4.1% vs. 2.6%); Key confounders: Stroke risk, bleeding risk; Blinding details: Double the proportion with a previous stroke/TIA in warfarin group compared with aspirin group - may have been monitored more closely/treated different if caregivers aware.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at longest follow up; Quality of life at longest follow up; Exacerbation of heart failure at longest follow up

Appendix E: Forest plots

E.1 Resolution after ablation stratum

E.1.1 Discontinuation versus continuation of oral anticoagulants in people with AF resolved by ablation

Figure 2: Stroke(mean follow-up 18±12.2 months)

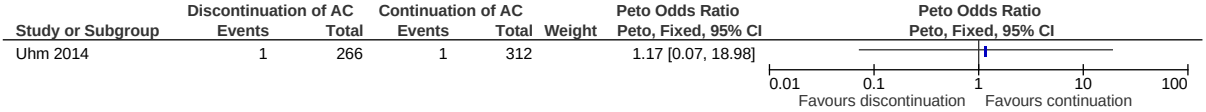


Figure 3: Transient ischaemic attack(mean follow-up 18±12.2 months)

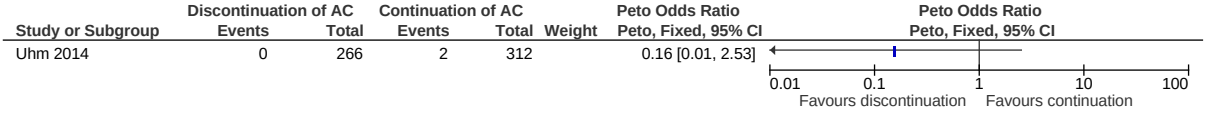


Figure 4: Major bleeding(mean follow-up 18±12.2 months)

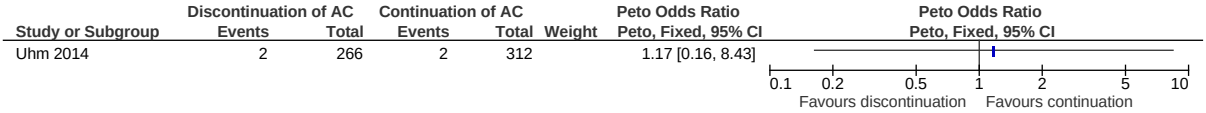
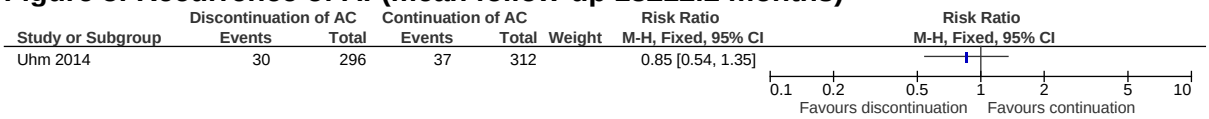


Figure 5: Recurrence of AF(mean follow-up 18±12.2 months)



Appendix F:GRADE tables

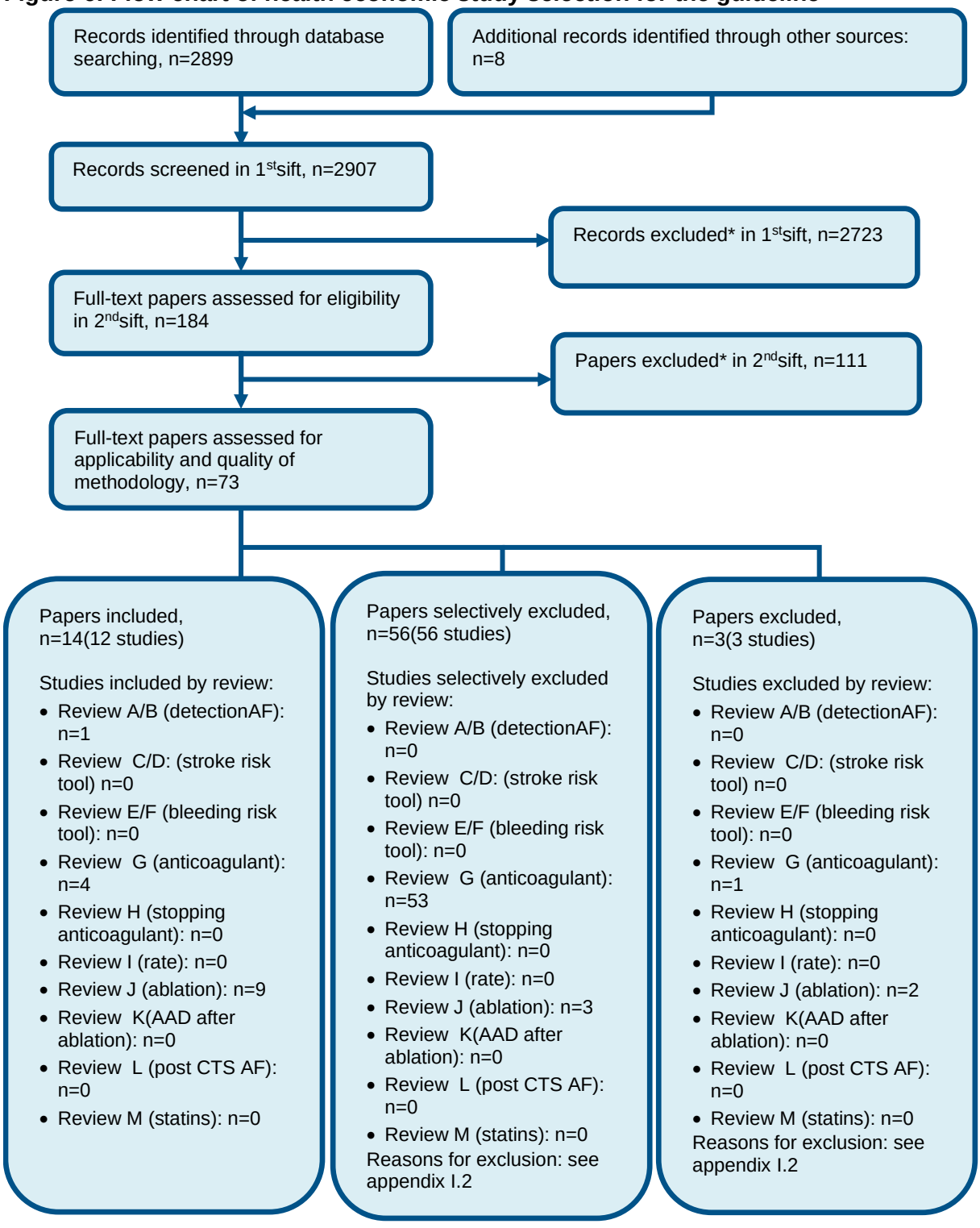
Table 9: Clinical evidence profile: Discontinuation versus continuation of oral anticoagulants in people with AF resolved by ablation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Discontinuation of anticoagulants	continuation of anticoagulants (at previous dose)	Relative (95% CI)	Absolute		
Stroke (follow-up median 18±12.2 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/266 (0.38%)	0.3%	Peto OR 1.17 (0.07 to 18.98)	1 more per 1000 (from 3 fewer to 51 more)	⊕OOO VERY LOW	CRITICAL
Transient ischaemic attack (follow-up median 18±12.2 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/266 (0%)	0.6%	Peto OR 0.16 (0.01 to 2.53)	10 fewer per 1000 (from 20 fewer to 0 more)[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding (follow-up median 18±12.2 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/266 (0.75%)	0.6%	Peto OR 1.17 (0.16 to 8.43)	1 more per 1000 (from 5 fewer to 42 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of atrial fibrillation (follow-up median 18±12.2 months)												
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	30/296 (10.1%)	11.9%	RR 0.85 (0.54 to 1.35)	18 fewer per 1000 (from 55 fewer to 42 more)	⊕OOO VERY LOW	CRITICAL

[1]Observational studies are automatically downgraded for selection bias. However, they can be further downgraded for other risk of bias
[2]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3]Zero events in one arm (intervention group) so absolute value calculated manually from risk difference

Appendix G: Health economic evidence selection

Figure 6: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Adderley 2018[1]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Ahluwalia 2019[2]	Incorrect study design
Almahameed 2007[3]	Not guideline condition
Antoniou 2020[4]	Incorrect study design
Arai 2019[5]	Not review population
Asberg 2017[6]	Not review population. Incorrect interventions
Bertrand 2019[7]	Not review population
Birnie 2018[8]	Not review population
Bunch 2009[10]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Chung 2015[11]	Not guideline condition
Dagres 2009[13]	Inappropriate comparison
De luca 2005[14]	Not review population
Di biase 2014[15]	Not review population. Incorrect interventions
Douketis 2018[16]	Not review population
Edgerton 2010[17]	Incorrect interventions
Gadiyaram 2019[18]	Inappropriate comparison
Gallo 2016[19]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Garcia-Fernandez2016[20]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Garcia-fernandez 2016[21]	Not review population
Geis 2020[22]	Not review population
Holmes 2009[24]	Not review population
Hussein 2011[25]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Jacobs 2017[26]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Johnsrud 2018[27]	Not review population
Kim 2018[28]	Incorrect interventions
Kjekshus 2020[29]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding. Inappropriate comparison
Kochhauser 2017[30]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Landmesser 2018[31]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Lauritzen 2020[32]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Li 2019[33]	Not review population
Liang 2018[34]	Not review population. Non randomised with uncorrected potential

Study	Exclusion reason
	confounding from stroke risk and/or bleeding
Mangner 2019[35]	Not review population
Martin 2015[36]	Not review population
Martinez-Comendador 2015[37]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Michael Gray 2011[23]	Systematic review: study designs inappropriate
Murashita 2018[38]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Nademanee 2015[39]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Nakamura 2018[40]	Not review population
Nuhrich 2015[43]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Okumura 2016[44]	Not review population. Incorrect interventions
Okumura 2019[45]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Oral 2006[46]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Ozaki 2020[48]	Not review population. Systematic review is not relevant to review question or unclear PICO
Paquette 2019[49]	Not review population
Patel 2013[50]	Not review population
Perreault 2019[51]	Not review population
Pet 2013[52]	Inappropriate comparison
Potpara 2015[53]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding. Not review population
Reddy 2013[54]	Not review population. Incorrect interventions
Reynolds 2018[55]	Not review population. Incorrect interventions
Riley 2014[56]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Romero 2019[57]	Incorrect study design
Saad 2011[58]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Saglietto 2020[59]	Systematic review: study designs inappropriate
Sakamoto 2019[60]	Not review population. Incorrect study design
Sambola 2019[61]	Not review population. Incorrect interventions
Schlingloff 2016[62]	Incorrect interventions
Shah 2008[63]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding. Incorrect interventions
Shah 2017[64]	Not review population. Incorrect interventions
Sjalander 2017[65]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Solla-ruiz 2019[66]	Not review population. Incorrect interventions
Sondergaard 2019[67]	Not review population
Tao 2010[68]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Tao 2017[69]	Not review population. Incorrect interventions
Themistoclakis 2010[70]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding

Study	Exclusion reason
Tingting 2019[71]	Incorrect interventions. Not review population
Tran 2015[72]	Inappropriate comparison
Tse 2002[73]	Not review population
Weimar 2012[75]	Incorrect interventions
Winkle 2013[76]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Yagishita 2011[77]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Yang 2020[78]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding
Zado 2019[79]	Inappropriate comparison
Zhang 2015[80]	Non randomised with uncorrected potential confounding from stroke risk and/or bleeding. Includes mitral stenosis - excluded from guideline
Zhao 2018[81]	Not review population. Incorrect interventions
Zhou 2018[82]	Systematic review is not relevant to review question or unclear PICO
Zink 2020[83]	Incorrect interventions

I.2 Excluded health economic studies

None.

Appendix J: Research recommendations

J.1 Discontinuing anticoagulation following resolution of post-cardiac surgery AF

Research question: A.1 What is the clinical and cost-effectiveness of discontinuing anticoagulation in people whose post-operative AF following cardiac surgery has resolved?

Why this is important:

Clinical opinion is generally that anticoagulation can be stopped after AF resulting from cardiac surgery has resolved. However this practice is not based on evidence, because no research has been conducted in this area. It is possible that removal of anticoagulation in people with resolution of cardiac surgery-induced AF may increase the risk of stroke. Hence robust evidence is required to allow recommendation of the safest and most effective practice.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People on anticoagulants due to AF directly resulting from cardiac surgery, who subsequently experience a resolution of that AF. These are people who do not have AF prior to cardiac surgery, but who develop AF as a result of the cardiac surgery. The population should be limited to those people where there is still an indication to continue, who are not low risk (i.e. CHADVASC score ≥2). Intervention(s): Discontinuation of OACs, but OACS will be re-instituted if the AF recurs. It would be interesting to undertake further studies with several intervention arms where OACs are discontinued at different time points (i.e. one month after AF resolution, two months, three months etc) after cardiac surgery in order to determine the optimal period of OAC after cardiac surgery Comparison: Continuation of OACs regardless of rhythm recurrence, throughout the period of usual post-operative follow up. Outcome(s): Quality of life, Mortality, stroke, recurrence of AF, AF burden, major bleeding, CRNMB
Importance to patients or the population	It is important to know whether continued anticoagulation is required if post-cardiac surgery AF has resolved. Although anticoagulation reduces the risk of stroke it increases the risk of bleeding, including major bleeding and intracranial bleeding. If this study shows that patients have no increased risk of stroke when not anticoagulated after a return to sinus rhythm, then stopping anticoagulants will safely reduce bleeding events in this population. On the other hand if the risk of stroke remains in these patients then anticoagulant use can be strongly recommended in all patients who developed AF after cardiac surgery regardless of resolution.
Relevance to NICE guidance	The results of this study would be highly relevant to future guidance as they could potentially change recommendations.
Relevance to the NHS	Anticoagulant use carries a cost from adverse events. If anticoagulant use can be reduced in those that do not require it, such costs can be reduced.

National priorities	This is a national priority area in the field of cardiac surgery. Please see: http://www.jla.nihr.ac.uk/priority-setting-partnerships/heart-surgery/downloads/Heart-Surgery-PSP-report-of-results.pdf
Current evidence base	The current evidence base is extremely sparse with no RCTs or observational evidence available.
Equality	This does not address equality issues.
Study design	Randomised controlled trial
Feasibility	This is a highly feasible study that will present no unacceptable financial costs. Clinical opinion is generally that OACs can be safely removed after post cardiac surgery AF has resolved, though this is not based on firm evidence. Given this consensus is it ethical to continue to give anticoagulants to people with resolved AF (the randomised comparison group), with the increased risk of bleeding this entails?
Other comments	None
Importance	• Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

J.2 Discontinuing anticoagulation following ablation

Research question:A.1 What is the clinical and cost-effectiveness of discontinuing anticoagulation in people that experienced resolution of AF following ablation?

Why this is important:

Currently all patients are given anticoagulation after ablation even if the ablation has successfully resolved AF. This is based on clinical consensus but little strong evidence. If it can be shown that the risk of stroke in people with post-ablation AF resolution is reduced to background levels, then anticoagulants need not be prescribed in these patients. This may reduce adverse events such as major or intracranial bleeding, with consequent improvements in quality of life and possible reductions in mortality.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People on anticoagulants due to pre-existing AF, who experienced resolution of AF after treatment with ablation. These are people who had AF prior to the ablation, and who were given an ablation to attempt to treat the AF and allow for successful restoration of sinus rhythm. The population should be limited to those people where there is still an indication to continue, who are not low risk (i.e. CHADVASC score ≥2). Intervention(s): Discontinuation of OACs whilst patients are in sinus rhythm after the 3 month blanking period. **If patients revert to AF after the blanking period, then OACs will be re-instituted.** However, any patients given a re-do of ablation after recurrence will be allowed to discontinue OACs again if reverting to sinus rhythm after a 3 month blanking period, provided this falls within the follow up period. Comparison: Continuation of OACs, regardless of the presence of arrhythmia recurrence. Outcome(s): Quality of life, Mortality, stroke, recurrence of AF, AF burden, major bleeding, CRNMB
Importance to patients or the population	It is important to know whether continued anticoagulation (to reduce/eliminate the incidence of thromboembolic events) is required if ablation has led to the resolution of AF. Although anticoagulation reduces the risk of stroke it increases the risk of bleeding, including major bleeding and intracranial bleeding. If this study shows that patients have no increased risk of stroke when not anticoagulated in post-ablation sinus rhythm, then stopping anticoagulants will safely reduce bleeding events in this population. On the other hand if the risk of stroke remains in these patients then anticoagulant use can be strongly recommended in all patients post-ablation regardless of rhythm.
Relevance to NICE guidance	The results of this study would be highly relevant to future guidance as they could potentially change recommendations.
Relevance to the NHS	Anticoagulant use carries a cost from adverse events. If anticoagulant use can be reduced in those that do not require it, such costs can be reduced.
National priorities	This is not a national priority
Current evidence base	Current recommendations are based on consensus opinion. There is a paucity of data regarding the optimal strategy and duration of anticoagulant treatment following successful ablation. The current evidence base is derived from observational and non-randomised, retrospective studies with short durations of follow up. Further high-quality, adequately powered, randomised controlled trials are required to inform clinical management/treatment decisions in this particular patient group.
Equality	This does not address equality issues
Study design	Randomised controlled trial. The suggested trial is pragmatic, allowing OACS to be withdrawn in the intervention group only when the patients

	are in sinus rhythm.
Feasibility	This is a highly feasible study that will present no unacceptable financial costs. There is a large ethical issue, however. Current opinion is quite firm that anticoagulation is required in this population regardless of the presence of sinus rhythm. Is it acceptable to remove anticoagulation from some patients given this clinical consensus? To counter this, it should be remembered that there is no rigorous evidence suggesting that stopping anticoagulants is dangerous in this population.
Other comments	
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.