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Action on Smoking and Health (ASH)	9	8-13	**2. Assessment of stroke and bleeding risks** Smoking is associated with 14% of deaths from heart and circulatory disease, and so smoking ought not be overlooked by any NICE guidance relating to heart and circulatory health.[i] This consultation response will focus primarily on the sections in the scope which relate to the management of stroke risk. i. Health and Social Care Information Centre (HSCIC), Lifestyles Statistics. Statistics on Smoking: England, 2012. Recording smoking status is a cost-effective tool for predicting stroke in all individuals, so the smoking status of patients with atrial fibrillation should not be overlooked. We know that smokers are more likely to have a stroke than non-smokers, and that the risk increases with the number of cigarettes smoked.[ii] [iii] In their recent report 'Hiding in Plain Sight: Treating Tobacco Dependency in the NHS',[iv] the Royal College of Physicians (RCP) references a 2013 meta-analysis of smoking risks for stroke in men and women. For current smokers, the study estimated the relative risk to be 1.57 (95% CI 1.49–1.88) for men and 1.83 (95% CI 1.58–2.12) for women, relative to non-smokers. For former smokers relative to never smokers, the study estimated the relative risk to be 1.08 (95% CI 1.03–1.13) for men and 1.17 (95% CI 1.12–1.22) for women.[v] [ii] Aldoori M, Rahman SH. Editorial: Smoking and stroke: a causative role. BMJ 1998; 317: 962	Thank you for this comment. Reducing the risks of smoking is important for general health and for the prevention of a wide range of conditions and is therefore not specifically included in a guideline on a specific condition. We agree with the vital importance of smoking cessation but this issue is covered by the NICE guideline on Stop smoking interventions and services (NG92).

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			[III] The Stroke Association. Smoking and the Risk of Stroke. April 2012. [IV] Royal College of Physicians, Hiding in Plain Sight, 2018: https://www.rcplondon.ac.uk/projects/outputs/hiding-plain-sight-treating-tobacco-dependency-nhs [v] Peters SAE, Huxley RR, Woodward, M. Smoking as a risk factor for stroke in women compared with men. A systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. NCBI, 2013. http://stroke.ahajournals.org/content/44/10/2821.long [Accessed 23 April 2018]. In RCP, Hiding in Plain Sight: Treating Tobacco Dependency in the NHS. This also highlights the importance of treating tobacco dependence in patients as the risk of stroke is lower in ex-smokers. This issue of treatment is elaborated on in comment number 2. Similarly, a number of other studies have also identified a relationship between smoking and stroke. For example: - It is estimated that 10% of deaths from stroke are due to active smoking and 3,500 deaths from passive smoking. [vi] [vii] - A Finnish cohort study conducted by the University of Helsinki found that smoking increased risks of subarachnoid haemorrhage, often leading to strokes, in both men and women but this risk was considerably	

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			greater for female smokers. Hazard ratios between smoking and strokes differed by sex in all categories studied, with women consistently being at greater risk.[viii] - Continued smoking following a stroke is related to prognosis. In a large Canadian study, continued smoking had a negative effect on functional outcome at discharge, mortality at 1 year and length of stay in hospital.[ix] - A study from Australia similarly found an increased risk of death following stroke among smokers compared to past smokers and never smokers, with the risk maintained for the 10 years of the study.[x] - The risk of stroke is particularly high among those who have other risk factors including hypertension or high serum cholesterol.[xi] [vi] The Stroke Association. Smoking and the Risk of Stroke. April 2012. [vii] Health Committee second report 2000: The Tobacco Industry and the health risks of smoking. The Stationery Office Ltd. P3 [viii] Lindbohm J et al. Sex, smoking, and risk for subarachnoid haemorrhage. Stroke 2016; 47: 1975-1981 [ix] Edjoc RK, Reid RD, Sharma M, Fang J. Registry of the Canadian Stroke Network. The prognostic effect of cigarette smoking on stroke severity, disability, length of stay in hospital, and mortality in a cohort with cerebrovascular disease. J Stroke	

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			Cerebovasc Disease 2013; doi:10.1016/j. jstrokecerebrovasdis.2013.05.001 [x] Kim J, Gall SL, Dewey HM, et al. Baseline smoking status and the long-term risk of death or nonfatal vascular event in people with stroke: a 10-year survival analysis. Stroke 2012; 43: 3173-8. [xi] Nakamura K, Nakagawa H, Sakurai M, et al. EPOCH-JAPAN Research Group. Influence of smoking combined with another risk factor on the risk of mortality from coronary heart disease and stroke: pooled analysis of 10 Japanese cohort studies. Carebrovasc Dis; 2012: 480-491. Given the scope's desired outcome of assessing health-related quality of life, mortality and stroke complications, the strong association between smoking status and stroke in should be taken into account, even though this evidence is not drawn solely from patients with atrial fibrillation.	
Action on Smoking and Health (ASH)	9	14-16	**3. Interventions to prevent stroke** Given the increased stroke prevalence associated with smoking, smoking cessation is a viable method of stroke prevention. A range of evidence exists to support the role of smoking cessation as a method for reducing the risk of stroke. For example: - Within two years of stopping smoking, a former smoker's risk of stroke is reduced to that of a non-smoker.[xii]	Thank you for your comments. Although we agree this is an important area, it is not included in this update of the guideline as new evidence in this area was not cited in the surveillance report. Whilst we agree with the importance of smoking cessation this is covered by NICE guidance Stop smoking interventions and services (NG92).

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			- A 12 year study of female nurses found that the elevated risk of stroke in smokers disappeared within 5 years of quitting and that the decline in risk was independent of age, highlighting that it is never too late to quit.[xiii] - Ex-smokers are less likely to die within a 10 year period from a stroke than current smokers.[xiv] - The beneficial effects of smoking cessation among former smokers is similar for men and women.[xv] [xii] Aldoori M, Rahman SH. (Editorial) Smoking and stroke: a causative role. BMJ 1998; 317: 962 [xiii] Kawachi,I et al. Smoking cessation and decreased risk of stroke in women. JAMA 1993; 269: 232-236 [xiv] The Stroke Association website. What is a stroke? Accessed 07 Sept 2016. [xv] Sanne et al. Smoking as a risk factor for stroke in women compared with men: A systematic review and meta-analysis of 81 Cohorts, including 3 980 359 Individuals and 42 401 strokes. Stroke 2013; DOI: 10.1161/ STROKEAHA.113.002342 Encouraging and supporting patients with atrial fibrillation to quit smoking is therefore a positive step in reducing the risk of stroke. This is why ASH supports the Royal College of Physicians in their call for treatment for tobacco dependence to be embedded into every NHS contact.	

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			Smoking exacerbates as well as causes disease, and helping smokers quit can reduce NHS treatment costs and increase quality of life for patients. As well as CVD, this includes pregnancy, COPD and other respiratory diseases, mental health, surgery, diabetes, HIV-AIDS, and 16 types of cancer. NHS policy, NICE guidance PH48 and financial commissioning tools do currently encourage the identification and referral for treatment of tobacco dependency alongside implementation of smokefree grounds. However, in practice identification and actual treatment of smokers is not embedded in service designs, patient pathways or disease treatment pathways. Typically where treatment is available opt-in referral to offsite local authority services is the model used, which is less effective than immediate treatment on site, or opt-out models, which when used with pregnant smokers have been shown to double quit rates. ASH therefore argues that treatment for tobacco dependence should be made available for all patients, including those with atrial fibrillation, in order to reduce the risk of stroke. Aside from its effectiveness, treatment of tobacco dependence is also a highly cost-effective intervention. The economic report accompanying the 2018 NICE NG92 guidelines for smoking cessation services and interventions analysed cost-effectiveness for smoking cessation interventions with modelling of six common conditions (lung cancer, stroke, COPD, myocardial infarction,	

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			asthma exacerbation and coronary heart disease) caused or exacerbated by smoking. The effectiveness evidence from 30 different interventions, with the costs of interventions ranging from £19 for brief advice to £763 for an extended course of NRT, and intervention effectiveness (quitting smoking) ranging from 9% to 47%, found all to be highly cost-effective. A threshold analysis showed that even when the lowest quit rate identified in the effectiveness study (9%) is combined with the most expensive intervention (£763 per person), the intervention is still cost-effective. If the aim of treatment for atrial fibrillation is to prevent complications, including stroke (as laid out in the Draft Guideline Scope), then it ought to include smoking cessation as a cost-effective prevention tool.	
AF Association	General	General	* The guideline scope does not specify if this is all AF or just 'non-valvular AF' * As the AF Assoc we completely support that the guideline should cover all those with AF with the exception of children and those with congenital heart diseases * HOWEVER we do feel it should include those with significant mitral valve disease (moderate to severe mitral stenosis) as the intervention for their stroke prevention is different and we should question if they need attention to the mitral valve	Thank you for raising this point. AF due to mitral stenosis involves very different management, so we have now explicitly excluded this group. A guideline has recently been commissioned on valvular heart disease.
AF Association	General	General	Inclusion of lifestyle management for AF prevention (particularly obesity)	Although we agree these are important areas, they are not included in this update of the guideline as new evidence in

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			Atrial Fibrillation in the setting of heart failure Anticoagulation in patients with AF and CKD Reconsideration of digoxin for rate control AV node ablation and pacing for rate control Anticoagulation during cardioversion and ablation How to deal with an irregular pulse detected by smart phones, etc., the proper and correct response to pulse irregularities (AF) detected by blood pressure machines Establishment of AF clinics with nurse-led services The use of AF heart teams Hybrid ablation techniques (surgery and catheter), etc.	these areas was not cited in the surveillance report. Trials on hybrid techniques are ongoing and the surveillance review identified this as an area that may be included in future updates. People with comorbidities may be included in the relevant evidence review.
AF Association	General	General	Anticoagulation THERAPY not treatment – anticoagulation does not *treat* the AF – it does however help prevent AF-related stroke. Better informed and educated patients are more likely to adhere to medication and realise that they will not feel better from the anticoagulation as it is not treating the AF. Treatment options then need to be discussed and agreed between patient and clinician and clearly understood that this is separate from anticoagulation therapy	Thank you for this suggestion. We believe these terms are interchangeable. When writing the recommendations the importance of helping patients realise that the anticoagulation is not aimed at treating AF (but is instead aimed at preventing strokes) will be given proper consideration.
AF Association	General	General	Refer to AF-related stroke rather than prevention of stroke in AF to encourage better understanding and education for both physician and patient. Evidence has shown that adherence is improved when patients understand why they need to take their anticoagulation regularly if they understand it is to reduce their risk of AF related stroke	Thank you for your comment. We feel 'prevention of stroke in AF' is appropriate in the context of a scoping document and clearly indicates the reason for offering anticoagulants.

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Anticoagulation UK	2	16-21	Awareness of roll out of handheld devices to detect AF currently being used within selected GP practices for diagnosis/monitoring of patients with AF* No national screening adopted to date, systematic review for screening strategies published in 2017* highlighted that systematic opportunistic screening more likely to be cost effective that systematic population screening with photoplethysmography being used as a method of diagnosis. Alivecor device is currently being used for this purpose and we note that the Lead I Electrocardiogram (ECG) devices for detecting AF using single – time point in primary care is currently in NICE diagnostics guidance development, publication date Feb 2019 which is timely for inclusion in the updated AF guidelines *Review Citation: Welton NJ, McAleenan A, Thom HHZ, Davies P, Hollingworth W, Higgins JPT, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technol Assess 2017;21(29)	Thank you for your comment. The reference and your comment about the Alivecor device will be used when devising the protocol for the review question.
Anticoagulation UK	3	1-3	Reference to NICE has not compared different DOACS …. See below for recent study comparing 4 DOACS and outcomes Lopez-Lopez JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ. 2017;359:j5058.	Thank you for your reference, which will help us in our review of the evidence.

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Anticoagulation UK	4	14-15	If women are at higher risk of stroke from AF, important that education and awareness is prioritised. All opportunities must be explored within primary care to ensure women are aware of AF risk when engaging with clinicians. Alternatively, National Screening scheme needs to be adopted	Thank you for your comments and we will ensure that guideline committee members are aware of these issues when making recommendations.
Arrhythmia Alliance	3	15	CHA2DS2-VASc is the most widely used (and validated) stroke risk scoring system and should be recommended in the updated NICE guidelines.	Thank you for your comment. Our evidence review, and subsequent guideline committee discussion, will help to determine which is the most clinically and cost effective risk scoring system.
Arrhythmia Alliance	3 9	15 9	Other stroke and bleeding risk scores have been proposed – it is very important for NICE to balance the use of complex scores that offer marginal improvements in predicting high risk patients (with the risk tool often derived in anticoagulated cohorts, some with biomarkers against simple, practical and user-friendly scores (eg. CHA2DS2-VASc, HAS-BLED). A recent European survey shows that these simple scores remain widely used. Dan et al Europace. 2018 Jun 8. doi: 10.1093/europace/euy094. [Epub ahead of print] PMID:29893840	Thank you for your comment. This will be considered by the guideline committee when assessing the benefits and risks of the different scales.
Arrhythmia Alliance	3 9	15 9	All clinical factor based risk scores have a c-index of approx. 0.6-0.65 i.e. modest predictive value for high risk; more complex clinical scores may improve the c-index to approx. 0.65 only. Addition of biomarkers may improve the c-index to approx. 0.67.	Thank you for your comment. Our evidence review, and subsequent guideline committee discussion, will help to determine which is the most clinically and cost effective risk scoring system. This will take into account study design and

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			Attention to study design is important. Some papers describe low event rates due to 'conditioning on the future' bias by excluding all patients ever started on anticoagulants. Some papers have looked at risk scores in anticoagulated cohorts in a highly selected clinical trial setting. To assess the value of a score in risk prediction, we need to see the predictive value in non-anticoagulated cohorts. Overall, all risk score only have limited value for predicting high risk. In contrast the CHA2DS2-VASc score performs well in identifying 'low risk' patients. This is the simple message to GPs and non-specialists made in the 2014 NICE guideline, to initially identify low risk patients first.	risk of bias, as well as issues around ease of use and shared decision making.
Arrhythmia Alliance	3 9	15 9	Many validation studies of risk scores look at baseline factors, and record the prediction of even rates many years later (sometimes 5-10 years!). The flaw of many of these studies is that patients get older and acquire incident risk factors. Recent analysis have shown clearly the dynamic nature of stroke *and* bleeding risk, such that the *change* in risk factors is a more powerful risk predictor.	Thank you for your comment. This point will be considered when drawing up the protocol for this review question, and when interpreting results from papers.

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			See: J Am Coll Cardiol. 2018 Jan 16;71(2):122-132. Thromb Haemost. 2018 Apr;118(4):768-777. Thromb Haemost. 2018 Jul;118(7):1296-1304.	
Arrhythmia Alliance	5	11	Ensure that stroke risk score identifies 'low risk' patients (CHA2DS2-VASc score of 0 in men and CHA2DS2-VASc score of 1 is women) rather than focussing on high-risk patients.	Thank you for your comment. The issue you highlight will be discussed by the guideline committee when reviewing the evidence.
Arrhythmia Alliance	5	11-12	Need to ensure clear information on the management of patients with CHA2DS2-VASc score of 1. US guidelines include females with score=1 into this group, when it is clear they are 'low risk'. Female sex is a risk modifier, rather than a risk factor (see Nielsen P et al Circulation. 2018 Feb 20;137(8):832-840). Low risk needs clearly defined as CHA2DS2-VASc score 0 in males or 1 in females. Such patients do not need antithrombotic therapy.	Thank you for your comment. The issue you highlight will be discussed by the guideline committee when reviewing the evidence.
Arrhythmia Alliance	6	3	Percutaneous atrial appendage occlusion is a treatment for prevention of AF-related stroke (albeit not widely used in the UK) and should at least be mentioned briefly with current evidence summarised (additional information is available since 2014 NICE).	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future.

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				Data collected during the CtE scheme is considered alongside published data from research trials to inform the development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.
Arrhythmia Alliance	6	6	Although a detailed review of how to manage co-morbidities associated with atrial fibrillation is not needed in the atrial fibrillation guideline, holistic management of the patient is required. Treating atrial fibrillation in isolation will not work; management of the comorbidities (e.g., hypertension, heart failure, diabetes mellitus etc.) is an essential part of atrial fibrillation management. The updated guidelines should at the very least highlight that the management of co-morbidities is important and provide a table listing comorbidities and current best practice/targets for each comorbidity. Simple approaches have been implemented in the West Midlands Academic Health Science Networks and local Clinical Commissioning Groups to simplify the approach to holistic management of atrial fibrillation – the ABC pathway See Nat Rev Cardiol. 2017 Nov;14(11):627-628. Something similarly simple and practical would help patient care	Thank you for your comment. We agree that a holistic patient-centred approach is essential, and all recommendations made after evaluation of the evidence will be guided by this.
Arrhythmia Alliance	6	7	Refer readers to a document that can provide information on the management of atrial fibrillation and ACS f not including in the update.	Thank you for your comment. We now refer to the NICE guideline on Acute Coronary Syndromes (in development).

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Arrhythmia Alliance	6	Table	Excellent that 'personalised package of care and information' is to be retained but a clear pathway on what elements this should ideally incorporate (individualised as needed) should be included in the update. Need to include list of patient resources which Healthcare Professional can use to educate/inform patients about atrial fibrillation and treatment options. – AF Association has extensive resources approved by DoH and reviewed by AF Medical Advisory Board – NICE have reference many of these resources previously	Thank you for your comments. Education and information was not an area highlighted by the guideline surveillance review as having new evidence and therefore requiring update.
Arrhythmia Alliance	9	12	There is often inappropriate abuse and misuse of bleeding risk assessment. This is an implementation and education issue, not a reason to recommend against use of bleeding risk assessment in guidelines A responsible approach should be emphasised – bleeding risk scores such as HASBLED draws attention to modifiable bleeding risks and 'flags up' the high risk patients for early review and follow-up (e.g. 4 weeks, rather than 4-6 months) J Thromb Haemost. 2016 Sep;14(9):1711-4. doi: 10.1111/jth.13386.	Thank you for your comment. Any drawbacks from a risk tool should be captured by the eventual health outcome. We will be comparing the outcomes from different risk tools, which should provide empirical answers to questions around the most effective tool.

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			Undue focus on modifiable bleeding risk factors is an inferior strategy to a formal bleeding risk score for bleeding risk assessment. Am J Med. 2018 Feb;131(2):185-192. Int J Cardiol. 2018 Mar 1;254:157-161. Thromb Haemost. 2017 Dec;117(12):2261-2266.	
Arrhythmia Alliance	General	General	Refer to AF-related stroke NOT prevention of stroke in AF. AF comes before the stroke and better educates both clinician and patient	Thank you for your comment. We feel 'prevention of stroke in AF' is appropriate in the context of a scoping document and clearly indicates the reason for offering anticoagulants.
Arrhythmia Alliance	General	General	Refer to anticoagulation therapy (not treatment as it does not treat AF)	Thank you for your comment. We believe these terms are interchangeable. When writing the recommendations the importance of helping patients realise that the anticoagulation is not aimed at treating AF (but is instead aimed at preventing strokes) will be properly considered.
Arrhythmia Alliance	General	General	Recommend after anticoagulation therapy patient should be involved in the decision making for treatment options for AF	Thank you for your comment. Decisions on recommendations will be made after the evidence has been analysed and discussed in the upcoming guideline development phase.
Arrhythmia Alliance	General	General	In 2018 there is the new focused update on the US guidelines (ACC/AHA/HRS) being published. Also, the new 2018 American College of Chest Physicians (ACCP) guidelines will be published in Q3 2018	Thank you for your comment. We will consider all primary evidence available to produce the most up to date and evidence-based recommendations possible.

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Association of British HealthTech Industries	4	17-24	Section 3.1 "Groups that will be covered". In the draft scope, patients who yet to have their AF detected are omitted "Adults 18 and over with AF to include: • new onset or acute atrial fibrillation, chronic atrial fibrillation, including paroxysmal (recurrent), persistent or permanent postoperative atrial fibrillation, atrial flutter "key issue and questions", Diagnosis and Assessment" is for patients presenting with symptoms but have not had their AF diagnosed. Please add the following in section 3.1 • People with pulse irregularities On page 3, lines 20 – 23 references are made to the importance of detection of AF in patients who have cryptogenic stroke and how insertable cardiac monitors are a new and useful detection of AF for this group of patients, though these people are not included in the section "groups that will be covered". Please add the following in section 3.1 • People with cryptogenic stroke	Thank you for your comment. We have added 'people with suspected AF' to 'groups that will be covered'. We have removed the reference to people with cryptogenic stroke from page 3 lines 20-23, as this group will not be covered in the guideline. This population is being covered by a NICE diagnostics guideline.

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Association of British HealthTech Industries	6	Table	Diagnosis and Assessment - "What Nice Plans to do" the review of the evidence for detecting AF in people with cryptogenic stroke is missing. We suggest a sentence is added: • Review evidence on the detection of AF in people with cryptogenic stroke	Thank you for your comment, We have removed the reference to people with cryptogenic stroke from page 3 lines 20-23, as this group will not be covered in the guideline. The reason is that this is being covered by a NICE diagnostic guideline (in development) 'Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke'.
Association of British HealthTech Industries	9	17	Regarding rate and rhythm control we believe the most pertinent questions for NICE to focus on and address by this clinical guideline is the effectiveness of non-drug therapy vs drug therapy, and all ablation vs drug therapy. In the UK, only 4% of patients with AF are currently referred for ablation, which is small proportion despite the published evidence supporting the clinical effectiveness of all ablation therapies, and recent publications showing the benefit of ablation over drug therapy. As a result of the limited referrals for ablation techniques, a significant number of patients are not getting access to clinically and cost effective ablation technology to not only manage, but cure their AF. Furthermore, an area of debate currently is the appropriate time period to determine the effectiveness of treatment. New data are driving a longer-term view, rather than short term management. We request that NICE pays careful consideration to the time horizon applied. Freedom of AF at 12-months would be an	Thank you for your comment. We have now amended the two questions of rate and rhythm control to form one larger question. This will compare all pharmacological and non-pharmacological approaches together. Thus this will permit drug vs drug, non-drug vs non-drug and drug vs non-drug. This will involve many head to head permutations and so will possibly require the use of a network meta-analysis (though of course with appropriate consideration given to the different populations that may be involved across interventions). We will not cover your third suggested question, as that is a research methodology question and outside the scope of this guideline.

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			appropriate minimum clinical endpoint when considering the comparative clinical effectiveness of ablation technologies. Finally, we consider that the choice of specific ablation technique should be a clinically led decision by the electrophysiologist based on the needs of that patient. We therefore propose that the rate and rhythm control review questions are edited as follows to focus this guideline on the areas we believe will most benefit patients and the NHS:- - What is the clinical outcome and cost effectiveness of non-pharmacological (cardioversion-acute care) vs pharmacological (ADDs-long term care)? - What is the clinical outcome and cost effectiveness of intervention (ablation) vs pharmacological (ADDs -long term care)? - What is the correct time period to re-assess the effectiveness of the treatment?	
Association of British HealthTech Industries	9	18	Section 4.1. We would like to highlight recent data presented at the Heart Rhythm Society meeting in the US from the study Catheter Ablation versus Antiarrhythmic Drug Therapy in Atrial Fibrillation Trial	Thank you for your comment. All relevant evidence will be picked up and analysed in the evidence reviews. We have noted your reference.
Association of British HealthTech Industries	9	20	Section 4.2. We would like to highlight the following publications: • Kuck, et al, Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation, N Engl J Med 2016;	Thank you for your comment. All relevant evidence will be picked up and analysed in the evidence reviews. We have noted your reference.

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			374:2235-2245 June 9, 2016 DOI: 10.1056/NEJMoa1602014 • Kuck et al, The Impact of Cryoballoon Versus Radiofrequency Ablation for Paroxysmal Atrial Fibrillation on Healthcare Utilization and Costs: An Economic Analysis From the FIRE AND ICE Trial, . Eur Heart J (2016) ehw285 DOI: http://dx.doi.org/10.1093/eurheartj/ehw285 First published online: 5th July 2016	
Association of British HealthTech Industries	9	3-7	"Key Issues and draft questions" a question to review the evidence of different monitoring strategies to detect AF in people with cryptogenic stroke is omitted, though the evidence is referenced in the draft scope. Please add a question to review the clinical and cost effective methods of cardiac monitoring strategies to detect AF in people with cryptogenic stroke.	Thank you for your comment. Cardiac monitoring in people with crytogenic stroke is being covered by a NICE diagnostic guideline (in development) 'Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke'. We have added this to the list of related NICE guidance in the scope.
Association of British HealthTech Industries	10	1	Main outcomes to be added to the NICE scope list when searching for and assessing the evidence should also include freedom of AF at 12months as a minimum, usually measured in clinical evidence to prove efficacy of treatment of AF.	Thank you for your comment. We have listed the main outcomes in the scope. The guideline committee will determine the specific outcomes for each evidence review.
Association of British	10	1	Main outcomes to be added to the NICE scope list when searching for and assessing the evidence should also include reduction in medication burden to capture the resource impact of	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions.

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HealthTech Industries			ablative technologies on the NHS and the effectiveness of treatments for patients.	
Association of British HealthTech Industries	10	1	Adverse events associated with ablation technologies and also drug therapies should be captured as key outcomes because of the significant resource and patient impact.	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions.
Association of British HealthTech Industries	10	1	We request that re-do ablation be included as a key outcome when considering the clinical and cost effectiveness of ablative technologies because of the NHS resource use and impact for patients associated with repeat ablation. Furthermore, re-do ablation should be defined specifically as a complication following primary ablation for AF, and not as an accepted outcome/occurrence for the patient.	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions.
Association of British HealthTech Industries	10	1	NICE should differentiate between cardiovascular death vs all-cause mortality when reviewing the clinical evidence on AF treatments. These are clinically differentiated end-points and data should not be pooled to lose the impact of treatment.	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions. With reference to your specific point, any mortality that is not related to treatment will be comparable between randomised groups and so will cancel out – therefore the impact of treatment will not be greatly affected.
Association of British HealthTech Industries	10	4	Health related quality of life scoring tools are inadequate for AF because they do not correctly or sufficiently capture the symptoms a patient experiences. Therefore, to capture the main patient outcomes the following should specifically be included:	Thank you for your comment. We have listed the main outcomes in the scope. The guideline committee will determine the specific outcomes for each evidence review.

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			-shortness of breath -palpitations -impact on physical activity	
Association of British HealthTech Industries	10	9	"exacerbation of heart failure" New evidence is available as follows: • Catheter Ablation versus standard conventional treatment in patients with Left ventricular dysfunction and Atrial Fibrillation. https://www.nejm.org/doi/full/10.1056/NEJMoa1707855	Thank you for your comment. We have noted your reference.
Association of British HealthTech Industries	General	General	"Diagnosis and Assessment". There is new evidence for people with suspected paroxysmal AF which remains undetected by standard ecg recording. We suggest guidance is updated to recommend the use of insertable cardiac monitors in symptomatic patients when AF has not been detected with standard ecg or event reorders. Please add: • "For people with suspected paroxysmal AF undetected by standard ecg recording or an event recorder, consider using an insertable cardiac monitor" We refer to the following publications to support this statement: • Nasir et al, Predicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for	Thank you for your comment. We have edited the review question on diagnosis and assessment to make it clearer that we are including paroxysmal AF. We have noted your references.

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			Thromboembolic Events (PREDATE AF) Study Heart Rhythm. 2017 Jul;14(7):955-961 • Reiffel et al, A comparison of atrial fibrillation monitoring strategies in patients at high risk for atrial fibrillation and stroke: results from the REVEAL AF. Volume 71, Issue 11 Supplement, March 2018DOI: 10.1016/S0735-1097(18)30815-5	
Atricure	1	18-19	We agree that the incidence of Afib in the general population is higher than previously reported. Many Afib patients would benefit with more aggressive screening and treatment strategies. For example, recent research using cardiac monitors suggest the incidence of Afib in some non-symptomatic high risk patient groups as great as 40%. More aggressive screening could help identify patients who could be helped with interventions. When patients are not appropriately diagnosed and treated, there could be downstream clinical events and healthcare costs for the NHS which could be avoidable with a more rigorous diagnostic and treatment paradigm. **Citation**: Reiffel JA, et al. Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk Population: The REVEAL AF. *JAMA cardiology* 2017;2:1120-1127.	Thank you for your comment. These issues will be addressed by our first review question 'What is the most accurate method for detecting pulse irregularities in people with symptoms suggestive of atrial fibrillation and in people with cardiovascular risk factors?'
Atricure	5	3-4	**Open concomitant treatment of Afib surgically may reduce stroke and mortality risk, restore sinus rhythm, and is considered cost effective.**	Thank you for your comments. Whilst we will be evaluating different forms of ablation relative to each other and to other therapies, we are unable to extend the scope to concomitant

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			Surgical ablation (Cryo or RF energy) for Afib at the time of structural heart procedures (CABG, MVR, AVR) **(concomitant)** has recently obtained Class I treatment recommendations from the STS, HRS, and AATS. Up to 1 in 3 patients who undergo structural heart procedure also present with Afib. Treating Afib with a surgical ablation during the structural heart procedure may add as little as an hour to the procedure, and is easy to accomplish for the provider since the patient is undergoing an open heart procedure. Numerous studies have shown the addition of a surgical ablation does not add adverse risk to the patient, and outcomes are significantly improved. Completing a surgical ablation concomitantly may also avoid other future interventions, such as a percutaneous catheter ablation, which adds costs to the NHS. Numerous studies have documented long term clinical improvement in mortality and stroke risk reduction with concomitant ablation, partially due to restoration of normal sinus rhythm. Furthermore, clinical benefit may also be imparted to the patient through a reduction in antiarrhythmic medications following the ablation procedure, resulting in additional savings for the NHS. Lastly, several cost effectiveness studies have demonstrated great value of concomitant ablation with structural heart procedures in Afib patients. ***Treating Afib concomitantly is a clinically and cost effective therapy that NHS could encourage during one hospital visit.***	treatment during other cardiac surgery as this was not an area highlighted by the surveillance review.

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			Citation: STS Guidelines. Badhwar V, et al. The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial Fibrillation. *Ann Thorac Surg*. 2017 Jan;103(1):329-341 **Citation**: HRS Guidelines: Calkins H, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2018 20(1):e1-e160. **Citation:** Musharbash FN, et al. Performance of the Cox-maze IV procedure is associated with improved long-term survival in patients with atrial fibrillation undergoing cardiac surgery. *J Thorac Cardiovasc Surg.* 2018 155(1):159-170 **Citation:** Rankin JS, et al. One-year mortality and costs associated with surgical ablation for atrial fibrillation concomitant to coronary artery bypass grafting. *Eur J Cardiothorac Surg*. 2017 52(3):471-477. **Citation:** Gillinov AM, et al. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med.* 2015 372(15):1399-409 **Citation:** Badhwar V, et al. Surgical Ablation of Atrial Fibrillation in the United States: Trends and Propensity Matched Outcomes. *Ann Thorac Surg.* 2017 104(2):493-500. **Citation:** CEA Quenneville S et al. The cost-effectiveness of Maze procedures using ablation techniques at the time of mitral	

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			valve surgery. *Int J Technol Assess Health Care.* 2009 25(4):485-96 **Citation:** CEA Lamotte M et al. A health economic evaluation of concomitant surgical ablation for atrial fibrillation. *Eur J Cardiothorac Surg.* 2007 32(5):702-10 **Citation**: CEA López Gude MJ et al. Cost-benefit analysis of concomitant atrial fibrillation management in Spain. *Gac Sanit.* 2010 24(1):59-65	
Atricure	5	3-4	**Minimally invasive surgical ablation for Afib may reduce stroke risk and restore normal sinus rhythm.** For many patients with de novo *symptomatic persistent Afib*, *medical management and catheter ablation is ineffective for Afib treatment*. For these patient's minimal invasive surgical ablation has been used with success in restoring normal sinus rhythm. Recently, the STS and HRS have provided Class IIb recommendations for minimal invasive surgical ablation (RF or CRYO) **(MIS sole therapy)** for persistent Afib treatment. Several studies have documented the safety and clinical benefit of this therapy. **Citation**: STS Guidelines. Badhwar V, et al. The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial Fibrillation. *Ann Thorac Surg*. 2017 Jan;103(1):329-341 **Citation**: HRS Guidelines: Calkins H, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus	Thank you for your comments. The details of the questions concerning ablation will be refined in the review protocols by the guideline committee, and minimal invasive surgical ablation will be considered for inclusion if relevant.

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			statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2018 20(1):e1-e160. **Citation:** Vos LM, et al. Totally thoracoscopic ablation for atrial fibrillation: a systematic safety analysis. *Europace.* 2018 Jan 18. doi: 10.1093/europace/eux385. [Epub ahead of print] **Citation:** van Laar C, et al. The totally thoracoscopic maze procedure for the treatment of atrial fibrillation. *Interact Cardiovasc Thorac Surg.* 2017 24(1):102-111 **Citation:** Geuzebroek GS et al. Totally thoracoscopic left atrial Maze: standardized, effective and safe. *Interact Cardiovasc Thorac Surg.* 2016 22(3):259-64 **Citation:** De Maat GE et al. Long-term results of surgical minimally invasive pulmonary vein isolation for paroxysmal lone atrial fibrillation. *Europace.* 2015 17(5):747-52.	
Atricure	5	3-4	**Treatment of persistent Afib with MIS hybrid surgical/catheter ablation may reduce stroke risk, mortality and be cost effective.** Surgical treatment for de novo persistent Afib with MIS surgical/catheter ablation **(hybrid)** has recently obtained a Class IIb treatment recommendation from the HRS. This procedure encompasses a multi-disciplinary approach where a surgeon and electrophysiologist work together. Recent studies on this approach have demonstrated restoration of normal sinus rhythm (clinically effective), a robust safety profile, and cost effectiveness. Cost effectiveness analysis demonstrated an	Thank you for your comments. The guideline committee will determine what interventions to include in the review protocol.

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			improved societal economic impact compared to medical management and catheter ablation over time, partly due to fewer repeat procedures and Afib related events. In addition, there are several multi centre trials underway to assess clinical effectiveness. **Citation**: HRS Guidelines: Calkins et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace*. 2018 20(1):e1-e160. **Citation:** Kress, DC, et al. Comparative Effectiveness of Hybrid Ablation Versus Endocardial Catheter Ablation Alone in Patients With Persistent Atrial Fibrillation. *JACC Clinical Electrophysiology* 2017; 3 (4) DOI: 10.1016/j.jacep.2016.10.010 **Citation:** Geršak, J, et al. Long-Term Success for the Convergent Atrial Fibrillation Procedure: 4-Year Outcomes. *Ann Thorac Surg*. 2016 102(5):1550-1557. **Citation:** Civello KC, et al. Combined Endocardial and Epicardial Ablation for Symptomatic Atrial Fibrillation: Single Center Experience in 100+ Consecutive Patients. *JICRM* 2013; 000: 1–7. **Citation**: Gehi et al. Hybrid epicardial-endocardial ablation using a pericardioscopic Technique for the treatment of atrial fibrillation. *Heart Rhythm* 2013; 10:22–28. **Citation:** CEA Anderson L, et al. Cost-effectiveness of the convergent procedure and catheter ablation for non-paroxysmal atrial fibrillation. *J Med Econ*. 2014 17(7):481-91	

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			Multi-Centre MIS Hybrid Ablation Trials: CONVERGE (ClinicalTrials.gov Identifier: NCT01984346), DEEP (ClinicalTrials.gov Identifier: NCT02393885), and CEASE (ClinicalTrials.gov Identifier: NCT02695277)	
Atricure	5	12	**Surgical management (epicardial occlusion) of the left atrial appendage (LAA) during concomitant open/minimal invasive cardiac surgery (CABG, valve, surgical ablation) may reduce stroke risk, including patients who present with Afib, or who have a high risk of developing Afib post cardiac surgery.** Patients with Afib have up to a 5x risk of stroke, with thrombi typically developing in the LAA. An **epicardial occlusion (AtriClip device) of the LAA** during a concomitant cardiac surgery has the potential to reduce the risk of thrombi and stroke. The average NHS and social care cost for each person that has a stroke is about £22,000 a year, and around £45,000 over five years (Royal College Physicians SSNAP). ***Occluding the LAA during concomitant cardiac surgery for Afib patients is quickly becoming a standard of care.*** Furthermore, as many as 30-40% of patients without Afib develop Afib post cardiac surgery resulting in an increased stroke risk. Treatment of these high-risk stroke patients in a prophylaxis manner may be warranted. There is some evidence that occluding the LAA may also provide electrical isolation of the LAA, reducing Afib incidence. Occluding the LAA during concomitant surgery is very cost effective as opposed to treating	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future. Data collected during the CtE scheme is considered alongside published data from research trials to inform the development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.

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			the patient later with a second procedure (percutaneous LAA, Watchman) or being left untreated and managing a future catastrophic stroke. Recent studies demonstrating stroke reduction risk following surgical epicardial occlusion of the LAA are included below. **Citation**: Yao X, et al. Association of Surgical Left Atrial Appendage Occlusion With Subsequent Stroke and Mortality Among Patients Undergoing Cardiac Surgery. *JAMA.* 2018 319(18):1889-1900. **Citation**: Friedman DJ, et al. Association Between Left Atrial Appendage Occlusion and Readmission for Thromboembolism Among Patients With Atrial Fibrillation Undergoing Concomitant Cardiac Surgery. *JAMA.* 2018 319(4):365-374. **Citation**: Elbadawi A, et al. Impact of Left Atrial Appendage Exclusion on Cardiovascular Outcomes in Patients With Atrial Fibrillation Undergoing Coronary Artery Bypass Grafting (From the National Inpatient Sample Database). *Am J Cardiol.* 2017 120(6):953-958 **Citation:** Park-Hansen J, et al. Adding left atrial appendage closure to open heart surgery provides protection from ischemic brain injury six years after surgery independently of atrial fibrillation history: the LAACS randomized study. *J Cardiothoracic Surg* (2018) 13:53 **Citation: AtriClip** Beaver T, et al. Thoracoscopic Ablation With Appendage Ligation Versus Medical Therapy for Stroke	

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			Prevention: A Proof-of-Concept Randomized Trial. *Innovations* 2016 11(2):99-105 **Citation: AtriClip** Caliskan E, et al. Epicardial left atrial appendage AtriClip occlusion reduces the incidence of stroke in patients with atrial fibrillation undergoing cardiac surgery. *Europace*. 2017 doi: 10.1093/europace/eux211. **Citation**: **AtriClip** Kurfirst V, Epicardial clip occlusion of the left atrial appendage during cardiac surgery provides optimal surgical results and long-term stability. *Interact Cardiovasc Thorac Surg*. 2017 25(1):37-40 **Citation: AtriClip** Ailawadi G, et al. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. *J Thorac Cardiovasc Surg.* 2011 142(5):1002-9. **Citation: AtriClip** Ellis, CR, et al. Angiographic Efficacy of the AtriClip Left Atrial Appendage Exclusion Device Placed by Minimally Invasive Thoracoscopic Approach. *JACC Clin Electrophysiol*. 2017 3(12):1356-1365.	
Atricure	5	12	**Minimally invasive sole therapy surgical management/epicardial occlusion (AtriClip) of the LAA may reduce stroke risk in patients who present with Afib, and may be recommended for those who are oral anti-coagulant (OAC) intolerant.** Many patients who are high risk for stroke may not be eligible for percutaneous LAA management (Watchman) due to OAC intolerance. OAC use is a post procedure recommendation for	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future. Data collected during the CtE scheme is considered alongside published data from research trials to

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			patients undergoing the Watchman procedure. In a recent study by Boersman et al. (*European Heart J*, 2016), only 38% of screened patients with Afib in the registry were deemed eligible for OAC. Patients ineligible for OAC have few treatment options to reduce stroke and mortality risk. For OAC intolerant patients, an alternative treatment option to mitigate risk is a minimal invasive thoracoscopic LAA/epicardial occlusion (**sole therapy**). Studies documenting clinical and safety benefit are below. **Citation**: **AtriClip** Acka F, et al. Is there an alternative treatment for patients intolerant to antiplatelet therapy if percutaneous left atrial appendage closure is considered? *Neth Heart J.* 2017 25(9):510-515 **Citation AtriClip:** Smith NE, et al. Initial Experience With Minimally Invasive Surgical Exclusion of the Left Atrial Appendage With an Epicardial Clip. *Innovations*. 2017 12(1):28-32. **Citation: AtriClip** Benussi S, et al. Thoracoscopic appendage exclusion with an atriclip device as a solo treatment for focal atrial tachycardia. *Circulation.* 2011 123(14):1575-8 **Citation:** Ohtsuka T, et al. Thoracoscopic stand-alone left atrial appendectomy for thromboembolism prevention in nonvalvular atrial fibrillation. *JACC* 2013 9;62(2):103-107 **Citation:** Blackshear JL, et al. Thoracoscopic extracardiac obliteration of the left atrial appendage for stroke risk reduction in atrial fibrillation. *JACC* 2003 42(7):1249-52.	inform the development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.

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Atricure	General	General	We would like to highlight that several surgical studies and speciality society Afib treatment guideline updates have been made since the last NICE update for Afib. STS, HRS, and the American Association Thoracic Surgery (AATS) have all made guideline updates and we encourage NICE to consider these speciality society recommendations as part of their analysis.	Thank you for your comment. We will use other guidelines to ensure we have sourced all relevant literature, but our recommendations are made based on the primary analysed evidence and discussions within the guideline committee.
Atricure	General	General	Based on recent multiple society guideline updates we recommend retiring IPG 122 and 184 that describe microwave and HIFU surgical treatment of Afib during cardiac surgery. Contemporary evidence from multiple society guidelines, including STS recommend CRYO and RF energy sources for ablation during cardiac surgery.	Thank you for your comment. We will use other guidelines to ensure we have sourced all relevant literature, but our recommendations are made based on the primary analysed evidence and discussions within the guideline committee.
Bayer plc	8 9	15-17 14-16	We understand that the guideline should not revisit areas already evaluated under the technology appraisal process. Technology appraisals have been published assessing the clinical and cost effectiveness of the DOACs (TA249, TA256, TA275 and TA355), all of which are recommended as options for preventing stroke and systemic embolism in selected adults with non‑valvular atrial fibrillation. Re-reviewing the evidence and carrying out further analyses for these anticoagulant therapies would be a duplication of effort and would represent a significant waste of public resources. We therefore suggest that these TAs should be incorporated unchanged in this guideline.	Thank you for your comment. Our aim is to use the technology appraisals, as well as any other evidence available, to decide on the best treatments to use.

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Bayer plc	8 9	15-17 14-16	In the UK there are four available DOACs approved for the treatment and prevention of thromboembolic disorders, including the thrombin (factor IIa) inhibitor dabigatran etexilate (*Pradaxa*)[1] and the three factor Xa inhibitors rivaroxaban (*Xarelto*),[2] apixaban (*Eliquis*)[3] & edoxaban (*Lixiana*).[4] However, although they share similar licensed indications, apart from rivaroxaban which has a broader range, there are clinically important factors which mean they cannot be considered interchangeable in the settings of initiation of, or switching between, DOAC treatment. For prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF), two of the DOACs (rivaroxaban & edoxaban) have once daily dosing regimens, and two of the DOACs (dabigatran & apixaban) have twice daily dosage regimens. Being able to select a DOAC with either a once or twice daily dosage regimen enables prescribers to align anticoagulation therapy with any other medications a patient may be receiving. Many patients with NVAF have multiple co-morbidities and polypharmacy is therefore very common. Aligning DOAC therapy patients' existing medication may improve adherence, an important consideration for DOACs as they should be taken regularly on a daily basis to maintain their therapeutic effect. All of the DOACs have both a standard & reduced dose, but there are significant differences in the requirements described in their	Thank you for your comment. Our analysis of the relevant evidence will consider all the available evidence, including the technology appraisals. We accept that the drugs may have different indications and so will ensure that any meta-analyses or network meta-analysis correctly take into account different population groups.

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			respective Summaries of Product Characteristics (SmPC), based on patients' clinical characteristics, that determine whether dosage reduction/ adjustment is required at treatment initiation or thereafter. Some DOACs have more complicated dosage recommendations than others requiring consideration of several factors, including patient status (age or weight), comorbidities (renal impairment), drug interactions, risk of bleeding or gastrointestinal symptoms. One of the DOACs, rivaroxaban, has only one consideration for dosage reduction, namely moderate-severe renal impairment, whereas all of the other DOACs require consideration of several patient factors which may or will definitely change over time. The multiple considerations for dosage reduction with the three other DOACs are: • body weight alone - edoxaban, or body weight in combination with age or serum creatinine - apixaban; • age alone - dabigatran, or age in combination with body weight or serum creatinine - apixaban; • specific drug interactions - dabigatran and edoxaban; • serum creatinine in combination with age or body weight - apixaban; • moderate renal impairment - dabigatran and edoxaban; • severe renal impairment - apixaban;	

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			• increased risk of bleeding or gastrointestinal symptoms - dabigatran. It is clear from the above that there are differences between the DOACs that require careful consideration of each patient's status and comorbidities, both at the time when a DOAC is first prescribed and with awareness that over time a patient's status and comorbidities may (e.g. weight, renal function) or will definitely (age) change. Another important practicality which differs between the DOACs is for patients who are unable to swallow whole tablets or for whom medicines have to be administered via a gastric tube. Only two DOACs, rivaroxaban & apixaban, have information in their SmPCs as to how the tablets can be crushed and suspended in water or another suitable vehicle. In addition to the differing considerations for dosage adjustment, before treatment initiation of some DOACs assessment of renal and/ or hepatic function is mandatory according to their respective SmPCs. For edoxaban this applies to both renal & liver function, for dabigatran this applies for renal function, and for apixaban this applies for liver function. For one DOAC alone, edoxaban, the SmPC also specifically recommends a careful evaluation of the individual thromboembolic and bleeding risk in patients with increasing	

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			creatinine clearance because a trend towards decreasing efficacy was observed compared to well-managed warfarin. Whilst all of the DOACs are licensed for prevention of stroke & systemic embolism in patients with NVAF, some DOACs have also been studied in NVAF patients in the setting of catheter ablation or cardioversion, or in patients with NVAF undergoing PCI (percutaneous coronary intervention) with stent placement, which has resulted in updates to the respective SmPCs. Catheter ablation is only included in the SmPC for dabigatran, whereas cardioversion is included in the SmPCs for all DOACs (rivaroxaban, edoxaban & apixaban can be initiated or continued in patients who may require cardioversion, whereas dabigatran can be continued but not initiated). For patients with NVAF undergoing PCI with stent placement only two DOACs, rivaroxaban and dabigatran, have information on this use in their respective SmPCs. Thus, there are differences in the breadth of the evidence base for the four DOACs in patients with NVAF, which along with the factors previously described - dosage adjustments according to patient characteristics, practicalities of administration & mandatory assessment before initiation - clearly demonstrate that dabigatran, rivaroxaban, apixaban and edoxaban are not interchangeable for treatment initiation or for switching between DOACs.	

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			There is one further important consideration which relates to the standard & reduced doses of the four DOACs, specifically whether they are being prescribed appropriately according to a correct interpretation of the dosing recommendations described in their respective SmPCs. Data for one of the DOACs, apixaban, shows that the proportion of the reduced dose compared to the standard dose differs considerably from the pivotal phase III ARISTOTLE study in NVAF. For example, data from Fay *et al.* 2016[5] based on prescribing by UK GPs for patients with NVAF demonstrated that the reduced dose of apixaban was prescribed for 36.3% of UK patients compared to 4.7% patients in ARISTOTLE, whereas a reduced dose of rivaroxaban was prescribed for 24.3% of UK patients compared to 20.7% in the pivotal phase III ROCKET-AF study in NVAF and a reduced dose of dabigatran was prescribed for 56.8% UK patients compared to 49.7% in the pivotal phase III RE-LY study in NVAF. No data on edoxaban prescribing in the UK was available at the time. The significance of appropriate dosing has been highlighted by Yao *et al*. 2017[6] who investigated DOAC dosing patterns and associated outcomes, i.e. stroke and major bleeding in patients treated in routine clinical practice using a large U.S. administrative database. They identified 14,865 AF patients with AF treated with apixaban, dabigatran, or rivaroxaban between 1/10/10 – 30/9/15. They examined potential overdosing with a	

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			standard dose in patients with a renal indication for dose reduction, and potential under-dosing with the use of a reduced dose when the renal indication was not present. Among 1,473 patients with a renal indication for dose reduction, 43.0% were potentially overdosed, which was associated with a higher risk of major bleeding (hazard ratio: 2.19; 95% confidence interval: 1.07 to 4.46) but no statistically significant difference in stroke (3 NOACs pooled). However, among the 13,392 patients with no renal indication for dose reduction, 13.3% were potentially under-dosed and in apixaban-treated patients this was associated with a higher risk of stroke (hazard ratio: 4.87; 95% confidence interval: 1.30 to 18.26) but no statistically significant difference in major bleeding. There were no statistically significant relationships in dabigatran- or rivaroxaban-treated patients. Thus, getting the right dose of a DOAC for the right patient is important in achieving the desired outcome of stroke prevention, and it appears from the Yao *et al* data that this is particularly important for apixaban. The EMA Pharmacovigilance Risk Assessment Committee (PRAC) has requested the marketing authorisation holder (MAH) of apixaban to perform a qualitative research study designed to understand prescribers' rationale behind dosing strategies in those situations where a lower dose of apixaban is prescribed without meeting SmPC dose reduction advice, and that the	

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			provision of the results should expedited if the results warrant an update of the product information. While there may be occasions when prescribers deliberately chose to use a different dose to that recommended in the SmPC, simplicity of the dosing recommendations described in the SmPC should facilitate selecting the right dose for the right patient. As described previously, for some DOACs there are multiple & changeable factors that need to be considered in dosage selection, whereas for one DOAC there is just a single consideration. Therefore for practical and patient safety purposes, all DOACs should remain available and certainly should not be considered interchangeable. (1) Boehringer Ingelheim Limited. Pradaxa 150 mg hard capsules, Summary of Product, 2018 Characteristics. Electronic Medicines Compendium. Available from: URL:https://www.medicines.org.uk/emc/product/4703/smpc (2) Bayer plc. Xarelto 20mg film-coated tablets, Summary of Product Characteristics, 2018. Electronic Medicines Compendium. Available from: https://www.medicines.org.uk/emc/product/2793/smpc (3) Bristol-Myers Squibb-Pfizer. Eliquis 5 mg film-coated tablets, Summary of Product Characteristics, 2018. Electronic	

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			Medicines Compendium. Available from: https://www.medicines.org.uk/emc/product/2878/smpc (4) Daiichi Sankyo UK Limited. Lixiana 60mg Film-Coated Tablets, Summary of Product Characteristics, 2017. Electronic Medicines Compendium. Available from: https://www.medicines.org.uk/emc/product/6905/smpc (5) Fay MR, Martins JL, Czekay B. Oral anticoagulant prescribing patterns for stroke prevention in atrial fibrillation among general practitioners and cardiologists in three European countries. ESC Congress 2016, Rome – Italy, 27 - 31 August. (6) Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. J Am Coll Cardiol 2017; 69(23):2779-2790.	
Bayer plc	9	14-16	In the absence of direct head to head data between the DOACS from prospective randomised clinical trials, and in view of the heterogeneity of the pivotal phase III studies underpinning the licensed indication for prevention of stroke/ systemic embolism in patients with NVAF, it is inappropriate to draw firm conclusions in relation to the relative benefits of the DOACs. Drawing conclusions about the relative efficacy & safety profiles of the individual DOACs from cross-trial comparison of the phase III studies will be potentially limited by a number of important factors. These include clinically significant differences in the patient populations recruited	Thank you for your comment. Our team will search for, and analyse, all the available literature in this area to produce an appropriate synthesis of the evidence.

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			into studies in terms of their stroke & bleeding risks; important differences in the definitions of stroke, major bleeding, and clinically relevant non-major bleeding; whether dose adjustment occurred at randomisation, or at any time in the trial or not at all; handling of the end of study transition period; and different treatment durations, all of which will affect the results. Please find reference to a publication which discusses these considerations in more detail.[1] Indeed, Bayer received expert advice from Kleijnen Systematic Reviews Ltd[2] in relation to the appropriateness of indirect comparisons specifically related to DOACs and key points are summarised below: An important part of network meta-analysis (NMA) is assessing the clinical heterogeneity of the included studies in terms of study design, treatments, patient characteristics etc. There should be no major differences between the studies in terms of treatment effect modifiers. Any major differences between included studies can limit the reliability of the NMA results. Kleijnen Systematic Reviews Ltd previously considered the appropriateness of a comparison between ROCKET-AF (rivaroxaban vs warfarin), RE-LY (dabigatran vs warfarin) and ARISTOTLE (apixaban vs warfarin) for Bayer and concluded that the trial ROCKET-AF cannot be combined with the other studies since it is dissimilar in baseline characteristics of the patients.	

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			Meta-regression (adjusting for baseline characteristics) can only be performed in a network analysis with at least 10 studies. This is referenced to the Cochrane Handbook section 8.8.4.1. Kleijnen Systematic Reviews Ltd therefore concluded that they would not be able to do such analyses on the pivotal studies alone but would need a wider network with at least 10 studies. (1) Camm, A.J. et al. Challenges in comparing the non-vitamin K antagonist oral anticoagulants for atrial fibrillation-related stroke prevention. Europace (2018) 20, 1–11 (2) Kleijnen Systematic Reviews Ltd. Professor Jos Kleijnen, Director of Kleijnen Systematic Reviews Ltd is a member of various steering groups and advisory committees related to systematic reviews and health technology assessment.	
Boehringer Ingelheim	3	10-11	The draft scope should include the use of anticoagulation to prevent periprocedural bleeding and stroke in patients undergoing catheter ablation of atrial fibrillation.	Thank you for your comment. We did not identify this as a high priority area to update as we are unaware of any evidence that will change current practice.
Boehringer Ingelheim	General	General	The draft scope does not specify whether real world evidence will be included, cf. Freedman, Lip (2016) for a discussion of RWE and RCT in the context of NVAF care using oral anticoagulation.  Freedman, B Lip G et al (2016).pdf	Thank you for your comment. When designing the protocols for each question the guideline committee will make a decision on the most appropriate study designs to include in the reviews.

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Boston Scientific	9	14	The surveillance report 2017 AF stated it would update the following evidence, "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?" This question has not been included for updates under section: Intervention to prevent stroke. We would kindly ask NICE to update this section as emphasised in the surveillance report.	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future. Data collected during the CtE scheme is considered alongside published data from research trials to inform the development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.
Boston Scientific	General	General	We are pleased that NICE is updating the management of Atrial Fibrillation (AF) to reflect the substantial growing body of evidence that supports a change in the management of patients with AF, providing better health outcomes and improvement in quality of life for these patients.	Thank you for your comment.
Boston Scientific	General	General	We would respectfully ask that NICE consider updating the systematic literature review as since the surveillance report was issued, other evidence has now become available, which provides relevant details on LAAO that was not included in the current search. Please see the following comments that summarise the findings of this evidence.	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future. Data collected during the CtE scheme is considered

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			Topic expert feedback indicated 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. We would like to highlight the findings of a systematic review including patient-level meta-analysis (that was not included in your systematic literature review) Holmes et al. "Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis." Journal of the American College of Cardiology 65.24 (2015): 2614-2623. This meta-analysis of the two WATCHMAN RCTs (PROTECT AF and PREVAIL), showed comparable efficacy for WATCHMAN and warfarin with no statistically significant difference in the rates of all cause stroke or systemic embolism. A significant reduction in haemorrhagic stroke was seen in favour of WATCHMAN (HR 0.22) as well as a reduction in major bleeding beyond seven days (HR 0.51) and a reduction in cardiovascular mortality (HR 0.48). We would kindly ask NICE to consider the review of this additional study in addressing areas of uncertainty concerning safety. The 5-Year outcomes paper was published in December 2017 in JAAC. Reddy et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. J Am Coll Cardiol. 2017 Dec 19;70(24):2964-2975. For the PREVAIL trial, the first composite coprimary endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve noninferiority (posterior probability for	alongside published data from research trials to inform the development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.

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			noninferiority = 88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve noninferiority (posterior probability for noninferiority = 97.5%); the warfarin arm maintained an unusually low ischemic stroke rate (0.73%). In the meta-analysis, the composite endpoint was similar between groups (hazard ratio [HR]: 0.820; p = 0.27), as were all-stroke/SE (HR: 0.961; p = 0.87). The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did not reach statistical significance (HR: 1.71; p = 0.080). However, differences in haemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAAC (HR: 0.20; p = 0.0022; HR: 0.45; p = 0.03; HR: 0.59; p = 0.027; HR: 0.73; p = 0.035; HR: 0.48; p = 0.0003, respectively). These 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial, demonstrate that LAAC with Watchman provides stroke prevention in nonvalvular atrial fibrillation comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality. We would like to kindly ask NICE to consider including this study within the evidence review.	
Boston Scientific	General	General	Sahay S, Nombela L. Efficacy and safety of left atrial appendage closure versus medical treatment in atrial fibrillation: a network metaanalysis from randomised trials. Heart. 2016;103:139.	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new

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			A network meta-analysis of 19 randomized controlled trials with a total 87 831 patients evaluated the safety and efficacy of LAAO with the Watchman device versus indirect comparison to Novel Oral Anticoagulation (NOAC), antiplatelet therapy (APT), placebo, and vitamin K antagonist (VKA). Indirect comparison using warfarin as the common comparator showed efficacy benefit favoring LAAC as compared with placebo (mortality: HR 0.38, P < 0.001; stroke/SE: HR 0.24, P < 0.001 and APT (mortality: HR 0.58, P = 0.0018; stroke/SE: HR 0.44, P = 0.017), and similar to NOAC (mortality: HR 0.76, P = 0.211; stroke/SE: HR 1.01, P = 0.969). LAAC showed similar rates of major bleeding when compared with placebo (HR 2.33, P = 0.183), APT (HR 0.75, P = 0.542), and NOAC (HR 0.80, P = 0.615). In direct comparisons of LAAC versus VKA, LAAC showed a trend toward lower mortality (OR 0.68, CI 0.45-1.02) and no difference in stroke or SE (OR 0.84, CI 0.48-1.49). Koifman E, Lipinski MJ, Escarcega RO, et al. Comparison of Watchman device with new oral anti-coagulants in patients with atrial fibrillation: a network meta-analysis. Int J Cardiol. 2015;205:17–22. Network meta-analysis of 14 studies with 246 005 patients compared warfarin, NOACs, and Watchman. Both NOACs and Watchman were superior to warfarin in reducing the risk for hemorrhagic strokes (OR 0.46 for NOACs, and OR 0.21 for Watchman).	clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future. Data collected during the CtE scheme is considered alongside published data from research trials to inform the development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.

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			These meta-analyses differ on the basis that the former found LAAO and NOAC comparable in outcomes of death, stroke prevention, and bleeding risks while the latter that concluded that the Watchman device trended toward greater risk of ischemic stroke but revealed significant reduction of hemorrhagic stroke with LAAO when compared with NOAC. Note : Like warfarin, persistence with NOACs is a barrier to achieving optimal stroke prevention in patients with AF. Similarly to warfarin, some patients are contraindicated to treatment with any of the NOACs, with the risk of bleeding of the NOACs being similar to that of warfarin We would like to respectfully ask for NICE to consider including the following relevant publications in the systematic literature review: Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Pokushalov E, Kische S, Schmitz T, Stein KM, Bergmann MW; EWOLUTION investigators. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. Eur Heart J. 2016;37(31):2465-74 Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, Gori T, Meincke F, Protopopov AV, Betts T, Foley D, Sievert H, Mazzone P, De Potter T, Vireca E, Stein K, Bergmann MW, for the EWOLUTION investigators, Efficacy and Safety of Left Atrial Appendage Closure with WATCHMAN in Patients with or without Contraindication to Oral Anticoagulation: 1-year follow-	

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			up outcome data of the EWOLUTION trial, Heart Rhythm 2017;14:1302–1308	
Boston Scientific	General	General	Reddy VY, Gibson DN, Kar S, et al. Post-approval US experience with left atrial appendage closure for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2017;69:253–261. In addition, the surveillance report did not include any study on the cost effectiveness of LAAO. We would kindly ask the committee to include the following available evidence that reviews the cost-effectiveness of LAAO compared with different standards of care: • Amarosi et al 2015, The budget impact of left atrial appendage closure compared with adjusted-dose warfarin and dabigatran etexilate for stroke prevention in atrial fibrillation • Reddy et al 2016, Cost effectiveness of left atrial appendage closure with the Watchman device for atrial fibrillation patients with absolute contraindications to warfarin • Panniker et al 2016, Outcomes and costs of left atrial appendage closure from randomized controlled trial and real-world experience relative to oral anticoagulation	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future. Data collected during the CtE scheme is considered alongside published data from research trials to inform the development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.

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			• Ont Health Technol Assessment 2017, Outcomes and costs of left atrial appendage closure from randomized controlled trial and real-world experience relative to oral anticoagulation	
Boston Scientific	General	General	We would also like to bring to NICE's attention a review conducted by NHSE titled Evidence review: Clinical and Cost- Effectiveness and Adverse Events Associated with Left Atrial Appendage Occlusion in Patients for Whom Anticoagulation Therapy is Contraindicated. This document reviewed articles that we believe NICE may have missed in the systematic literature review of the evidence above.	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future. Data collected during the CtE scheme is considered alongside published data from research trials to inform the development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.
Boston Scientific	General	General	We are pleased to see that NICE will be updating this section of the guidance to reflect the advance in pharmaceutical and medical interventions in the management of AF Regarding Rate and Rhythm control: 4.1 What is the clinical and cost effectiveness of ablative therapy comparted to non-ablative therapies in people with Atrial fibrillation? We would like NICE to kindly consider inclusion of the following evidence that was not included in the systematic literature review of the evidence:	Thank you. The evidence we include will be based on the protocol designed by the guideline committee. The first evidence you cite appears to be an RCT protocol and not a study report, and so will not be included in the review.

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			• Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Moretz K, Poole JE, Mascette A, Rosenberg Y, Jeffries N, Al-Khalidi HR, Lee KL. Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial: Study Rationale and Design. Am Heart J. 2018; 199: 192-9. Mansour M, Heist EK, Agarwal R, Bunch TJ, Karst E, Ruskin JN, Mahapatra S. Stroke and Cardiovascular Events After Ablation or Antiarrhythmic Drugs for Treatment of Patients With Atrial Fibrillation. Am J Cardiol. 2018	
Boston Scientific	General	General	Regarding 4.2. Which ablative technique is the most clinically and cost-effective therapy in people with atrial fibrillation? Kindly consider inclusion of the following evidence that was not included in NICE systematic literature review of the evidence: • Chun KRJ, Brugada J, Elvan A, Geller L, Busch M, Barrera A, Schilling RJ, Reynolds MR, Hokanson RB, Holbrook R, Brown B, Schluter M, Kuck KH. The Impact of Cryoballoon Versus Radiofrequency Ablation for Paroxysmal Atrial Fibrillation on Healthcare Utilization and Costs: An Economic Analysis From the FIRE AND ICE Trial. J Am Heart Assoc. 2017; 6 (8)	Thank you. The evidence we include will be based on the protocol designed by the guideline committee. We have noted your references.

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			• Yokokawa M, Chugh A, Latchamsetty R, Ghanbari H, Crawford T, Jongnarangsin K, Cunnane R, Saeed M, Hornsby K, Krishnasamy K, Lohawijarn W, Keast R, Karpenko D, Bogun F, Pelosi F, Jr., Morady F, Oral H. **Ablation of paroxysmal atrial fibrillation using a 2nd generation cryoballoon catheter or contact-force sensing radiofrequency ablation catheter: A comparison of costs and long-term clinical outcomes**. ***J Cardiovasc Electrophysiol.*** 2017 • Baykaner T, Duff S, Hasegawa JT, Mafilios MS, Turakhia MP. Cost effectiveness of focal impulse and rotor modulation guided ablation added to pulmonary vein isolation for atrial fibrillation. J Cardiovasc Electrophysiol. 2018: • Barnow A, Goldstein L, Kalsekar I, Liao R, Khanna R. Use of the THERMOCOOL SMARTTOUCH catheter for ablation of atrial fibrillation: the relationship between hospital procedure volume, re-admissions, and economic outcomes. J Med Econ. 2018 • Martin CA, Curtain JP, Gajendragadkar PR, Begley DA, Fynn SP, Grace AA, Heck PM, Salaunkey K, Virdee MS, Agarwal S. Improved outcome and cost effectiveness in	

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			ablation of persistent atrial fibrillation under general anaesthetic. Europace. 2017 • Allan KS, Henry S, Aves T, Banfield L, Victor JC, Dorian P, Healey JS, Andrade J, Carroll S, McGillion M. Comparison of health-related quality of life in patients with atrial fibrillation treated with catheter ablation or antiarrhythmic drug therapy: a systematic review and meta-analysis protocol. BMJ Open. 2017; 7 (8) • Rottner, L., Metzner, A., Ouyang, F., Heeger, C., Hayashi, K., Fink, T., Lemes, C., Mathew, S., Maurer, T., B, R. E., Rexha, E., Riedl, J., Saguner, A. M., Santoro, F., Kuck, K. H. and Sohns, C. Direct Comparison of Point-by-Point and Rapid Ultra-High-Resolution Electroanatomical Mapping in Patients Scheduled for Ablation of Atrial Fibrillation. J Cardiovasc Electrophysiol. 2017; 28 (3): 289-297. • Segerson NM, Lynch B, Mozes J, Marks MM, Noonan DK, Gordon D, Jais P, Daccarett M, High Density Mapping and Ablation of Concealed Low Voltage Activity Within Pulmonary Vein Antra Results in Improved Freedom from Atrial Fibrillation Compared to Pulmonary	

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			Vein Isolation Alone, Heart Rhythm (2018), doi: 10.1016/j.hrthm.2018.04.035. • Garcia-Bolao I, Ballesteros G, Ramos P, Menendez D, Erkiaga A, Neglia R, et al. Identification of pulmonary vein reconnection gaps with high-density mapping in redo atrial fibrillation ablation procedures. Europace. 2017	
Boston Scientific	General	General	Regarding section 6: Prevention and management of postoperative atrial fibrillation: 6.2.We would ask NICE to consider including: • Nashef SAM, Fynn S, Abu-Omar Y, Spyt TJ, Mills C, Everett CC, Fox-Rushby J, Singh J, Dalrymple-Hay M, Sudarshan C, Codispoti M, Braidley P, Wells FC, Sharples LD. Amaze: a randomized controlled trial of adjunct surgery for atrial fibrillation. Eur J Cardiothorac Surg. 2018	Thank you for your comment. The evidence we include will be based on the protocol designed by the guideline committee. We have noted your reference.
Boston Scientific	General	General	Regarding section 5, Preventing of recurrence of atrial fibrillation please consider including: • Mansour M[1], Karst E[2], Heist EK[3], Dalal N[4], Wasfy JH[3], Packer DL[4], Calkins H[5], Ruskin JN[3], Mahapatra S[6].The Impact of First Procedure Success Rate on the Economics of Atrial Fibrillation Ablation. JACC Clin Electrophysiol. 2017 Feb;3(2):129-138. doi: 10.1016/j.jacep.2016.06.002. Epub 2016 Aug 3.	Thank you for your comment. The evidence we include will be based on the protocol that is designed by the guideline committee. We have noted your references.

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			Yin G, Xie R, You L, Yin H, Sun Y, Wu J, Zhao Y, Geng X, Zhang Y. Left atrial function, inflammation, and prothrombotic response after radiofrequency ablation for atrial fibrillation. J Chin Med Assoc. 2018	
Boston Scientific	General	General	Regarding 4.2. Which ablative technique is the most clinically and cost-effective therapy in people with atrial fibrillation? Kindly consider inclusion of the following evidence that was not included in NICE systematic literature review of the evidence: Conte G, Soejima K, de Asmundis C, Chierchia GB, Badini M, Miwa Y, Caputo ML, Özkartal T, Maffessanti F, Sieira J, Degreef Y, Stroker E, Regoli F, Moccetti T, Brugada P, Auricchio A. Value of high-resolution mapping in optimizing cryoballoon ablation of atrial fibrillation. Int J Cardiol. 2018 Jun 1	Thank you for your comment. The evidence we include will be based on the protocol designed by the guideline committee. We have noted your reference.
Bristol-Myers Squibb Ltd. and Pfizer Ltd.	9	4	**Diagnosis and assessment** We agree that the most accurate, clinically and cost-effective screening strategies, potentially including wearable technologies, need to be identified to help improve diagnosis and outcomes of patients with atrial fibrillation/flutter (AF/F). Paroxysmal AF/F is particularly difficult to detect, and we support the development of guidance on longer-term monitoring to improve patient identification and outcomes in this cohort.	Thank you for your comment.
Bristol-Myers Squibb Ltd. and Pfizer Ltd.	9	8	**Assessment of stroke and bleeding risks** We support the evaluation of evidence to identify the most clinically and cost-effective risk stratification tools for both	Thank you for your comment. We aim to incorporate all validated tools so your information is useful.

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Stakeholder comments table

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Stakeholder	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			stroke/thromboembolic and bleeding risks in patients with atrial fibrillation. Guidance will be valuable to the NHS on the application of tools including the GARFIELD-AF prediction tool and the SAMe-TT_2R_2 score, in addition to the more established CHA_2DS_2-VASc and HASBLED.	
Bristol-Myers Squibb Ltd. and Pfizer Ltd.	9	14	**Interventions to prevent stroke** We believe that the question, '*What is the most clinically and cost-effective anticoagulant therapy for stroke prevention in people with atrial fibrillation*?' is directly addressed by the recent NIHR-sponsored study carried out by Lopez-Lopez *et al* (BMJ 2017)[1], '*Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis*'. Recommendations for each direct oral anticoagulant (DOAC) should be included in the guideline as per the licence and NICE Technology Appraisal guidance for each. In the absence of head-to-head randomised trials, the Lopez-Lopez comparative evaluation[1] by the University of Bristol provides robust, independent and practical guidance to support physicians on the value of each DOAC and warfarin. This study shows some clinical and economic differences between the DOACs and warfarin in AF, and provides evidence to guide prescribers and policy-makers on the most effective interventions to prevent AF-stroke.	Thank you for your comment. We will carry out a complete search of the literature to ensure all current evidence is included in the review for consideration by the guideline committee. We have noted this reference to aid the literature search.

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			In addition, there is a growing body of real-world evidence directly comparing the DOACs (e.g., Noseworthy PA *et al*[2]). Warfarin remains the mainstay of AF management. Despite existing NICE AF guideline recommendations (current CG180), many clinicians believe that assessing a patient's time in therapeutic range (TTR) is sufficient to monitor how effectively the patient is protected from stroke and/or bleeding events. We believe it is important for this guideline to be emphasising that patients can be inadequately controlled despite having a TTR within range (e.g., infrequent INR above 8 or below 2), that these patients are at an increased risk of stroke/bleeding, and that alternative anticoagulation should be considered.	
Bristol-Myers Squibb Ltd. and Pfizer Ltd.	General	General	***References*** 1 Lopez-Lopez JA, *et al*. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017;**359**:j5058 2 Noseworthy PA *et al*. Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Non-valvular Atrial Fibrillation. Chest 2016;**150(6)**:1302-12	Thank you for these references, which will help us ensure that review question searches are detecting the appropriate papers.
British Acupuncture Council	General	General	Are you going to consider the acupuncture evidence in respect of managing atrial fibrillation? There have been a number of randomised controlled trials and at least one meta-analysis (in English)	Thank you for your comment. This is an update of the guideline. The surveillance review of the guideline did not identify this as a priority area for update..

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British Association of Stroke Physicians	General	General	BASP welcomes this review of management of Atrial Fibrillation. There is underdiagnosis of atrial fibrillation in cryptogenic stroke and treatment with anticoagulation would prevent strokes, reduce co-morbidity and death and reduce costs to the NHS. The best method for detecting AF in cryptogenic stroke is unclear and BASP would recommend including this in the scope of the review.	Thank you for your comment. Detection of AF in cryptogenic stroke is not included in this update because this is being covered by a NICE diagnostic guideline (in development) 'Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke'.
British Cardiovascular Society	General	General	The British Cardiac Society has reviewed the Guideline scope for Atrial fibrillation: management (update). We agree that in view of the importance of AF with regard to its clinical impact and that the fact there is considerable new research since the last guidance was published (CG180) that the guidance should be updated. We have reviewed the suggested scope for the guideline development group and we are content that it covers all the main areas that need addressing.	Thank you for your comment.
British Heart Rhythm Society	General	General	When is Af no longer considered a diagnosis attributable to the patient? This is asked by primary care members and nurses who have many queries from patients and colleagues regarding a patient who has reached 65, has hypertension and has had one episode of documented AF in their 30s or 40s and none since, but according to guidelines should be anticoagulated. Clarification of this would be helpful	Thank you for your comment. We have added a question on 'What is the clinical and cost effectiveness of discontinuing anticoagulation in people following ablation or spontaneous resolution of atrial fibrillation?'
British Heart Rhythm Society	General	General	Guidance on the utility and accuracy of single lead ECG's to diagnose AF, a commonly used technology in primary care and in the view of BHRS very useful.	Thank you for your comment. This will be included under 'diagnosis and assessment'

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British Heart Rhythm Society	General	General	Guidance on the impact of AF ablation on stroke and mortality. Is there any evidence of prognostic benefit? CABANA will publish its results soon and other trials may also complete during the review period	Thank you for your comment. We will be looking at 'What is the clinical and cost effectiveness of different ablative therapy compared to and non-ablative therapies in people with atrial fibrillation? We have noted the trial you refer to.
British Heart Rhythm Society	General	General	Guidance on the role of AF ablation in heart failure patients. Multiple trials have now published since the last guidance and this is an important issue affecting significant numbers of patients.	Thank you for your comment. This population will be included
Daiichi-Sankyo	3	4	The inclusion of Edoxaban as a treatment option (since the previous CG180 was published in 2014 prior to TA355).	Thank you for your comment. We refer to the relevant technology appraisal in the scope.
Daiichi-Sankyo	General	General	To include the comment, if more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.	Thank you for your comment. Both the clinical and cost effectiveness will be considered for each review question.
Johnson & Johnson Medical Ltd.	6	10	Agree with decision to exclude LAO from the scope of this guideline update. Already covered by NHS England evaluations with funding decision in progress.	Thank you for this comment.
Johnson & Johnson Medical Ltd.	9	17	For rate and rhythm control, we feel strongly that the most pertinent questions for NICE to focus its resource and address by this clinical guideline is the effectiveness of non-drug therapy vs drug therapy, and all ablation vs drug therapy. In the UK, only 4% of patients with AF are currently referred for ablation, which is small proportion despite the published evidence supporting the clinical effectiveness of all ablation therapies, and recent publications showing the benefit of ablation over drug therapy. As a result of the limited referrals for ablation techniques, a	Thank you for your comment. We have now amended the two questions of rate and rhythm control to form one larger question. This will compare all pharmacological and non-pharmacological approaches together. Thus this will permit drug vs drug, non-drug vs non-drug and drug vs non-drug. This will involve many head to head permutations and so will possibly require the use of a network meta-analysis. We will not cover your third suggested question, as that is a research methodology question and outside the scope of this guideline.

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			significant number of patients are not getting access to clinically and cost effective ablation technology to not only manage, but cure their AF. Furthermore, an area of debate currently is the appropriate time period to determine the effectiveness of treatment. New data are driving a longer-term view, rather than short term management. Finally, we consider that the choice of specific ablation technique should be a clinically led decision by the electrophysiologist based on the needs of that patient. We therefore propose that the rate and rhythm control review questions are edited as follows to focus this guideline on the areas we believe will most benefit patients and the NHS What is the clinical outcome and cost effectiveness of non-pharmacological (cardioversion-acute care) vs pharmacological (ADDs-long term care)? What is the clinical outcome and cost effectiveness of intervention (ablation) vs pharmacological (ADDs -long term care)? What is the correct time period to re-assess the effectiveness of the treatment?	
Johnson & Johnson Medical Ltd.	9	17	When answering the rate and rhythm control questions, we specifically request that NICE pays careful consideration to the time horizon applied. Freedom of AF at 12-months would be an	Thank you for your comment. We have listed the main outcomes in the scope. The guideline committee will determine the specific outcomes for each evidence review.

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			appropriate minimum clinical endpoint when considering the comparative clinical effectiveness of ablation technologies.	
Johnson & Johnson Medical Ltd.	10	1	Main outcomes to be added to the NICE scope list when searching for and assessing the evidence should also include freedom of AF at 12months as a minimum, usually measured in clinical evidence to prove efficacy of treatment of AF.	Thank you for your comment. Thank you for your comment. We have listed the main outcomes in the scope. The guideline committee will determine the specific outcomes for each evidence review.
Johnson & Johnson Medical Ltd.	10	1	Main outcomes to be added to the NICE scope list when searching for and assessing the evidence should also include reduction in medication burden to capture the resource impact of ablative technologies on the NHS and the effectiveness of treatments for patients.	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions.
Johnson & Johnson Medical Ltd.	10	1	Adverse events associated with ablation technologies and also drug therapies should be captured as key outcomes because of the significant resource and patient impact.	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions.
Johnson & Johnson Medical Ltd.	10	1	We request that re-do ablation be included as a key outcome when considering the clinical and cost effectiveness of ablative technologies because of the NHS resource use and impact for patients associated with repeat ablation. Furthermore, re-do ablation should be defined specifically as a complication following primary ablation for AF, and not as an accepted outcome/occurrence for the patient.	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions.

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Johnson & Johnson Medical Ltd.	10	1	NICE should differentiate between cardiovascular death vs all-cause mortality when reviewing the clinical evidence on AF treatments. These are clinically differentiated end-points and data should not be pooled to lose the impact of treatment.	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions. With reference to your specific point, any mortality that is not related to treatment will be comparable between randomised groups and so will cancel out – therefore the impact of treatment will not be greatly affected.
Johnson & Johnson Medical Ltd.	10	4	Health related quality of life scoring tools are inadequate for AF because they do not correctly or sufficiently capture the symptoms a patient experiences. Therefore, to capture the main patient outcomes the following should specifically be included: -shortness of breath -palpitations -impact on physical activity	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions.
Medtronic	4	17-24	Section 3.1 "Groups that will be covered". In the draft scope, only patients who have been detected with AF are included: "Adults 18 and over with AF to include: • new onset or acute atrial fibrillation, chronic atrial fibrillation, including paroxysmal (recurrent), persistent or permanent postoperative atrial fibrillation, atrial flutter	Thank you for this comment. We have added 'people with suspected AF' to ' groups that will be covered' . Cryptogenic stroke will be covered by a NICE diagnostics guideline and therefore it won't be covered here. The scope has been amended to reflect this.

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			However, in the "key issue and questions" on page 9, line numbers 3-7, "Diagnosis and Assessment" is for patients who are presenting with symptoms but are yet to have AF detected and these people are not included in the section "groups that will be covered" Additionally, on page 3, lines 20 – 23 references are made to the importance of detection of AF in patients who have cryptogenic stroke and how insertable cardiac monitors are a new and useful tool for detection of AF for this group of patients. However these people are not included in the section "groups that will be covered". We therefore suggest in section 3.1 the following are added: • People with pulse irregularities People with cryptogenic stroke	
Medtronic	6	Table	"Area of Care" "Diagnosis and Assessment. In the box "What Nice Plans to do" the review of the evidence for detecting AF in people with cryptogenic stroke is missing. On page 3, lines 20 – 23 references are made to the importance of detection of AF in patients who have cryptogenic stroke and how insertable cardiac monitors are a new and useful method for detection of AF for this group of patients. We suggest the following is added into the table for "Diagnosis and Assessment":	Thank you for your comment. We have removed the reference to people with cryptogenic stroke from page 3 lines 20-23, as this group will not be covered in the guideline. The reason is that this is being covered by a NICE diagnostic guideline (in development) 'Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke'.

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			• Review evidence on the detection of AF in people with cryptogenic stroke	
Medtronic	7	General	We would like to highlight "NICE MIB 151 Reveal Linq insertable cardiac monitor to detect AF after cryptogenic stroke" and request it's added to the list of related NICE publications	Thank you for your comment. This has been added.
Medtronic	9	18	Section 4.1. We would like to highlight recent data presented at the Heart Rhythm Society meeting in the US from the study Catheter Ablation versus Antiarrhythmic Drug Therapy in Atrial Fibrillation Trial in order it can be included in the evidence review	Thank you for your comment. All relevant evidence will be picked up and analysed in the evidence reviews. We have noted your reference.
Medtronic	9	20	Section 4.2. We would like to highlight the following publications of the data from the FIRE and ICE Trial so they may be included in the evidence review. Primary results were published in *The New England Journal of Medicine* and showed comparable safety and effectiveness of cryoballoon ablation and RF catheter ablation[1]. In a health economic analysis published in the Journal of the American Heart Association[2] the data show that treating paroxysmal atrial fibrillation (AF) with cryoballoon catheter ablation may result in substantial cost savings as compared to radiofrequency (RF) ablation. These findings were driven by fewer repeat ablations and cardiovascular (CV) rehospitalizations in patients treated with the cryoballoon and were consistently observed in multiple healthcare systems internationally included in the analysis.	Thank you for your comment. All relevant evidence will be picked up and analysed in the evidence reviews. We have noted your reference.

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			Secondary analyses, which demonstrated significantly fewer repeat ablations and lower cardiovascular hospitalization rates with cryoablation, were published in the *European Heart Journal*[3]. • [1]Kuck et al, Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation, N Engl J Med 2016; 374:2235-2245 June 9, 2016 DOI: 10.1056/NEJMoa1602014 • [2]Chun et al, The Impact of Cryoballoon Versus Radiofrequency Ablation for Paroxysmal Atrial Fibrillation on Healthcare Utilization and Costs: An Economic Analysis from the FIRE AND ICE Trial, Journal of the American Heart Association. 2017;6:e006043 • [3]Kuck et al, The Impact of Cryoballoon Versus Radiofrequency Ablation for Paroxysmal Atrial Fibrillation on Healthcare Utilization and Costs: An Economic Analysis From the FIRE AND ICE Trial, . Eur Heart J (2016) ehw285 DOI: http://dx.doi.org/10.1093/eurheartj/ehw285 First published online: 5th July 2016	

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Medtronic	9	21	We would like to highlight the results of the study Catheter Ablation versus standard conventional treatment in patients with Left ventricular dysfunction and Atrial Fibrillation (reference below). We propose the Key Issues and Draft Questions (section 4 on Rate and Rhythm Control) be expanded with an additional question to examine the effectiveness and cost-effectiveness of catheter ablation in patients with atrial fibrillation and heart failure. These are common co-existing conditions, however, current clinical guidelines do not provide clear consensus recommendations regarding the best management approach for these patients, and it may be appropriate to change this situation now that a randomized controlled trial with patient-relevant hard endpoints has been published. Accordingly, we requestthis publication to be included in the evidence review Marrouche et al, Catheter Ablation versus standard conventional treatment in patients with Left ventricular dysfunction and Atrial Fibrillation, N Engl J Med 2018; 378:417-427	Thank you for your comment. All relevant evidence will be picked up and analysed in the evidence reviews. We have noted your reference. We will stratify meta-analyses for different population groups (such as people with HF) where we think that this will make a difference to the effect. Such covariables will be discussed in detail by the guideline committee prior to starting the review.
Medtronic	9	3-7	Section 3.5 "Key Issues and draft questions" there is no question to review the evidence of different monitoring strategies to detect AF in people with cryptogenic stroke. We suggest the following question is added:	Thank you for your comment. Cardiac monitoring in people with crytogenic stroke is being covered by a NICE diagnostic guideline (in development) 'Reveal LINQ insertable cardiac monitor to detect atrial fibrillation after cryptogenic stroke'. We have added this to the list of related NICE guidance in the scope.

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			• "What is the most clinically and cost-effective method of different cardiac monitoring strategies to detect AF in people with cryptogenic stroke?"	
Medtronic	General	General	"Diagnosis and Assessment". We would like to highlight recent evidence for people with suspected paroxysmal AF undetected by standard ECG recording. Currently the guidance for those with symptomatic episodes more than 24 hours apart. [2006] is to use an event recorder. This new evidence supports an update of the guidelines and we suggest the following is added: • "For people with suspected paroxysmal AF undetected by standard ecg recording or an event recorder, consider using an insertable cardiac monitor" We refer to the following publications to support this statement: • Nasir et al, Predicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for Thromboembolic Events (PREDATE AF) Study Heart Rhythm. 2017 Jul;14(7):955-961 • Reiffel et al, A comparison of atrial fibrillation monitoring strategies in patients at high risk for atrial fibrillation and stroke: results from the REVEAL AF. Volume 71, Issue	Thank you for your comment. We have edited the review question on diagnosis and assessment to make it clearer that we are including paroxysmal AF. We have noted your references.

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			11 Supplement, March 2018DOI: 10.1016/S0735-1097(18)30815-5	
Medtronic	General	General	"Diagnosis and Assessment". We would like to highlight the growing evidence base on device-detected asymptomatic AF episodes captured by implantable cardiac devices. The poor correlation of symptoms and underlying abnormal rhythms was investigated in early studies[1], and it was already known that intermittent monitoring would miss most episodes[2]. AF detected by implantable cardiac devices, that were implanted for other reasons, may be associated with important clinical sequalae[3,4] and, thus, may warrant pointed effort to identify if it occurs and afterwards specific additional management. This was recognized in recent consensus papers[5]. • [1]Arya et al. Clinical implications of various follow up strategies after catheter ablation of atrial fibrillation. Pacing Clin Electrophysiol. 2007 Apr;30(4):458-62. • [2]Ziegler et al. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. Heart Rhythm. 2006 Dec;3(12):1445-52. Epub 2006 Aug 3. • [3]Healey et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012 Jan 12;366(2):120-9. doi: 10.1056/NEJMoa1105575. • [4]Wong et al. Progression of Device-Detected Subclinical Atrial Fibrillation and the Risk of Heart Failure. J Am Coll	Thank you for your comments. This was not identified by the surveillance review as a priority area to update.

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			Cardiol. 2018 Jun 12;71(23):2603-2611. doi: 10.1016/j.jacc.2018.03.519. [5]Gorenek et al. Device-detected subclinical atrial tachyarrhythmias: definition, implications and management-an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace. 2017 Sep 1;19(9):1556-1578. doi: 10.1093/europace/eux163.	
Medtronic	General	General	Medtronic proposes the addition of a section on AF detection and management in special populations, specifically patients implanted with cardiac devices. The following evidence are available to support recommendations for patients implanted with cardiac devices: • use of enhanced pacing modalities for patients with bradycardia can slow the progression of AF. The results of the MINERVA (MINimizE Right Ventricular pacing to prevent Atrial fibrillation and heart failure) randomized trial showed that pacemakers with atrial antitachycardia pacing (Reactive ATP), managed ventricular pacing (MVP®) and atrial intervention features were able to significantly decrease the incidence of mortality, cardiovascular hospitalizations or permanent AF at two years compared to pacemakers without these features.	Thank you for your comments. No new evidence that could potentially change recommendations were identified in the guideline surveillance review on these areas.

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			The effects of these features were most evident by a significant delay in the progression of atrial tachyarrhythmias to permanent AF, with a 61 percent relative risk reduction at two years. • Furthermore, in a real-world analysis of a cardiac device remote monitoring dataset, Reactive ATP slowed AF progression over 2 years across pacemakers, ICD and CRT devices: 21% relative risk reduction in AF episodes ≥ 1 day; 40% relative risk reduction in AF episodes ≥ 7 days; 49% relative risk reduction in AF episodes ≥ 30 days. Reactive ATP effects were independent to device type. • Continuous optimization of cardiac resynchronization therapy (CRT) reduces atrial fibrillation in heart failure patients. The Adaptive CRT randomized trial in patients implanted with CRT devices found that patients treated with a new device algorithm called Adaptive CRT had a reduced risk of AF compared with those receiving conventional CRT devices. Further analysis of the same trial found that AF-related healthcare utilization was lower in patients treated with the Adaptive CRT algorithm compared to conventional CRT devices. • Effective CRT combines algorithms to identify situations where pacing delivery does not result in enhanced myocardial contractility[1]; and, when the reason for this	

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			"ineffective" pacing is AF, increase effective pacing during AF[2]. [1]Hernandez-Madrid A et al. Device pacing diagnostics overestimate effective cardiac resynchronization therapy pacing results of the hOLter for Efficacy analysis of CRT (OLÉ CRT) study. Heart Rhythm. 2017 Apr;14(4):541-547. doi: 10.1016/j.hrthm.2017.01.022. Epub 2017 Jan 17. [2]Plummer CJ et al. A novel algorithm increases the delivery of effective cardiac resynchronization therapy during atrial fibrillation: The CRTee randomized crossover trial. Heart Rhythm. 2018 Mar;15(3):369-375. doi: 10.1016/j.hrthm.2017.10.026. Epub 2017 Nov 11.	
NHS Leeds Clinical Commissioning Group	4	14	*'3.1 What is the most clinically and cost-effective anticoagulant therapy 15 for stroke prevention in people with atrial fibrillation'* Consideration of patient choice in joint decision making prior to commencement of therapy will influence cost effectiveness. What are the review criteria (including time interval) for consideration of review of therapy including both clinical and cost effectiveness criteria	Thank you for your comments. We agree that patient choice is an integral part of good practice and will be considered throughout the development of the guideline. No new evidence on review was identified by the guideline surveillance report and it is therefore not included in this update.
NHS Leeds Clinical Commissioning Group	5	9	*Diagnosis and assessment: presenting symptoms and pulse assessment 4* *1.1 What is the most accurate method for detecting pulse irregularities in 5 people with symptoms suggestive of atrial fibrillation and in people with 6 cardiovascular risk factors?*	Thank you for this comment. We will consider those devices when devising the protocol for this review question.

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			Consideration of adoption of Watch BP Home A medical technologies needs to consider other available devices including Kardia Alivecor and home BP monitoring devices. Patients with established hypertension monitor BP readings at home and are at risk of AF.	
Roche Diagnostics Limited	2	28-31	We would suggest a rewording of the description of warfarin as a 'traditional anticoagulant' and alternatives to warfarin as 'newer antithrombotic agents', as 'traditional' could imply inferiority. Moreover, the 'newer antithrombotic agents' such as the DOACs, have been on the market for a number of years (e.g. dabigatran etexilate received its marketing authorisation over 10 years ago) and have been routinely prescribed for a substantial period of time.	Thank you for your comments. We do not agree that 'traditional' necessarily implies inferiority – it merely reflects the fact that Warfarin has been the established drug of choice for a prolonged period before DOACs were authorised. We agree that the DOACs may not all be 'new' but they are newer than warfarin.
Roche Diagnostics Limited	3	15-17	Although the current guideline recommends HAS-BLED to assess the risk of bleeding, it is not currently part of the Quality and Outcome Framework (QOF) and is not widely used. Further information on how this or any other identified bleeding risk tool could be included in QoF would be useful.	Thank you for your comment. It is beyond the scope of this guideline to consider how the risk tools could be part of the QOF.
Roche Diagnostics Limited	3	18-19	The scope guideline states that new evidence has been identified for new stroke and bleeding risk scores. However, more detail is needed on which scores will be considered and the evidence that supports their use.	Thank you for your comment. The surveillance report highlighted new evidence around several tools (such as Q-Stroke, Q-Bleed and ABC). The evidence will be scrutinised thoroughly once all the available data has been reviewed during the guideline development process.

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Roche Diagnostics Limited	3 9	18-19 9-13	There is evidence to support the inclusion of the biomarker GDF-15 in the ABC risk scores which has been previously shown to have predictive value for stroke and bleeding. Please see the references below which support the use of the GDF-15 assay. 1. Wallentin L., Hijazi Z., Andersson U., Alexander J. H., Caterina R. D., Hanna M., et al. Growth Differentiation Factor 15, a Marker of Oxidative Stress and Inflammation, for Risk Assessment in Patients With Atrial Fibrillation: Insights From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation. 2014Jul;130(21):1847–58. 2. Hijazi Z., Oldgren J., Andersson U., Connolly S. J., Eikelboom J. W., Ezekowitz M. D., et al. Growth-differentiation factor 15 and risk of major bleeding in atrial fibrillation: Insights from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. American Heart Journal. 2017;190:94–103. Hijazi Z., Lindbäck J., Alexander J. H., Hanna M., Held C., Hylek E. M., et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. European Heart Journal. 2016;37(20):1582–90.	Thank you for your comment. The specific tools will be defined by the guideline committee in a review protocol. If relevant, your references will be used to inform the search strategy.

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Roche Diagnostics Limited	3	2-4	We would suggest that the committee also consider the populations used in the DOAC appraisal and the point-of-care coagulometers guidance in their comparisons, particularly in terms of outcomes and time in therapeutic range (TTR). We would recommend that any analysis comparing DOACs considers real-world patient compliance.	Thank you for your comments. We will stratify any meta-analyses into distinct population groups. Point-of-care coagulometers were not suggested by the surveillance report as a priority area requiring the specific evaluation of new evidence. However their use is intrinsic to the DOACs, and so, like reversal agents, they should be an important part of the intervention protocols in trials. Thus their efficacy will be reflected in the eventual study outcomes. The level of evidence that will be sought in the searches will be determined by the guideline committee.
Roche Diagnostics Limited	3	2-4	We would recommend the inclusion of patient self monitoring and patient self management in the comparison of interventions that should be compared with DOACs.	Thank you for your comment. The extent to which trials include self-monitoring and self-management in their treatment protocols will be recorded as an important feature of treatment. This may be reflected in any sub-grouping strategies to explain any heterogeneity in the meta-analysis.
Roche Diagnostics Limited	8	1-14	We would recommend the inclusion of DG14 "Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point-of-care coagulometers (the CoaguChek XS system)" or the Technical supplement "Summary of main changes to the CoaguChek XS system" as guidances that will be incorporated unchanged in this guideline as this has been updated recently.	Thank you for your comment. This has been added. In accordance with NICE policy we will cross-refer to this guidance but we are unable to summarise it.

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			We believe that the reader of the guideline would benefit from a summary of these guidelines around the option of patient self monitoring.	
Roche Diagnostics Limited	9	15-16	There is clinical and cost-effectiveness evidence that supports the use of the CoaguChek XS system as a point-of-care coagulometer for self-monitoring in atrial fibrillation and heart valve disease which is listed on the NICE website. A technical supplement was recently published by NICE as an addendum to the diagnostics guidance. This provides updated information on the CoaguChek XS. Please see the references below which support the use of the patient self-monitoring: 1. National Institute for Health and Care Excellence. NICE. DG14. Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point-of-care coagulometers (the CoaguChek XS system). https://www.nice.org.uk/guidance/dg14 [Accessed 4th July 2018] 2. National Institute for Health and Care Excellence. NICE. Technical supplement: Summary of main changes to the CoaguChek XS. systemhttps://www.nice.org.uk/guidance/dg14/resources/summary-of-the-main-changes-to-the-coaguchek-xs-system-pdf-4844245789 [Accessed 4th July 2018]	Thank you for this comment. We refer to the NICE technology appraisal on CoaguChk XS in the scope.

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			Craig J. A., Chaplin S., Jenks M. Warfarin monitoring economic evaluation of point of care self-monitoring compared to clinic settings. Journal of Medical Economics. 2014;17(3):184–90.	
Roche Diagnostics Limited	10	14	It is stated that the quality standard will be revised or updated once this guideline is published. Will there be an update of the Quality statement 6 (developmental): Self‑monitoring of anticoagulation recommendation to make it non-developmental?	Thank you for your comment. We have revised the scope to indicate the quality standard may be updated. We are not planning to update the recommendations on self monitoring.
Roche Diagnostics Limited	General	General	There is clinical and cost-effectiveness evidence that supports the use of the CoaguChek XS system as a point-of-care coagulometer for self-monitoring in atrial fibrillation and heart valve disease which is listed on the NICE website. A technical supplement was recently published by NICE as an addendum to the diagnostics guidance. This provides updated information on the CoaguChek XS. Please see the references below which support the use of patient self-monitoring: 3. National Institute for Health and Care Excellence. NICE. DG14. Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point-of-care coagulometers (the CoaguChek XS system). https://www.nice.org.uk/guidance/dg14 [Accessed 4th July 2018] 4. National Institute for Health and Care Excellence. NICE. Technical supplement: Summary of main changes to the CoaguChek XS.	Thank you for your comment. We refer to the NICE technology appraisal 'Atrial fibrillation and heart valve disease: self-monitoring coagulation status using point-of-care coagulometers (the CoaguChek XS system)' (2017) NICE diagnostic guidance DG14 in this scope.

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			systemhttps://www.nice.org.uk/guidance/dg14/resources/summary-of-the-main-changes-to-the-coaguchek-xs-system-pdf-4844245789 [Accessed 4th July 2018] Craig J. A., Chaplin S., Jenks M. Warfarin monitoring economic evaluation of point of care self-monitoring compared to clinic settings. Journal of Medical Economics. 2014;17(3):184–90.	
Royal College of General Practitioners	2	General	The guideline states stroke risk 5 times increased but this can depend on multiple factors some incorporated in chadsvasc2 some not	Thank you for your comment. Our epidemiological statistic is meant to give an overall picture of the elevated risk, although we agree that this will vary depending on other risk factors.
Royal College of General Practitioners	9	15	3.1 What is the most clinically and cost-effective anticoagulant therapy for stroke prevention in people with atrial fibrillation? Any cost effectiveness analysis most take due account of workload on primary care and must not assume these are zero costs or costs that can be just be accommodated as anticoagulation monitoring either with warfarin or the newer DOACS has considerable resource implications for primary care as the long term prescriber / monitor of these drugs.	Thank you. The cost-effective analysis will be conducted using NICE methodology and will include all relevant NHS costs.
Royal College of General Practitioners	General	General	AF predominantly effects the elderly so this review must be compatible with the NICE guidance on multi-morbidity	Thank you for your comment. We will be referring to this guidance.
Royal College of General Practitioners	General	General	NICE should consider providing advice to clinicians on when to stop (or not start) anticoagulation for AF (for example extreme age, comorbidity, frailty etc)	Thank you for your comment. We will cross refer to the relevant recommendations in the NICE guideline on multi-morbidity.

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Royal College of General Practitioners	General	General	This guideline does not go into screening. It is essential that this guideline makes clear that this is the case.	Thank you for your comment. The scope and guideline will make it clear that we are not including screening.
Royal College of General Practitioners	General	General	1 The whole life effect of AF on the psych of sufferers including booking holiday insurance travel etc especially if paroxysmal and unpredictable 2 The access to cardioversion in people with known recurrent paf needing cardioversion 3 does the maths of number of strokes vs the prevalence of af (including that detected coincidentally) add up or has the risk been over stated as total stroke risk is perhaps falling? 4 the role of diet (nuts alcohol etc) 5 so called cryptogenic strokes . note recent trial stopped due to high bleeding risk of doacs 6 i think as yet no trial has shown anticoagulating asymptomatic screen found af has net benefit? 7 the fit athlete and their af is this different?	Thank you for your comment. The scope of this update has been informed by the NICE surveillance review which identified areas in the existing guideline for which new evidence existed, and also identified new areas where evidence existed.

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			8 i don't think you can omit the group also on antiplatelets if this review to be of value. The ESC has produced guidelines but in this country the BJGP and the BMJ have each recently given different views . 9 In my practice we had an af booth for a year for screening and sadly nearly all the af found was in people already known to have it 10 GP had a tendency to exclude anticoagulating in the past and often re classified pts as resolved. This group probably very high risk	
Royal College of Nursing	General	General	The Royal College of Nursing (RCN) welcomes proposals to develop guidelines for the management of atrial fibrillation. The RCN invited members who care for people with this condition to review the draft scope on its behalf. The comments below reflect the views of our reviewers.	Thank you for your comment.
Royal College of Nursing	General	General	The draft scope consultation document seems very comprehensive. It seems to have included the salient points associated with this condition. We look forward to contributing further during the next stage of the development of these guidelines.	Thank you for your comment.

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Royal College of Pathologists and British Society of Haematology	4	20-24	It would also be helpful to clarify what is meant by non-valvular atrial fibrillation as there is some variability in the application of this term in different studies	Thank you for your comment. We have added those people with mitral valve stenosis to people who will be excluded. A guideline on valvular heart disease has recently been commissioned.
Royal College of Pathologists and British Society of Haematology	6	7-9	We are disappointed that antiplatelet and anticoagulation combination therapy is not covered. Most patients should discontinue antiplatelet therapy when starting anticoagulation, but in a few there is a strong indication for continuing with both treatments. Clinicians will look to this guideline for advice on the risks and benefits of combination therapy. We appreciate that there is relatively little data on this subject but this is an opportunity to bring together expert opinion on this area. We would recommend that this area is included.	Thank you for this comment. This area is being covered in the NICE Acute Coronary Syndrome guideline (in development). We now refer to this guidance in the scope.
Royal College of Pathologists and British Society of Haematology	9	12-13	We agree that evaluation of the tools for assessing bleeding risk is important and hope that the committee will provide a clear statement on how the balance of risks and benefits of anticoagulation changes (or doesn't) with age. The HAS-BLED score simply gives +1 to all persons >65 years of age although there is good evidence that the risk of bleeding with anticoagulation can be further stratified by decade.	Thank you for your comment. We will be comparing the tools to establish which leads to the best outcomes, and if a tool has insufficient resolution to detect different risk factors (such as age), and those risk factors are indeed important, this will be reflected in the outcomes achieved.
Royal College of Pathologists and British Society of Haematology	9	14-16	It is essential that this guideline covers patients with renal failure (especially dialysis dependent). Currently these patients are treated in the same was as other patients with atrial fibrillation. However, in the absence of trial data, there is plenty of observational data to suggest that these patients have a worse	Thank you for your comment. We routinely stratify analyses for covariables that could influence the effect size and direction, and we will consider renal failure as a stratification covariable for the anticoagulation question.

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			outcome when anticoagulated. Other countries (e.g. US and Canada) recommend against primary prophylaxis with anticoagulation for atrial fibrillation with renal failure.	
Royal College of Physicians and Surgeons of Glasgow	General	General	The Royal College of Physicians and Surgeons of Glasgow, although based in Glasgow represents Fellows and Members throughout the United Kingdom. While NICE has a remit for England, many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved Governments. The College welcomes the review of Atrial fibrillation and its management. This is a condition which affects people who are often elderly with comorbidities. These need to be considered when offering treatment for atrial fibrillation. It particularly welcomes the cost benefit assessment. This is important with some of the newer interventional treatments such as ablation or appendage closure. Our reviewer considered it was important to have realistic goals in recommending treatments. He considered a cost effective analysis could recommend against expensive interventions with limited longer term gains.	Thank you for your comment.
The College of Podiatry	General	General	The College of Podiatry support the draft AF management scope. We would however wish to see specific mention of Podiatrists as a defined workforce who are competent and actively involved in	Thank you for your comments. We have a review question on 'What is the most accurate method for detecting pulse irregularities in people with symptoms suggestive of atrial

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			the early detection of undiagnosed AF in adults. Podiatrists perform routine foot pulse checks at assessment and actively refer on any irregular pulses/ suspected arrhythmias (that are unknown to the patient and not in their medical history) for consideration of further AF diagnostic assessment via Primary Care. A three month pilot study saw forty five Podiatrists from North Durham CCG, Darlington CCG and Durham Dales, Easington and Sedgefield CCGs assessing the foot pulses of 15,873 patients, of these ten patients were identified with previously undiagnosed AF. Public Health England estimates that 1.36 million people aged over 65 are living with AF, giving a prevalence of in the population of 2.4% with just 1.6% of those with a diagnosis. Therefore Podiatrists are a vital aspect of the workforce, both NHS and independent practice, in early detection of AF and stroke prevention.	fibrillation and in people with cardiovascular risk factors?'. The guideline committee may refer to who performs these assessments when considering the evidence.
The Stroke Association	2	14	Add bullet point: "AF is a contributing factor in up to 1 in 5 strokes in the UK"[1] to set out clearly how big the scale of the problem is.	Thank you for your comment. We have made the suggested edit.

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			[i] Royal College of Physicians Sentinel Stroke National Audit Programme (SSNAP). National clinical audit annual results portfolio March 2016-April 2017. Available: http://bit.ly/1NHYlqH	
The Stroke Association	2	21	We would suggest adding a point here setting out that AF is poorly understood by the public as a major stroke risk factor, as well as how modifiable risk factors such as those relating to lifestyle can be a contributing factor in developing AF. Indeed, an IPSOS MORI survey of over 9,000 people in 2012 showed that while around a quarter of people in the UK fear having a stroke above some other serious health conditions, only 3% are fearful of AF, despite it being a major stroke risk factor, suggesting a lack of awareness.	Thank you for your comment. Although we agree that these issues are important, the guideline surveillance report did not highlight the need for this update to focus on increasing public awareness of AF as a major stroke risk factor.
The Stroke Association	2	21	We strongly welcome the guideline giving greater consideration to new or emerging ways of detecting AF, including the use of technology such as mobile apps. Using technology in a home or community setting can also help share the responsibility of AF detection and ensure the pressure is not solely on GPs because whilst we would obviously support encouraging people at risk of stroke and AF to visit their GP to be assessed, diagnosing in a GP setting only captures those who visit their GP and not the wider population, many of whom do not regularly attend and some of whom are not even registered with a GP.	Thank you for your comments. These important issues will be borne in mind by the guideline committee when making recommendations based on the evaluated evidence.

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			Over a third of GPs (35%) we surveyed said they would like more information on identifying AF, perhaps suggesting a lack of confidence or awareness around AF. The vast majority said they do not display AF literature in their practice and in another survey, 25% said they felt not very well or not at all well equipped to provide patients with the information they need on the condition (Primary Healthcare Monitory May 2017). This lack of confidence or awareness could also suggest that some GPs will not necessarily actively seek out AF by testing opportunistically.	
The Stroke Association	2	22	ECGs are hugely important in confirming suspected AF but the guideline should consider that a considerable barrier to effective diagnosis is variable access to ECG equipment, particularly in rural areas. Immediate access to ECG equipment can vary across practices, meaning some people are not being diagnosed due to a lack of suitable equipment. We believe this need not be the case given the availability and low purchase cost of simple ECG equipment and new technology such as smartphone applications which are recommended and used by a growing number of practitioners. It might be worth considering the option to start patients on anti-coagulation treatment based on an approved mobile ECG reading by a qualified professional, for full ECG review at a later time. This will ensure there is not a delay between AF diagnosis and treatment, which leaves some people unnecessarily at risk of stroke.	Thank you for your comments Although we agree this is an important area, it is not included in this update of the guideline as new evidence in these areas was not cited in the surveillance report However, there is a question on the most accurate methods for detecting pulse irregularities in people with cardiovascular risk factors. Issues around implementation may be considered by the guideline committee, but are outside the scope of this guideline.

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			When we surveyed GPs through doctors.net, 58% said they do not use new technologies to detect AF, suggesting more work needs to be done to improve the awareness and use of detection technologies. This guideline is a good opportunity to improve awareness in this area.	
The Stroke Association	3	1	New oral anti-coagulants are now available to reduce stroke risk for patients in atrial fibrillation, which justify a review of the pharmacological treatments section of this guideline. Specifically, new recommendations are needed to address what should be done to start patients on long term anti-coagulation who do not spend a full two weeks in hospital, as length of stay is continuing to decline.	Thank you for your comment. This issue will considered by the guideline committee when recommendations are made.
The Stroke Association	3	1	Additionally, new reversal agents are now approved for new oral anti-coagulations which should be included as a part of this review. This will change the relative risks of bleeding and addressing bleeds when comparing warfarin and NOACs and will therefore have an impact on clinical and patient decision-making.	Thank you for your comment. Reversal agents will have been used in trials (where they are available) and so their effects will be reflected in the outcomes. In addition, issues around reversibility will be considered by the guideline committee when discussing evidence prior to such reversal agents being used.
The Stroke Association	3	27	NHS England has also recently approved left atrial appendage occlusion for those with AF who are not able to take anti-coagulations. The review of this guideline should consider the evidence around this and include recommendations around the procedures use.	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future.

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				Data collected during the CtE scheme is considered alongside published data from research trials to inform the development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.
The Stroke Association	4	14	We welcome the guideline looking at inequalities relating to women, who carry a greater risk of stroke from AF. However, we would also like to see ethnicity considered as a key inequality, particularly as white people are more likely to have AF than other ethnicities, and black and those of South Asian descent in the UK have a generally increased risk of stroke.[23] We would also like consideration given to income and social deprivation as inequalities. As we know, AF is a key stroke risk factor and those from more deprived area have a generally increased risk of stroke[4] as well as having a higher incidence of multi-morbidity which increases the risk of developing AF and other stroke risk factors[5]. [3] Gov.uk (2017) Ethnicity fact and figures. Available: https://www.ethnicity-facts-figures.service.gov.uk/health	Thank you for these comments. In the light of these we have decided to add in ethnicity as a special group because it seems on the basis of the evidence to have a direct intrinsic effect on the likelihood of stroke in people with AF. We have not included deprivation as a special group criterion however, as although this group is at greater risk of stroke we felt that this is not an intrinsic effect of deprivation but rather a result of associated risk factors that are dealt with in other guidance.

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			[4] Wang Y, Rudd AG, Wolfe CD (2013). Age and ethnic disparities in incidence of stroke over time: the South London Stroke Register. Stroke 44: 3298-3304. [5] Marshall IJ, et al (2015). The effects of socioeconomic status on stroke risk and outcomes. Lancet Neurology 14: 1206-1218. [6] Understanding the challenge of Multi-morbidity. The Richmond Group of Charities. 2018. Available at: https://richmondgroupofcharities.org.uk/sites/default/files/multimorbidity_-_understanding_the_challenge.pdf	
The Stroke Association	5	10	Given that there is not a proactive screening programme for AF due to the lack of evidence in this area, we strongly suggest that the scope of this guideline be expanded to give GPs, pharmacists and other health professionals more information about what best-practice in opportunistic pulse detection looks like. Currently, there is a gap in policy in this area with these guidelines only starting when a health professional might suspect AF. Given the challenging nature of the condition, in that it is not always persistent and often doesn't show symptoms, more opportunistic pulse checking for high risk groups, such as those with other long term health conditions, should be encouraged in absence of a full screening programme. Without this, we will continue to see a high under-diagnosis rate and too many avoidable and devastating AF related strokes. In order to develop recommendations around this, we suggest looking at the work undertaken by Academic	Thank you for your comments. Opportunistic screening is outside of the remit of this guideline. We are covering 'What is the most accurate method for detecting pulse irregularities in people with symptoms suggestive of atrial fibrillation and in people with cardiovascular risk factors?'

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			Health Science Networks across the country to explore different options for opportunistic pulse checking[6]. [2] AHSN Network. Available: http://www.ahsnnetwork.com/about-academic-health-science-networks/national-programmes-priorities/atrial-fibrillation/	
The Stroke Association	5	9	We strongly urge consideration of the other challenges behind AF diagnosis. There are the basic characteristics of AF which make diagnosis challenging. For example, if someone is experiencing paroxysmal AF, their symptoms may not be evidence during a visit to the GP or at some other defined point. Without knowledge, persistence and the appropriate equipment, opportunities to explore further and potentially diagnoses through longer-term monitoring could be lost such is the nature of AF.	Thank you for this comment. Paroxysmal AF is included in the scope area 'Diagnosis and assessment'. We have edited the draft review question to make this clearer.
The Stroke Association	General	General	The Stroke Association welcomes development of this guideline on the management of atrial fibrillation – a key stroke risk factor - and the opportunity to provide comments on the scope.	Thank you for your comment.
University of Birmingham	3	1-3	The data suggest that some (dabigatran 150mg bid and apixaban) are more efficacious than warfarin for stroke prevention and therefore warfarin should not be on an equal footing with all NOACs for stroke prevention. In addition, all NOACs are associated with significantly lower risk of intracranial haemorrhage.	Thank you for your comment. When we conduct the review of the evidence we will be able to form a clear picture of the relative benefits and risks of each agent.

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University of Birmingham	3	3	There are no head-to-head trials but there are several meta-analyses/indirect network meta-analyses which have been conducted comparing the non vitamin K oral anticoagulants (NOACs) or direct oral anticoagulants (DOACs) and these should be reviewed. The conflicting results of these analyses illustrate the methodological weaknesses of indirect comparisons. Similar to b blockers, ACE inhibitors, or sartans, there is probably no major reason to differentiate between the four approved NOACs.	Thank you for your comments. We plan to review the published evidence on DOACs in this guideline. Our evaluation of the evidence will determine whether differentiation between the DOACs is appropriate.
University of Birmingham	3	15	CHA2DS2-VASc is the most widely used (and validated) stroke risk scoring system and should be recommended in the updated NICE guidelines.	Thank you for your comment. Our evidence review, and subsequent guideline committee discussion, will help to determine which is the most clinically and cost effective risk scoring system.
University of Birmingham	3 9	15 9	Other stroke and bleeding risk scores have been proposed – it is very important for NICE to balance the use of complex scores that offer marginal improvements in predicting high risk patients (with the risk tool often derived in anticoagulated cohorts, some with biomarkers - against simple, practical and user-friendly scores (eg. CHA2DS2-VASc, HAS-BLED). Indeed, there is often inappropriate abuse and misuse of bleeding risk assessment. This is an implementation and education issue, not a reason to recommend against use of bleeding risk assessment in guidelines	Thank you for your comment. Our evidence review, and subsequent guideline committee discussion, will help to determine which is the most clinically and cost effective risk scoring system. This will take into account study design and risk of bias, as well as issues around ease of use and shared decision making.

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			A responsible approach should be emphasised – bleeding risk scores such as HASBLED draws attention to modifiable bleeding risks and 'flags up' the high risk patients for early review and follow-up (e.g. 4 weeks, rather than 4-6 months) *J Thromb Haemost. 2016 Sep;14(9):1711-4. doi: 10.1111/jth.13386.* The committee should carefully look into the effects of proposing a bleeding risk score which is identified as one of the major reasons why anticoagulation is still underused, particularly in patients at high stroke (and bleeding) risk. Nevertheless, a recent European survey shows that these simple scores remain widely used. *Dan et al Europace. 2018 Jun 8. doi: 10.1093/europace/euy094. [Epub ahead of print] PMID:29893840* Other guidelines have focussed on modifiable bleeding risk factors but recent studies have shown that this is clearly an *inferior strategy* to a formal bleeding risk score for bleeding risk assessment / prediction Am J Med. 2018 Feb;131(2):185-192. Int J Cardiol. 2018 Mar 1;254:157-161. Thromb Haemost. 2017 Dec;117(12):2261-2266.	
University of Birmingham	3 9	15 9	All clinical factor based risk scores have a c-index of approx. 0.6-0.65 i.e. modest predictive value for high risk; more complex	Thank you for your comment. Our evidence review, and subsequent guideline committee discussion, will help to

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			clinical scores may improve the c-index to approx. 0.65 only. Addition of biomarkers may improve the c-index to approx. 0.67. Attention to study design is important. Some papers describe low event rates due to 'conditioning on the future' bias by excluding all patients ever started on anticoagulants. Some papers have looked at risk scores in anticoagulated cohorts in a highly selected clinical trial setting. To assess the value of a score in risk prediction, we need to see the predictive value in non-anticoagulated cohorts. *Sci Rep. 2016 Jun 6;6:27410. doi: 10.1038/srep27410.* Overall, all risk score only have limited value for predicting high risk. In contrast the CHA2DS2-VASc score performs well in identifying 'low risk' patients. This is the simple message to GPs and non-specialists made in the 2014 NICE guideline, to initially identify low risk patients first.	determine which is the most clinically and cost effective risk scoring system. This will take into account study design and risk of bias, as well as issues around ease of use and shared decision making.
University of Birmingham	3 9	15 9	There is an increasing body of evidence illustrating that female sex (one of the components of CHADSVASc) does not increase stroke risk in patients at low stroke risk. Also, the indication for anticoagulation with one CHA2DS2VASc factor (i.s. a CHADSVASc score =1 in men, and CHADSVASc score = 2 in women) should be reviewed, as not all risk factors carry equal	Thank you for your comment. Our decision to look at other risk prediction tools was initiated by the guideline surveillance report that highlighted new evidence that needs to be considered.

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			weight. The reported stroke risk in this particular patient group is variable – depending on the particular risk factor involved. The CHA2DS2-VASc score – ignoring the "risk modifier" female sex - performs well in identifying 'low risk' patients. This is the simple message to GPs and non-specialists made in the 2014 NICE guideline, to initially identify low risk patients first. It took many years to educate the UK community on the use of the CHA2DS2VASc score – keeping it therefore has value.	
University of Birmingham	3 9	15 9	Many validation studies of risk scores look at baseline factors, and record the prediction of even rates many years later (sometimes 5-10 years!). The major flaw of many of these studies is that patients get older and acquire incident risk factors. Recent analysis have shown clearly the dynamic nature of stroke *and* bleeding risk, such that the *change* in risk factors is a more powerful risk predictor. See: J Am Coll Cardiol. 2018 Jan 16;71(2):122-132. Thromb Haemost. 2018 Apr;118(4):768-777. Thromb Haemost. 2018 Jul;118(7):1296-1304.	Thank you for your comment. This point will be considered when drawing up the protocol for this review question, and when interpreting results from papers.

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			Reassessing stroke risk regularly in patients with atrial fibrillation seems important in this context.	
University of Birmingham	5	11-12	Need to ensure clear information on the management of patients with CHA2DS2-VASc score of 1. US guidelines include females with score=1 into this group, when it is clear they are 'low risk'. Female sex is a risk modifier, rather than a risk factor (see Nielsen P et al Circulation. 2018 Feb 20;137(8):832-840). Low risk needs clearly defined as CHA2DS2-VASc score 0 in males or 1 in females. Such patients do not need antithrombotic therapy. Those with one risk factor should be considered for anticoagulation, esp in the era of NOACs. Patients at high stroke risk should be offered anticoagulation on prognostic grounds.	Thank you for your comment. The issue you highlight will be discussed by the guideline committee when reviewing the evidence.
University of Birmingham	6	3	Percutaneous atrial appendage occlusion is a treatment for stroke prevention in atrial fibrillation (albeit not widely used in the UK) and should at least be mentioned briefly with current evidence summarised (additional information is available since 2014 NICE), particularly as an alternative treatment in patients who are clearly not suitable for any oral anticoagulant.	Thank you for your comment. NICE recently published (July 2018) a report on left atrial appendage occlusion (LAAO) through NHS England's Commissioning through Evaluation (CtE) programme. This programme enables valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future. Data collected during the CtE scheme is considered alongside published data from research trials to inform the

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				development of NHS England's clinical commissioning policy for LAAO. LAAO occlusion has therefore been excluded from the scope.
University of Birmingham	6	6	Although a detailed review of how to manage co-morbidities associated with atrial fibrillation is not needed in the atrial fibrillation guideline, holistic management of the patient is required. Treating atrial fibrillation in isolation will not work; management of the comorbidities (e.g., hypertension, heart failure, diabetes mellitus etc.) is an essential part of atrial fibrillation management as well as anticoagulation, rate control, and rhythm control. This includes an assessment of symptoms – something that is often overlooked in current practice. Simple approaches have been implemented in the West Midlands building integrated, patient-centred models of care across sectors and institutions. Such models will help to improve holistic assessment and management of patients with AF in all domains (concomitant conditions, anticoagulation, rate control, rhythm control). Such an approach has been implemented in the West Midlands ASHN and local CCGs, to simplify the approach to holistic management of atrial fibrillation – the ABC pathway See Nat Rev Cardiol. 2017 Nov;14(11):627-628.	Thank you for your comment. We agree that a holistic patient-centred approach is essential, and all recommendations made after evaluation of the evidence will be guided by this.

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University of Birmingham	6	7	Several underpowered but informative controlled clinical trials comparing different warfarin-based anticoagulation strategies with different DOAC-based anticoagulation strategies have been published or will be published between now and the finalisation of this guideline. This evidence should be considered and potentially guidance of the possible combination treatment options included in the update. This may require focussed specialist input from interventional cardiologists.	Thank you for your comments. We will be including all evidence that meets the protocol in our review of the evidence.
University of Birmingham	6	Table	Excellent that 'personalised package of care and information' is to be retained but a clear pathway on what elements this should ideally incorporate (individualised as needed) should be included in the update. Need to include list of tested / validated patient resources (leaflets, web sites, online tools, apps – e.g. from charities or professional organisations, or those verified by the committee) which health care professionals can use to educate/inform patients about atrial fibrillation and treatment options. There is a real opportunity to encourage the development of integrated care models offering care in the community with a clear path to specialist and subspecialist therapy in those who need it. This is a big challenge due to the large number of patients with atrial fibrillation and the need to adequately identify those who need continued specialist input (a few) in the large number of patients who may do quite well without subspecialty input.	Thank you for your comment. Although we agree these are important areas, they are not included in this update of the guideline as new evidence in these areas was not cited in the guideline surveillance report.

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University of Birmingham	9	12	There is often inappropriate abuse and misuse of bleeding risk assessment. This is an implementation and education issue that still leads to discontinuation of anticoagulation therapy, or even to withholding therapy. Drawing attention to modifiable bleeding risks and identifying patients who may need more intensive, early follow-up. However, recent studies have shown that tsimply focusing on modifiable bleeding risk factors is clearly an *inferior strategy* to a formal bleeding risk score for bleeding risk assessment / prediction Am J Med. 2018 Feb;131(2):185-192. Int J Cardiol. 2018 Mar 1;254:157-161. Thromb Haemost. 2017 Dec;117(12):2261-2266. A responsible approach should be emphasised – bleeding risk scores such as HASBLED draws attention to modifiable bleeding risks and 'flags up' the high risk patients for early review and follow-up (e.g. 4 weeks, rather than 4-6 months) *J Thromb Haemost. 2016 Sep;14(9):1711-4. doi: 10.1111/jth.13386.*	Thank you for your comment. Any drawbacks from a risk tool should be captured by the eventual health outcome. We will be comparing the outcomes from different risk tools, which should provide empirical answers to questions around the most effective tool.
University of Birmingham	General	General	The existing NICE guidelines have improved the care of patients with AF, particularly increasing the appropriate use of oral anticoagulants in patients with AF at risk of stroke. This translated into better outcomes, less strokes, and better survival of affected patients.	Thank you for your comments. Service delivery is outside of the scope of this guideline.

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			Even on oral anticoagulation, patients with AF are at high risk of cardiovascular complications such as cardiovascular death, heart failure, and unplanned hospitalisations. Approximately 30-50% of patients with AF on current management remain symptomatic. We would wish the new NICE AF guidelines to cover integrated models of care that ensure that patients with AF receive the appropriate treatment in all relevant domains, particularly 1. Acute management in symptomatic patients 2. Diagnosis and treatment of underlying conditions 3. Stroke prevention 4. Rate control therapy and 5. Rhythm control therapy	
University of Birmingham	General	General	A major weakness of current AF management, despite the improvements in recent years, is the continuation of oral anticoagulation. Discontinuation rates of anticoagulants in published cohorts are 30% to 60% in the first year after initiation. The committee should look into evidence supporting best care to reduce reductions.	Thank you for your comment. We will cross refer to the NICE guideline on Medicine Adherence: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (CG76).
University of Birmingham	General	General	There is increasing evidence that atrial fibrillation is not only a major cause of stroke, but also a major driver of cognitive decline and dementia. The committee should look into the growing evidence of treatments that improve or preserve cognitive function in patients with atrial fibrillation, including anticoagulation, but possibly also antihypertensive therapy, heart failure therapy, rate control, or rhythm control therapy.	Thank you for your comment. The outcomes listed are those that would apply to most questions, but we will also consider other outcomes for specific questions.

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University of Birmingham	General	General	There is still a deplorable lack of evidence to inform rate control therapy in patients with atrial fibrillation.	Thank you for your comment. Where we find a dearth of evidence in certain areas we will recommend research recommendations.
University of Birmingham	General	General	While there is an increasing body of data supporting the use of rhythm control therapy (antiarrhythmic drugs and catheter ablation) to improve symptoms in patients with atrial fibrillation on adequate rate control, the committee should look into the best way to assess AF-related symptoms in clinical practice.	Thank you or your comment. The scope of this update has been informed by the surveillance review which identified areas in the existing guideline for which new evidence existed, and also identified new areas where evidence existed.
University of Birmingham	General	General	In 2018 there is the new focused update on the US guidelines (ACC/AHA/HRS) being published. Also, the new 2018 American College of Chest Physicians (ACCP) guidelines will be published in Q3 2018	Thank you for your comment. We have noted your references.
University of Birmingham	General	General	Atrial fibrillation patients need regular follow up and integrated care. This particularly applies to patients with AF and heart failure, but also to others with comorbidities. Often they need attention to comorbidities, nutritional advice, cognitive testing, rehab, this can be hard to get if not post MI or stroke. Further needs arise when rate control is difficult and, in symptomatic patients, when rhythm control is indicated. "Holistic care", "patient centred care", and "integrated care" have been proposed to improve the management of patients with atrial fibrillation.	Thank you for your comment. The guideline committee will consider these issues when making the recommendations.

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University of Birmingham	General	General	Detection of atrial fibrillation – There has been an explosion of devices to detect atrial fibrillation both in the general population and in post stroke patients- I think NICE should be very careful about encouraging their use until we have clear evidence that device detected arrhythmia has the same risks as ECG documented atrial fibrillation and that anticoagulation has the same beneficial effects. There is emerging evidence that even external event monitors do not adequately detect AF. There is an emerging risk for overdiagnosis of AF, and subsequent overtreatment with anticoagulants. In this context, the results of NAVIGATE-ESUS and the results of several other ongoing large trials of NOACs / DOACs should be considered in the revised guidance. Ablation this remains a symptomatic therapy. The committee should look into recent trials, e.g. CASTLE AF in patients with heart failure and AF. This group of patients requires particular attention, also in view of the paucity of data on effective therapies (including b blockers and digoxin) – see prior comments. There is emerging evidence that high volume ablation centres provide better quality care than smaller centres. A formal way of assessing symptoms (e.g. PROMs, symptoms scores, etc) could be useful to evaluate the effectiveness of rhythm control therapy,	Thank you for your comment. The accuracy of techniques to detect pulse irregularities will be considered by the guideline committee and this will include overdiagnosis (false positives) People with heart failure may be identified as a separate group requiring consideration when devising the review protocol for this question Where services are delivered is outside of the scope of this guideline We have now amended the two questions of rate and rhythm control to form one larger question. This will compare all pharmacological and non-pharmacological approaches together. Thus this will permit drug vs drug, non-drug vs non-drug and drug vs non-drug.

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			particularly AF ablation, as the treatment is primarily directed to improve symptoms. Quality indicators for therapy delivery would be helpful – but there may not be sufficient evidence supporting such a quality-based approach at present. At the same time, the safety of antiarrhythmic drug therapy seems very good even in high risk patients (see presentation of CABANA, and recent observational data sets) when administered and monitored in large centres. Rate control versus rhythm control – There is almost no data on optimum rate control in terms of hard or clinically relevant endpoints – We need this data to inform the best management of symptomatic patients with atrial fibrillation.	

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