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AliveCor Ltd.	Guideline	004	011	We are concerned that this recommendation is not aligned with the European Society of Cardiology guidelines for AF diagnosis and management 2020. This will be confusing for patients and physicians as this is considered a class 1 recommendation in diagnosing AF under the new ESC guidelines. ESC guideline states the following *"ECG documentation is required to establish the diagnosis of AF. A standard 12-lead ECG recording or a **single-lead ECG tracing of >_30 s** showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF."* *https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa612/5899003* Will the NICE guideline consider modifying the guideline to include single lead ECG tracing of >30s(as above)?	Thank you for your comment. The evidence showed that single lead would miss up to 10% of people with AF detected on 12 lead. The committee therefore agreed that the benefits of recommending 12 lead outweighed the disadvantages (see the committee's discussion in evidence review B).
Aneurin Bevan University Health Board	Guideline	009	011	We are concerned with the recommendation to offer apixaban and dabigatran as first line. We would like to highlight that the cost effectiveness analysis does not take into account any potential local or national rebates. If the procurement price changes then the cost effectiveness as calculated in the guideline will be inaccurate and will require updating.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case

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				We are aware of the forthcoming advice from NHSE however from a Welsh perspective we are not subject to the same procurement arrangements that NHSE are negotiating and therefore NHS Wales could be disadvantaged via any subsequent decisions regarding a review of the recommendations on cost effectiveness and choice of agent. As such we would support a less prescriptive approach to recommending specific agents, with acknowledgement that the cost effectiveness may be variable across different areas depending on local rebates and over time, especially with patent expiries for dabigatran and rivaroxaban in 2023. The choice of DOAC agent in Wales is also influenced by the All Wales Advice on Oral Anticoagulation for Non-valvular Atrial Fibrillation Guidance. The guidance recommends that any DOAC can be considered as an option and if no specific patient characteristics or preferences, the agent with the lowest acquisition cost should be considered.	analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available.
Anticoagulation UK	Guideline	008	022 - 024	Emphasis on use of clinical risk profiles and personal preferences to guide treatment options. How effectively will this be managed in primary care when an individual is going to be 'guided' towards specific DOACS as the guideline will direct. Patient choice is critical here – we anticipate that clinicians will have to direct/ prescribe as to what is directed by their commissioners. The proposed guidelines conflict in part with *Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes NICE guideline [NG5]*	Thank you for your comment. We have edited recommendations 1.6.3 and 1.6.4 and now recommend any licensed DOAC. We do now cross refer (recommendation 1.6.2) to the guidance on shared decision making in the NICE guidelines on medicines adherence, medicines optimisation and patient experience in adult NHS services.

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Arrhythmia Alliance	Guideline	004	011	Although a 12-lead ECG is recommended for confirmation of AF following a manual pulse rhythm check, during the Covid-19 pandemic access to ECG services has greatly reduced and clinics have even been cancelled therefore a recommendation of using a NICE recommended/approved holter/patch (iRhythm ZIO, Bardydx) or mobile ECG (such as AliveCor Kardia) should be recommended. Delay to accessing a 12-lead ECG could lead to more AF-related strokes occurring during the period between detection and confirmation of AF and lack of anticoagulation during this period. Many GPs are no longer relying on a 12-lead ECG to confirm diagnosis and certainly during the pandemic Arrhythmia Alliance facilitated so that healthcare professional could request a patch or holter be sent directly from the manufacturer to the patient to ensure a speedy diagnosis was obtained and anticoagulation commenced without delay and therefore reducing the risk of an AF-related stroke. In the 'new' digital world many healthcare professionals will continue to use this route and ensure faster diagnosis even after the restrictions caused by Covid-19. We therefore suggest this guideline reflects an already existing service adopted by many healthcare professionals by using the latest technology.	Thank you for your comment. The evidence showed that single lead would miss up to 10% of people with AF detected on 12 lead. . For paroxysmal AF we have made a similar suggestion however, in that people should be given ambulatory measurement for as long as possible. The committee therefore agreed that the benefits of recommending 12 lead outweighed the disadvantages (see the committee's discussion in evidence review B).
Arrhythmia Alliance	Guideline	005	012	Most HCP are unaware of and do not use the ORBIT bleeding score. We would ask the committee to review this recommendation and look at the HAS-BLED bleeding risk score. ORBIT is based on elderly patients and yet many people with AF are younger and yet using the ORBIT bleeding score these patients would not be identified. Many healthcare professional are uninformed and unaware of ORBIT and its use could lead to an excuse not to anticoagulate (no clear direction towards modifiable bleeding risk factors (unlike HAS-BLED). NICE guidance does not reflect	Thank you for your comment. The committee were confident that the benefits of ORBIT will outweigh any disadvantages from the need for some degree of initial adaptation on the part of new users. The derivation methodology of a tool is not crucial if it is still able, despite sub-optimal developmental methodology, to achieve better predictive capacity than other tools. The committee agreed that the calibration data

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				that of the European Society of Cardiology recently published updated AF Guidelines which does not use the ORBIT bleeding score and recommends the HAS-BLED. The ESC Guidelines are accepted throughout Europe. Introducing ORBIT would cause unnecessary confusion. At best there is only a minor advantage to ORBIT, which was derived from data from USA patients. Most of our HCPs prefer to use HAS-BLED.	demonstrated that ORBIT was best placed to predict absolute bleeding risk in relevant patient populations. NICE guidelines are meant to reflect the full body of relevant literature available at the time, and so may not produce the same guidelines as earlier work. Thank you for your point that ORBIT may be used as an excuse not to anticoagulate, because of the lack of any clear directions towards modifiable risk factors. The committee agreed that the primary concern of a bleeding risk tool is to provide an accurate identification of absolute risk to provide context to the patient/clinician discussion about modification of risk factors. Our committee agreed that ORBIT was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk. The question is whether this advantage is sufficient to warrant the apparent disadvantages of ORBIT incorporating less modifiable risk factors. Whilst it is true that the ORBIT does not involve measurement of some of the important modifiable risk factors, such as labile INR, such modifiable risk factors can be measured in other ways, and may already be available on the patient's data. Furthermore, whether ORBIT or HAS-BLED are used does not actually change the amount of modifiable risk factor investigations that need to be carried out by the investigating clinician. For example, measurement of haemoglobin, labile INR, blood pressure, liver function tests and renal function tests will need to be carried out in both cases to

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					evaluate whether current bleeding, increased blood pressure or treatable liver or renal disorders are present, each of which can be treated if needed to reduce bleeding risk. The only difference is that the results of labile INR, blood pressure, liver function tests and renal function tests will feed into informing the HAS-BLED score whereas haemoglobin and renal function results (GFR) will feed into the ORBIT score. This does not make ORBIT any more costly in terms of clinician time and resources, as other variables in ORBIT do not require invasive investigations. In addition, the notion that if the modifiable risk factors are not part of the tool then clinicians will not be prompted to discuss their modification is not a real disadvantage. This is because checking the modifiable risk factors of bleeding forms part of routine assessment for any clinician dealing with AF patients . We would therefore argue that the real benefits of the greater absolute risk prediction accuracy from ORBIT outweigh the disadvantages of ORBIT not incorporating some of the modifiable risk factors, because the advantages are very real but the disadvantages are surmountable.
Arrhythmia Alliance	Guideline	007	022	Personalised package of care and information is a welcomed recommendation however the guidance does not provide signposting as to where this information should be obtained. Patients will therefore not receive optimal support and information as it will vary from centre to centre and could be dependent on where they live. Organisations such as AF Association, Arrhythmia Alliance, BHF, Stroke Association should be listed as approved, recommended professional charitable organisations. If	Thank you for your comment. This recommendation was not part of the current update. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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				patient choice is removed regarding anticoagulation therapy and access to various treatment options then this will remove the personalised package of care and patient choice.	
Arrhythmia Alliance	Guideline	009	006	In line with this guidance we strongly support the recommendation of all four DOACs (NOACs) (apixaban, dabigatran, edoxaban and rivaroxaban) for help prevent AF-related strokes and systemic embolism in people with non-valvular atrial fibrillation as per specified NICE technology appraisal guidance. However we strongly recommend that ALL DOACs are recommended as part of these AF guidance and based on NICE TAs Patients must be involved in the discussion and decision making of their anticoagulation therapy and have access to all available anticoagulation medication	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend that any licensed DOACs should be offered. We do now cross refer people (recommendation 1.6.2) to the guidance on shared decision making in the NICE guidelines on medicines adherence, medicines optimisation and patient experience in adult NHS services.
Atrial Fibrillation Association	Guideline	004	011	We welcome that a manual pulse rhythm check is being recommended to detect AF however we have concerns that the referral for a 12-lead ECG may delay anticoagulation being prescribed and therefore lead to potential disabling or fatal AF-related strokes whilst waiting for an appointment for the 12-lead ECG. During the pandemic many clinics were cancelled or postponed delaying access to a 12-lead ECG and therefore AF Assoc worked with healthcare professionals and industry to deliver holters, ECG patches or mobile ECGs (AliveCor Kardia for example) direct to patients in the safety of their own home. This reduced the wait (often months even prior to the pandemic) to access a 12-lead ECG and therefore a diagnosis was made quicker, safely and appropriate anticoagulation drug prescribed sooner. Many healthcare professionals have stated they will continue with this even after the restrictions of the pandemic as this is more cost-effective and time-effective for the NHS and most importantly the person with AF. It	Thank you for your comment. The evidence showed that single lead would miss up to 10% of people with AF detected on 12 lead. The committee therefore agreed that the benefits of recommending 12 lead outweighed the disadvantages (see the committee's discussion in evidence review B).

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				reduces appointment time and hospital visit for a 12-lead ECG. We therefore suggest that the committee review this recommendation and include diagnosis by medically approved ECG monitors, whether a patch or mobile app.	
Atrial Fibrillation Association	Guideline	005	012	AF Assoc is unsure why NICE have recommended the ORBIT bleeding score rather than the much more recognised and widely used HAS-BLED score. As most healthcare professionals do not use and are unaware of ORBIT we are concerned that due to no clear direction towards modifiable bleeding risk factors (unlike HAS-BLED) may lead to fewer people being anticoagulated and lead to more (not less) devasting AF-related strokes. The recently published updated ESC (European Society of Cardiology) guidelines recommend HAS-BLED and are accepted throughout Europe. Introducing ORBIT would cause unnecessary confusion and lead to under-anticoagulation. HAS-BLED is validated across all parts of the patient pathway – newly diagnosed (so on no anti-thrombotics or aspirin) as well as oral anticoagulant (DOAC or not). ORBIT is only validated in anticoagulated patients, and in a number of direct comparisons is inferior to HAS-BLED Also, hardly any components of ORBIT are modifiable risks, whereas the responsible way to use bleeding scores is to focus on modifiable risks and flag up high-risk patients for follow up! ORBIT is based on the elderly population with AF and derived from data from USA patients. Many people	Thank you for your comment. The committee were confident that the benefits of ORBIT will outweigh any disadvantages from the need for some degree of initial adaptation on the part of new users. The derivation methodology of a tool is not crucial if it is still able, despite sub-optimal derivation methodology, to achieve better predictive capacity than other tools. The committee agreed that the calibration data demonstrated that ORBIT was best placed to predict absolute bleeding risk in relevant patient populations. NICE guidelines are meant to reflect the full body of relevant literature available at the time, and so may not produce the same guidelines as earlier work. The committee agreed that the fact that ORBIT is only validated in anticoagulated patients is not a limitation because ORBIT will only be used in that population. This review has been restricted to anticoagulated validation studies because it is only in that population that we need to know how accurate the tools are. ORBIT does not involve measurement of some of the important modifiable risk factors, but such modifiable risk factors can be measured in other ways, and may already be available on the

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				with AF are younger and if ORBIT bleeding score was used these patients would not be identified and appropriately anticoagulation. We therefore strongly recommend this be changed and use the HAS-BLED score rather than ORBIT.	patient's data. Furthermore, whether ORBIT or HAS-BLED are used does not actually change the amount of modifiable risk factor investigations that need to be carried out by the investigating clinician. For example, measurement of haemoglobin, labile INR, blood pressure, liver function tests and renal function tests will need to be carried out in both cases to evaluate whether current bleeding, increased blood pressure or treatable liver or renal disorders are present, each of which can be treated if needed to reduce bleeding risk. The only difference is that the results of labile INR, blood pressure, liver function tests and renal function tests will feed into informing the HAS-BLED score whereas haemoglobin and renal function results (GFR) will feed into the ORBIT score. This does not make ORBIT any more costly in terms of clinician time and resources, as other variables in ORBIT do not require invasive investigations. In addition, the notion that if the modifiable risk factors are not part of the tool then clinicians will not be prompted to discuss their modification is not a real disadvantage. This is because enquiring about modifiable risk factors of bleeding forms part of routine clinical assessment.. We would therefore argue that the real benefits of the greater absolute risk prediction accuracy from ORBIT outweigh the disadvantages of ORBIT not incorporating some of the modifiable risk factors, because the advantages are very real but the disadvantages are surmountable. The committee agreed that the primary function on the tool is to accurately predict risk.

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Atrial Fibrillation Association	Guideline	007	022	The recommendation of a Personalised Package of Care and Information is welcomed however it does not provide signposting as to where to access this information. This recommendation maybe overlooked or ignored. Patients will therefore not receive optimal support and information as it will vary from centre to centre and could be dependent on where they live. With the removal of patient choice re anticoagulation therapy and access to various treatment options this will lead to removal of a Personalised Package of Care and Information. AF Assoc therefore recommends established, recognised organisations such as the AF Association, Arrhythmia Alliance, BHF, Stroke Association should be listed as approved, recommended professional charitable organisations.	Thank you for your comment. This recommendation was not part of the current update. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Atrial Fibrillation Association	Guideline	009	006	AF Assoc strongly supports the recommendation of all four DOACs (NOACs) (apixaban, dabigatran, edoxaban and rivaroxaban) in the prevention of AF-related strokes and systemic embolism in people with non-valvular atrial fibrillation as per NICE technology appraisal guidance. We were surprised therefore to see that this guidance is only recommending the use of Apixaban or Dabigatran as first-line anticoagulation therapies – this recommendation removes patient choice and access to all previously recommended anticoagulation therapies. Patients must, at all times, be involved in the discussion and decision making of their anticoagulation therapy and have access to all available anticoagulation medication	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. We do now cross refer people (recommendation 1.6.2) to the guidance on shared decision making in the NICE guidelines on medicines adherence, medicines optimisation and patient experience in adult NHS services.

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				AF Assoc strongly recommends that ALL DOACs are recommended as part of these AF guidance and based on NICE TAs	
Bayer PLC Current Situation •Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. •Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.co	Comments Form Question 1	N/A	N/A	**Question 1:** The recommendations which will have the biggest impact on practice and be challenging to implement are those in section 1.6 of the guideline – stroke prevention. Bayer have set out in their response that had the NICE guideline committee considered different evidence within the NMA, the value of real world evidence, the importance of patient adherence on outcomes and critically, the price the NHS actually pays for the DOACs, that they may have come to different conclusions. Bayer are concerned that the draft guideline as it stands could lead to flawed decision-making regarding choice of DOAC and inappropriate switching with the associated waste of valuable NHS resources and risk of adverse patient outcomes. Bayer supports the use of all DOACs within their marketing authorisations and according to the respective NICE technology appraisals. Had the guideline development taken into account different evidence in the SLR and NMA, considered the value of RWE, and applied the true NHS acquisition costs of DOACs, then the committee would likely have been presented with different findings and drawn different conclusions about the most clinically and cost-effective DOACs. Without head to head studies, there is insufficient and indeed conflicting evidence regarding the relative clinical and cost-effectiveness of the DOACs.	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making.

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resta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. •It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. Past Situation In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by					We now cross refer to the NICE guidelines with recommendations on adherence in recommendation 1.6.2.

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Nomad Bioscience GmbH from Bayer in 2012.					
Bayer PLC	Comments Form Question 2	N/A	N/A	**Question 2:** Implementation of section 1.6 of the guideline may have significant cost implications. Bayer have set out in their response that had the NICE guideline committee considered different evidence within the NMA, the value of real world evidence, the importance of patient adherence on outcomes and critically, the price the NHS actually pays for the DOACs, that they may have come to different conclusions. The recommendations on cost-effectiveness and DOAC ranking may not apply at local levels in the NHS due to commercial arrangements, leading to confusion, potentially flawed decision-making and waste of valuable NHS resources associated with switching treatments. Bayer supports the use of all DOACs within their marketing authorisations and according to the respective NICE technology appraisals. Had the guideline development process considered different evidence in the SLR, considered the value of RWE and applied different costs and assumptions within the economic model, then the committee would have been presented with different analyses on which to base their conclusions. There are insufficient robust analyses to recommend one DOAC over another.	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs (1.6.3 and 1.6.4). It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making.

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Bayer PLC	Comments Form Question 3	N/A	N/A	**Question 3**: Bayer considers that to overcome the challenges which will be raised by the draft recommendations in section 1.6, the NICE guideline committee should reconsider the preference given to two DOACs. Bayer supports the use of all DOACs within their marketing authorisations and according to the respective NICE technology appraisals. They have all been evaluated as being clinically and cost-effective based on their respective NHS list prices. Had the guideline development process considered different evidence in the SLR, considered the value of RWE and applied different costs and assumptions within the economic model, then the committee would have been presented with different analyses on which to base their conclusions. There are insufficient robust analyses to recommend one DOAC over another.	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee are no longer confident to recommend a specific DOAC or DOACs (1.6.3 and 1.6.4). It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making.
Bayer PLC	Comments Form Question 4	N/A	N/A	**Question 4:** The recommendations in this guideline were developed before the coronavirus pandemic. Please tell us if there are any particular issues relating to COVID-19 that we should take into account when finalising the guideline for publication.	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA

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				Bayer welcomes the displacement of vitamin K antagonists (VKAs) for appropriate patients needing an anticoagulant for stroke prevention in atrial fibrillation. The well-known limitations of VKA prescribing, monitoring and management have been further highlighted during the ongoing COVD-19 pandemic, with national guidance issued earlier in 2020, to review the management of patients taking warfarin (1-3). In light of this advice to review patients treated with warfarin during the ongoing COVID-19 pandemic, many patients will have been switched from warfarin to a DOAC. Switching to another DOAC within such a short period of time could undermine the doctor-patient relationship and would be a waste of valuable NHS resource. The recently published document by the NHS Confederation sets out the resource challenges and pressures ahead for the NHS in an era peri- and post-COVID 19 (4). The pandemic's impact on the capacity in the NHS is being felt and is likely to be felt for several years leading to a back-log of patients needing care as well as new demands on services. Switching 'programmes' would unnecessarily add to this pressure. Bayer supports the use of all DOACs within their marketing authorisations and according to the respective NICE technology appraisals. Had the guideline development process considered different evidence in the SLR, considered the value of RWE and applied different costs and assumptions within the economic model, then the committee would have been presented with different analyses on which to base their conclusions. There are insufficient robust analyses to recommend one DOAC over another.	estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs (1.6.3 and 1.6.4). It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making.

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				(1) Clinical guide for the management of anticoagulant services during the coronavirus pandemic. NHS England and NHS Improvement. March 2020. Publications approval reference: 001559 (2) NHS. Specialist Pharmacy Service. Management of patients currently on warfarin during Covid-19. April 2020, updated September 2020. https://www.sps.nhs.uk/articles/management-of-patients-currently-on-warfarin-during-covid-19/ (3) RPSGB. Guidance for the safe switching of warfarin to direct oral anticoagulants (DOACs) for patients with non-valvular AF and venous thromboembolism (DVT / PE) during the coronavirus pandemic. March 2020. https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Coronavirus/FINAL%20Guidance%20on%20safe%20switching%20of%20warfarin%20to%20DOAC%20COVID-19%20Mar%202020.pdf?ver=2020-03-26-180945-627 (4) NHS Confederation. NHS Reset: A New Direction for Health and Care. September 2020. https://www.nhsconfed.org/-/media/Confederation/Files/Publications/Documents/NHS-Reset-a-new-direction-for-health-and-care.pdf	
Bayer PLC	Economic Model	File: 'generat	443-444	**Utility estimation**	Thank you for your comment. It is correct that we assumed the utility following bleed was the same

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		e.transition.matrix.15'		There appears to be an error in the NICE model, in the estimation of utilities. The utility of a patient who has had a stroke is used for all patients who have experienced a non-cranial major bleeding event, even though these events are without lasting consequences. The model code notes this as "***Need evidence for post bleed utility (for now assume same as Stroke)***". The model should be re-run with a correct utility value for patients who have experienced a major bleeding event. Based on this and all of the feedback in this response, had the model used different evidence sources, inputs and assumptions, then the guideline committee will have been presented with different results and may have come to different conclusions.	as stroke. However, published EVPPI analysis on the pre-guidelines version of the model indicates that utilities have no impact on the results (EVPPI for utilities = 0) (Thom HHZ, Hollingworth W, Sofat R, et al. Directly Acting Oral Anticoagulants for the Prevention of Stroke in Atrial Fibrillation in England and Wales: Cost-Effectiveness Model and Value of Information Analysis. MDM Policy Pract 2019; 4(2): 2381468319866828.) We acknowledge that this is a limitation with the model. We have conducted a new sensitivity analysis where the utility in post-bleed states is set to be the same as AF well health state. The results and conclusions are unchanged.
Bayer PLC	Evidence Review G1	005	024 (Table 1: PICO characteristics of review question)	The guideline development group conducted their own systematic literature review (SLR) to support this guideline update, but it was the SLR and subsequent network meta-analysis (NMA) conducted by Lopez Lopez et al (1) that was used for decision making. The types of studies included in the SLR will play a major role in determining the reliability and relevance of the results. The CRD guidance for undertaking reviews in health care (2) states that *'the population considered should be relevant to the population to which the review findings will be applied'.* Of note, the Lopez Lopez NMA included 7/23 studies from China and Japan. It is generally believed that Asians are prone to bleeding when treated with warfarin, and the optimal range of INR for Asians might be narrower than that for non-Asians (3).Bayer therefore considers that these 7	Thank you for your comment. The protocol for the systematic literature review (SLR) did not exclude any populations based on ethnicity, and the array of studies in the SLR was very similar to that of Lopez-Lopez. Having decided on these studies pre-hoc it would be inappropriate to change the inclusion criteria post-hoc. Nevertheless, issues around differing ethnicities were taken into account by the committee during discussion, and the consensus was that the overall effects were relatively unaffected by the data from China and Japan.

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				studies were not conducted in a relevant patient population to answer the review question. Bayer considers that a review including Phase III RCTs and those conducted in a global population would be more relevant to the review question in England and Wales than one which includes Phase II RCTs, with limited patient numbers (7/23 studies), and those conducted exclusively in an Asian population (7/23 studies). If different study inclusion/ exclusion criteria been applied in the evidence review, then the findings and subsequent conclusions drawn by the guideline committee may have been different and of more relevance to the NHS. (1) Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN 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) Centre for Reviews and Dissemination, University of York. Systematic Reviews. CRD's guidance for undertaking reviews in health care. 2009. (3) Chiang et al. Stroke prevention in atrial fibrillation: An Asian perspective. Thromb Haemost 2014; 111: 789–797	
Bayer PLC	Evidence Review G1	005	024 (Table 1: PICO characte ristics of	The types of study included in the systematic review will play a major role in determining the reliability and relevance of the results. While some study designs are clearly more robust than others, this should not be the only factor in determining which types of study are	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.

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			review question)	eligible for inclusion (1). Bayer note that Real World Evidence (RWE) was not considered by the guideline committee and considers that it would have been appropriate and informative to do so. ***Summary*** Whilst RCTs are the gold standard for establishing the effects of an intervention, well conducted RWE studies could add value to decision making, especially considering the DOACs have been in routine NHS clinical practice for almost 10 years. Had RWE been considered as part of the SLR and subsequent decision making, the guideline committee would have been presented with different results and would likely have come to different conclusions. There are many limitations in making indirect comparisons between the DOACs based on RCTs, due to important differences in study design, patient characteristics and outcome definitions (2). RWE can address some of the difficulties of between trial comparisons especially if the patients treated in clinical practice have the same characteristics and the same outcome measures are used. Indeed, when an SLR and meta-analyses (MA) were conducted on RWE, the hazard ratio (HR) for ischaemic stroke for rivaroxaban compared with VKAs was more favourable (0.83, 95% CI 0.75-0.93) than that of apixaban vs VKA (1.01, 95% CI 0.87-1.17). A large proportion of the data contributing to the analyses were from the same populations (3,4). When incorporating the HRs for all outcomes considered in the MA, into an economic model, the ICER for rivaroxaban vs VKA was more favourable than the ICER for apixaban vs VKA (5). ***RCTs and NMA*** Well conducted RCTs are designed to give an unbiased estimate of treatment effects, but they are highly controlled experimental studies and cannot fully reflect	It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making. In addition, the NMA method used in Lopez-Lopez is specifically designed to not break randomisation.

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				what happens in uncontrolled routine clinical practice. The draft guideline recommendations however are based on a Network Meta-Analysis (NMA) of RCTs. NMAs do not preserve randomisation. Inclusion criteria of individual trials will lead to systematic differences between populations contributing to individual comparisons and introduce risk of bias. NMAs attempt to adjust for this by comparing relative risks rather than absolute event rates but this leaves open the possibility that patient characteristics may influence effectiveness (effect modification). As such, NMAs introduce the possibility that unobserved differences between populations will bias the results observed. In the work to support the guideline recommendations, a meta-regression was attempted to adjust for effect modifiers, but this was not universally possible. RWE can overcome some of these issues and contribute to the development of a comprehensive body of evidence on treatments from wide, unselected and diverse patient populations, and it can provide data on long-term effectiveness and safety and important information on treatment adherence and persistence. ***SLR and MA and cost effectiveness analysis using RWE*** When considering the DOACs, the differences in the design, patient populations and outcome definitions between the pivotal RCTs are evident, leading to limitations in making robust between study comparisons (2). DOACs have been in widespread NHS clinical practice for nearly 10 years, therefore Bayer considers that RWE should have been used to complement the data from RCTs, helpfully informing decision making and adding value to the guideline. RWE generated in study populations which have similar patient characteristics and use the same outcome definitions	

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				would be particularly valuable in decision making, overcoming those limitations when comparing the RCTs. A systematic literature review of RWE was recently undertaken and meta-analyses for rivaroxaban vs VKA and apixaban vs VKA were conducted (3,4). When the outputs of these analyses were included in a health economic model (5), the incremental cost per quality-adjusted life year was £14,437 for rivaroxaban, and £20,101 for apixaban, compared with VKA. The major driver of this economic model was ischaemic stroke. The meta-analyses for ischaemic stroke were based on 8 RWE studies for rivaroxaban and 4 RWE studies for apixaban. The results of the meta-analyses for this outcome were significantly in favour of rivaroxaban vs VKA, with a HR of 0.83 (95% CI 0.75;0.93), while the HR was calculated as 1.01 (95% CI 0.87;1.17) for apixaban vs VKA. As 3 studies (6-8), representing a large proportion of the data used in these meta-analyses, reported results for both treatments, no impact of study design, outcomes definition or population should be expected. Of note, another large study (9), contributing to the meta-analysis for rivaroxaban, reported very similar results, suggesting the results of this meta-analysis are robust. This supports the view that some of the differences observed in the outcomes reported in the pivotal Phase III studies could have been due to differences in study design, outcomes definition and baseline characteristics. Had the guideline committee considered RWE evaluating the DOACs, then the results and conclusions would be different. ***Importance of RWE in decision making*** From a methodological point of view, it has been widely recognised that, with the ever-expanding base of high-	

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				quality RWE globally, there is a growing need for the integration of RWE approaches to supplement existing methods of health technology assessment (HTA) and guideline development by assessment authorities (10). Bayer considers that evaluation of RWE is reflective of the position held in the manual PM20: 'Developing NICE guidelines: the manual'. It is stated that when writing guidance, a key stage involves a consideration of the harms and benefits of an intervention. In so doing, the following commitment is made: "*The committee should assess the extent to which the available evidence is about efficacy (the extent to which an intervention produces a beneficial result under controlled experimental conditions), effectiveness (the extent to which a specific intervention, when used under 'real world' circumstances, does what it is intended to do) or both*."(3). Health care decisions should be made with the benefit of all available information and Bayer believes that appropriately conducted and implemented RWE projects would reduce decision uncertainty. This is something currently being explored in the ongoing health technology evaluation methods review (12). The NICE statement of intent, "Widening the evidence base: use of broader data and applied analytics in NICE's work" details the variety of circumstances under which the use of RWE would be desirable in decision making, including addressing the efficacy - effectiveness gap (13). It is of interest to note that one of the research recommendations of Sterne et al, on which this guideline review was based, was '*information on long-term rates of the main efficacy and safety outcomes*	

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				among patients receiving anticoagulants for AF, for example from registries or health record data'(14). Further, Thom et al, on which the cost-effectiveness model was based (15) noted that '*considering AF is a lifetime chronic condition, the trials have (also) been of relatively short duration*' and '*NHS health record data could provide further evidence on absolute event rates'*, as well as acknowledging that (in relation to the RCTs), the '*differences from (the) general population are a limitation'*. Given these long-term data are now available in RWE studies, and are a key driver of cost effectiveness, they should be included in the evidence base. When the outcomes from clinical practice are considered the rankings of the DOACs for clinical and cost effectiveness will change. Therefore, recommending one DOAC over another within the guideline based purely on evidence from RCTs is flawed. ***High quality RWE*** As stated above, the DOACs have been used in clinical practice for many years resulting in an extensive body of RWE. As with RCT evidence, it should not be assumed that all studies are equally well conducted. The quality of the included studies should be formally assessed as this will impact on the reliability of the results and conclusions drawn. Bayer considers that the research question, the data source, the study population, treatment exposure, follow-up, outcomes as well as assessment of bias are all important considerations when evaluating RWE. A prospectively designed study, evaluating both safety and effectiveness in a relevant study population with sufficient follow-up to capture outcomes of interest, a	

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				clear definition of outcomes, and an assessment for selection bias could be considered an appropriate source of evidence. According to these criteria, XANTUS (a Phase IV post-approval safety study which was required and approved by the EMA) (16,17) and the independent Dresden registry (18-22) could be evaluated to inform decision making. The Phase IV XArelto on preveNtion of sTroke and non-central nervoUS system systemic embolism in patients with non-valvular atrial fibrillation (XANTUS) study was the first large, international, prospective, observational study of a DOAC in stroke prevention in patients with non-valvular atrial fibrillation (NVAF). The study was a post-approval safety study which was required and approved by the EMA. Independently adjudicated primary outcomes in XANTUS included major bleeding (using International Society on Thrombosis and Haemostasis [ISTH] criteria), all-cause mortality, stroke, systemic embolism, myocardial infarction (MI) and transient ischaemic attack (TIA). The outcome definitions of individual events were the same as those applied in the phase III ROCKET-AF study (23). Whilst the results of XANTUS cannot be directly compared with those from the Phase III ROCKET-AF study, stroke/ systemic embolism (SE) occurred at a rate of 0.8 events per 100 patient-years in XANTUS; in ROCKET AF the rate was 1.7 events per 100 patient years in the per-protocol, as treated population. The rate of major bleeding in XANTUS (2.1 events per 100 patient-years) was lower with that observed for patients receiving rivaroxaban in ROCKET AF (3.6 events per 100 patient-years) and rates of ICH, critical organ bleeding and fatal bleeding were similarly low. Major GI	

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				bleeding incidence rates observed in XANTUS (0.9 events per 100 patient-years) were lowerthan rates in ROCKET AF (2.0 events per 100 patient-years) (24). When rivaroxaban is used in uncontrolled clinical practice, the results of XANTUS indicate substantially lower event rates compared to those reported in the ROCKET AF RCT. This is an important finding - of the four pivotal Phase III studies, the ROCKET AF (rivaroxaban) study included patients with the highest risk profiles and greatest number of co-morbidities, which would have contributed to differences in event rates between studies. Had RWE such as XANTUS been considered by the committee in their decision making, the conclusions and recommendations may have been different. The DRESDEN NOAC Registry (18-22) is an ongoing prospective, observational database of private practices and community hospitals in Germany. It is unique in that it has been supported by all 4 DOAC companies whilst retaining its independence. In a pre-specified prospective manner, it has characterised NVAF patients allocated to each DOAC (separate streams published) and reported effectiveness and safety outcomes using the same pre-defined outcomes. The combined endpoint of stroke/transient ischaemic attack/systemic embolism occurred at a rate of 2.03 per 100-patient years (ITT - intention-to-treat analysis) for rivaroxaban (18), 2.4/100 patient-years for apixaban (20) and 2.93/100 patient-years for dabigatran (21). On-treatment major bleeding occurred at a rate of 3.0 per 100-patient years for rivaroxaban (18), 2.8/100 patient-years for apixaban (20) and 2.3/100 patient-years for dabigatran (21). Recently published data for edoxaban	

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				in this regard was 3.1/100 patient-years for major bleeding (22) with effectiveness data for edoxaban still awaiting publication. Considering this is the closest data to a direct head to head study, there is nothing within this unique independent data set to suggest a preference for one DOAC over another. ***Conclusion*** Based on all of this evidence, had high quality RWE been considered as part of the SLR and subsequent decision making, the guideline committee would have been presented with different results and come to different conclusions, as evidenced by the published RWE SLR, MA and cost-effectiveness analysis (3-5). Given that using alternate but valid data sources gives different results, limiting clinician and patient choice to two DOACs is inappropriate. (1) Centre for Reviews and Dissemination, University of York. Systematic Reviews. CRD's guidance for undertaking reviews in health care. 2009. (2) Camm et al. Challenges in comparing the non-vitamin K antagonist oral anticoagulants for atrial fibrillation-related stroke prevention. European Society of Cardiology. Europace. 2017. 1, 1-11. Doi: 10.1093/europace/eux086 (3) Briere et al. Real-world clinical evidence on rivaroxaban, dabigatran, and apixaban compared with vitamin K antagonists in patients with nonvalvular atrial fibrillation: a systematic literature review. Expert Review of	

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				Pharmacoeconomics & Outcomes Research 2019. 19:1, 27-36. (4) Coleman C et al. Meta-analysis of real-world evidence comparing non-vitamin K antagonist oral anticoagulants with vitamin K antagonists for the treatment of patients with non-valvular atrial fibrillation. J Mark Access Health Policy. 2019 Feb 4;7(1):1574541 (5) Bowrin K et al. Real-world cost-effectiveness of rivaroxaban and apixaban vs VKA in stroke prevention in non-valvular atrial fibrillation in the UK. J Mark Access Health Policy. 2020 Jun 25;8(1):1782164. (6) Yao X, et al. Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. Journal of the American Heart Association 2016;5(6) doi: 10.1161/jaha.116.003725 (7) Larsen TB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ (Clinical research ed) 2016;353:i3189. doi: 10.1136/bmj.i3189 (8) Naganuma M, et al. Renal Function and Treatment Persistence with Non-Vitamin K Antagonist Oral Anticoagulants in Japanese Patients with Atrial Fibrillation: A Single-Center Experience. Rinsho yakuri/Japanese Journal of Clinical Pharmacology and	

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				Therapeutics 2016;47(3):115-22. doi: 10.3999/jscpt.47.115 (9) Norby FL, et al. Abstract P005: Comparative Effectiveness of Rivaroxaban versus Warfarin for the Treatment of Patients with Non-valvular Atrial Fibrillation. Circulation 2016;133(suppl_1):AP005-AP05. doi: doi:10.1161/circ.133.suppl_1.p005 (10) Klonoff D C. The expanding role of real-world evidence trials in health care decision making. Journal of Diabetes Science and Technology. 2020 Jan; 14 (1): 174-179 (11) NICE. Developing NICE guidelines: the manual. October 2014. www.nice.org.uk/process/pmg20 (12) NICE news. https://www.nice.org.uk/news/article/nice-announces-details-of-health-technology-evaluation-methods-review (13) NICE. Widening the evidence base: use of broader data and applied analytics in NICE's work https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-guidelines/how-we-develop-nice-guidelines/statement-of-intent.docx (14) Sterne et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis	

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				(15) Thom et al. Directly Acting Oral Anticoagulants for the Prevention of Stroke in Atrial Fibrillation in England and Wales: Cost-Effectiveness Model and Value of Information Analysis. MDM Policy and Practice. 2019:1-14.DOI: 10.1177/2381468319866828 (16) Camm AJ, et al. XANTUS: rationale and design of a noninterventional study of rivaroxaban for the prevention of stroke in patients with atrial fibrillation. Vasc Health Risk Manag 2014; 10: 425–434. (17) Camm AJ, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2016; 37: 1145–1153. (18) Hecker J, et al. Effectiveness and safety of rivaroxaban therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. Thromb Haemost 2016; 115: 939–949 (19) Beyer-Westendorf J et al. Rivaroxaban real-world evidence: Validating safety and effectiveness in clinical practice. Thromb Haemost 2016; 116 (Suppl 2): S13–S23 (20) Helmert S et al. Effectiveness and safety of apixaban therapy in daily care patients with atrial fibrillation: results from the Dresden NOAC Registry. J Thromb Thrombolysis 2017;44:169–178. (21) Beyer-Westendorf et al. Effectiveness and safety of dabigatran therapy in	

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				daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. Thromb Haemost. 2015 Jun;113(6):1247-57 (22) Beyer-Westendorf et al. Rates, management and outcome of bleeding complications during edoxaban therapy in daily care - results from the DRESDEN NOAC REGISTRY. Thromb Res. 2020 Jun;190:91-98 (23) Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883–891. (24) Sherwood et al. Gastrointestinal Bleeding in Patients With Atrial Fibrillation Treated With Rivaroxaban or Warfarin. ROCKET AF Trial. J Am Coll Cardiol 2015;66:2271–81	
Bayer PLC	Evidence Review G1	041 056	018 - 019 010-015 Table 17	In the absence of head to head trial data, comparisons based on indirect evidence are possible however, depending on the methodology applied, different indirect comparisons may come to different conclusions. The DOACs are a great example of this, with multiple indirect comparisons and network meta-analyses being published over the past decade, often with inconsistent findings. Regardless of how well planned and rigorous the analysis is conducted, there will be important limitations that need to be considered when interpreting the findings (1). When conducting a systematic literature review to identify the evidence for inclusion in any indirect comparison, the types of study included will play a major role in determining the reliability of the results.	Thank you for your comments. On further discussion the committee agreed that the NMA by Lopez Lopez was probably not able to adequately adjust for the differences between treatment comparisons in terms of population characteristics that could affect outcome. Initially the committee agreed that the meta-regressions used were adequate, but after consideration of the numbers of studies involved it does seem unlikely that the meta-regression would have been able to make realistic adjustments to effect that were sufficient to negate inter-comparison differences in prognostic characteristics. We have therefore amended the guideline to not recommend any of the 4 DOACs over any other (1.6.3 and 1.6.4).

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				When making indirect comparisons, the analyses and findings are limited by factors such as differences in study design, study size, patient characteristics, dose adjustments and study outcome definitions. If all potential sources of heterogeneity and all potential treatment effect modifiers are not considered and adjusted for, then it will limit the reliability of the results. Whilst it would appear that treatment effect modifiers were considered in developing this guideline (page 43), ***"there were insufficient data to evaluate all potential effect modifiers***(page 56)." Those not sufficiently evaluated included ethnicity or race, body mass index or weight, renal status or creatinine clearance, blood pressure, diabetes mellitus, hypertension, previous thrombotic event, liver disease, chronic heart failure, cancer, pregnancy, intervention dose, CHA2DS2-VASc score, HAS-BLED score, history of previous stroke or transient ischaemic attack, previous myocardial infarction (taken from the list on page 43). As such, it would appear that the evidence does not allow for any of these important potential treatment effect modifiers to be taken into account. Amongst the pivotal Phase III trials there are important differences in the risk profiles of the patients included. As an example, within ROCKET-AF (2) more than half the population had already had a prior stroke or TIA – within the ARISTOTLE study (3) that figure was only 19%. Similarly, 63% of patients in ROCKET-AF had heart failure v 36% in ARISTOTLE and regarding diabetes it was 40% vs 25%. There were also important differences in the pivotal Phase III studies in outcome definitions, for example, major bleeding. The definition of a major bleed in relation to a drop in haemoglobin was similar in all the	

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				DOAC studies (2,4,5) with the exception of the apixaban study (3). Within ARISTOTLE, a 2g/dl drop in haemoglobin was only considered a major bleed if the drop occurred within a 24-hour period (6). In all the other studies, the same drop in haemoglobin was counted as a major bleed irrespective of how long it took for the concentration to drop. This difference in definition, and failure to account for it, reduces the certainty regarding the comparative bleeding profile of the DOACs. Furthermore, and noticeably incongruous are the results in the respective Phase III studies regarding clinically relevant non-major (CRNM) bleeding rates (1). A key method for assessing the potential impact of differences in bleeding definitions is to compare the bleeding rates in the reference warfarin arms of the respective trials. If the trial populations were very similar, and the definitions and study methods were similar, then the warfarin arms would be expected to report similar rates of bleeding However, differences in defining CRNM bleeding events, appear to have a marked effect on the differences in recorded incidences of CRNM bleeding in the warfarin arms across the studies. In ARISTOTLE, the reported annual incidence of CRNM bleeding for warfarin was 2.92% (3), which was less than one-third of the incidence reported for ROCKET AF (11.4%) (2) and ENGAGE AF (10.2%) (4). Clinically relevant non-major bleeding was not reported in RE-LY (5). That such significant differences exist in one of the key safety outcomes across the Phase III studies but with the same drug (warfarin), renders direct or indirect comparisons of bleeding event rates across the trials unreliable. Comparisons of reported bleeding events	

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				are thus misleading unless they take all these factors into consideration (1). Of additional concern is the assumption in the NMA that time in therapeutic range with warfarin has no impact on either stroke risk or risk of bleeding. [Appendix 5, page 56, lines 10-15]. *"For mean TTR, there was no evidence that effect modification had taken place for the outcome of stroke/SE (estimated coefficient 0.0021 with 95% CI −0.07 to 0.08 per 1% increase in mean TTR) or major bleeding (estimated coefficient 0.04 with 95% CI −0.03 to 0.12 per 1% increase). The estimated coefficients were not reported for the other NMA outcomes but Sterne, 2017 stated in their conclusions that there was no evidence of effect modification due to TTR".* However, the suggestion that lower TTR is associated with higher bleeding risk is not an isolated finding in this analysis. The link between INR and bleeding risk is well documented and understood. The inability of this meta-regression to detect a statistically significant association between TTR and bleeding does not prove that this relationship does not exist and should be considered in the light of broader evidence and opinion. The TTR in individual studies ranges from 45.1% and 83% [Page 41, Table 17] and the NMA in effect assumes all these arms are equally effective. The guidelines committee should seek expert medical input as to whether TTR values of 45.1% and 83% are meaningfully different. If this degree of TTR difference meaningfully impacts the effectiveness of warfarin then it is not robust to treat the warfarin arms from the individual trials as a single identical intervention, and the relative risks in the NMA are not robust.	

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				Without taking account of, and adjusting for, **all** potential sources of heterogeneity and treatment effect modifiers, it is statistically and clinically inconsistent to draw robust conclusions about the respective risk-benefit of the DOACs. Bayer considers that in light of the challenges associated with conducting robust NMA, that the evidence presented to the guideline committee is hypothesis generating rather than definitive and should not be used as the basis of advice to the NHS. The guideline committee could therefore have come to the alternative conclusion that there is insufficient evidence to recommend one DOAC over another. Consideration of RWE could have led to the committee being presented with different results and coming to different conclusions. As such, Bayer considers there is a lack of robust evidence to recommend any DOAC over another. (1) Camm et al. Challenges in comparing the non-vitamin K antagonist oral anticoagulants for atrial fibrillation-related stroke prevention. European Society of Cardiology. Europace. 2017. 1, 1-11. Doi: 10.1093/europace/eux086 (2) Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883–891. (3) Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2011; 365(11):981-992 (4) Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al. Edoxaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2013; 369(22):2093-2104	

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				(5) Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2009; 361(12):1139-1151 (6) Protocol for: Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.	
Bayer PLC	Evidence Review G1	053- 055	003 - 008	The rankings reported in these graphs are not accompanied by statements about statistical significance. On visual inspection it appears that very few estimates reach the conventional threshold of 95% confidence. It is also not stated how the confidence levels have been adjusted for the multiple comparisons performed. In the absence of this information Bayer, concludes that these graphs show that none of the DOACs has been shown to be significantly more likely than any other to be higher or lower ranked.	Thank you for your comment. The rankings are themselves probabilistic, and provide a *probability* that a treatment is the best, without making a definitive statement that a treatment *is* the best.
Bayer PLC	Evidence Review G2	042 073 074 092	020-023 016 - end 001 - 034 016	Economic models have inherent limitations and results are affected by decisions taken by the developers while creating the model, as well as by the underlying evidence. If a different model structure is considered, different selection criteria are used for identifying the data, or different assumptions are used, then the model may give different findings. The committee should consider the strengths and limitations of the modelling methodology when deciding how the model results should contribute to guidelines. Bayer considers that if different approaches to modelling had been taken, according to the evidence found in the SLR of economic models, different assumptions, different evidence (including RWE) and importantly, costs applied, then the committee may have been	Thank you for your comment. We acknowledge the issue of not using reference costs for ICH and stroke event or management costs. Reference costs were not available for management costs, so it was necessary to use the Luengo 2013 study in the UK. As it would be difficult to avoid double counting costs if using reference costs for event costs and Luengo 2013 for management costs, we took both from Luengo 2013 to be consistent. In acknowledgement of this limitation, we have added a sensitivity analysis setting MI, ICH, and stroke event and management costs to zero. In this extreme sensitivity analysis, Apixaban remains the most cost-effective treatment,

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				presented with different results on which to base their recommendations. The decision to recommend two of the four available DOACs ahead of others appears to be influenced by the reported finding of the probabilistic analysis, in particular that "*Apixaban had the highest incremental net monetary benefit and a probability of being the most cost effective of 46%. This was followed very closely by dabigatran (41% probability cost effective)"* [Page 73 lines 27-29]. Similar results are subsequently reported for certain scenario analyses. Bayer believes that the results reported do not reflect all the potential uncertainties in the modelling and overstate the strength of evidence available to compare different DOACs. If other valid approaches or data sources had been used, then the findings and conclusions may have been different. ***Model states*** The NICE model considers four main events: stroke, MI, intracranial haemorrhage (ICH) and major bleeding. Subsequent states in the model occur when patients have experienced two or more of these events. Other model structures are consistent with the evidence available. For example: • The NICE model considers a single state for stroke. However, of 12 published UK models that were identified in the systematic review but not considered by the committee,10/12 models consider separate cost and utility decrements for strokes of different severity levels. Stroke costs and prognosis vary	although rivaroxaban is more cost-effective than dabigatran. In response to the query about list prices, we have now included a threshold analysis with results below. This indicates that edoxaban (£178 per year) and rivaroxaban (£139 per year) would need to be available at implausibly low prices to be considered more cost-effective than apixaban. We acknowledge the comment that absolute costs on each of the drugs are higher than in previous economic models. Part of this was due to an error in the coding of the annual stroke costs. Now this is corrected there is less of a difference. However, the cost differences between drugs are very small and, as suggested by our threshold analysis and sensitivity setting ICH, MI, and stroke costs to zero, changes have very little impact. Furthermore, it is the relative costs that affect results, not the absolute costs. Previous models have not captured the compounding risks - for example, patients who experience stroke are then at higher risk of more stroke, and thus are more likely to accrue higher costs. We also generally modelled more events and included both acute and management costs. These differences affect all drugs equally and, as explained above, do not affect results or conclusions. Please note that this model underwent rigorous validation/peer review by the BMJ group who have expertise in R and Bayesian statistics. The inclusion of only the costs and not effectiveness of reversal agents was a noted

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				substantially by severity and the effect of this simplification on the model findings is unknown • Some but not all of the NMA findings were implemented in the model. The model developers do not appear to have considered all-cause mortality, although NMA data were available. The rationale for not using the mortality data is not stated. The effect of this decision on the model findings is unknown. Alternative model structures were possible and have been used in many other analyses. Uncertainty introduced by the choice of model states is not reflected in the confidence intervals reported. If other health states had been included within the chosen model, then the findings and conclusions may be different. ***Cost sources*** Cost sources used in the NICE model [appendix 6, page 92, line 16 – table 12] are not consistent. NHS reference costs are used for most events, and this approach is consistent with recommendations in the NICE reference case. Costs for stroke and ICH are however taken from an alternative source; Table 12 notes that the cost of ICH is based on 17 cases. The cost of AMI has also been arbitrarily multiplied by 2 ("*doubled to include follow-up costs*"). For other events, follow up costs were estimated using a separate post event maintenance cost per time period, allocated to patients who are alive after experiencing an event. Bayer also notes that the stroke and ICH costs are very high compared to the costs of events estimated using standard NHS reference costs. The	limitation of the analysis hence why this was only included in a sensitivity analysis. With regard to the other points raised in your comment, please note that recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC, thus minimising the impact of these concerns on the final recommendation.

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				effect of this decision on the model findings is however unknown. If NHS reference costs and more granular health state costs been applied e.g. by stroke severity, then the findings and conclusions may be different. Another point to highlight is that Bayer notes that NHS list prices of DOACs have been used in the analyses [Evidence review 5 – page 66 , line 24 (Table 28)], which are misleading and undermine the results as they are not reflective of the true drug acquisition cost to the NHS. ***Switching*** The model assumes lifetime treatment with DOACs unless patients experience a relevant event, and that patients experiencing certain events on a DOAC will be switched to warfarin. The converse is not true – warfarin patients who experience events do not switch to DOACs. The model does not appear to contain any evidence about effectiveness and safety that is specific to second line patients. The size of the additional uncertainty introduced by the inconsistent treatment pathways or lack of relevant data is unknown. ***Validation*** The guideline does not report external validation of the model, for example comparing cost-effectiveness findings against other models or comparing predicted event rates to those observed in other data sources. A number of other UK based models exist that could allow comparison. The systematic review identified a large number of economic evaluations. However, the guideline committee considered as relevant only two economic models, chosen because they contained all of the alternatives of interest. The models chosen are however not the only or necessarily the best way to address the question. Thirteen UK based economic	

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				analyses (12 were full economic models) were identified but not reviewed, so potentially relevant alternative approaches to the model structures and data inputs were not considered, and this aspect of external validity was not explored. Some differences exist between the NICE model and much of the published literature. One important model output is the expected cost per patient. Estimated per patient costs in the NICE model for warfarin treated patients is £28,796. The cost per patient for the DOACs range from £25,922 to £30,427. In the 12 full economic models identified but not reviewed, the cost per patient for warfarin varies and the median value is £7,694, around a quarter of the matching cost in the NICE model. The median values for individual DOACs range from £8,941 to £10,631. No explanation is offered for this large discrepancy in expected cost between the NICE model and other analyses. The large difference in cost per patient (despite all models using list prices e.g. BNF) suggests to Bayer that there are other valid approaches. Had these different approaches to costing been considered, they may have resulted in different DOACs being found to be the most cost effective. Without a valid justification, it seems inappropriate to base the recommendation of one DOAC over another on results from a model where per patient costs are so inconsistent with that reported in the wider body of evidence. The multitude of models in the literature have been produced over a period of time in which there was little change in the underlying RCT clinical evidence. The models reflect the pivotal trials undertaken during the development of the DOACs, or quantitative synthesis of these trials. The NICE model is more comprehensive than some others in that it is based on	

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				an SLR of RCT data available up to ~2017; other models have been more selective in the evidence sources used. However, inspection of the comparative effectiveness inputs suggest that the models are broadly consistent in the sources used to estimate comparative effectiveness. The large differences in per patient cost appears to result from choices made by model developers, not the underlying evidence. As such, the NICE model gives very different results from other models that use similar underlying data. Bayer does not believe that the confidence intervals reported by NICE fully reflect the uncertainty in the underlying evidence. Bayer believes that a fuller assessment of uncertainty, considering alternative modelling methods from the literature, would find that the economic evidence is not sufficient to make a robust ranking of DOACs. Considering a different, yet valid approach would likely have generated different results and subsequent recommendations, especially if the true acquisition cost of the DOACs to the NHS been considered. ***Costs of reversal agents*** The inclusion of the costs of reversal agents in the model is a novel feature of the NICE analysis and reflects newly available and potentially costly additions to the treatment pathway. However, no effectiveness data for these agents was included. Presumably these agents have clinical value in improving bleeding outcomes which has not been addressed, so this change increases costs in some but not all the model arms without reflecting QALY gain. Bayer suggests that this introduces additional uncertainty to the expected QALY value per patient which is not reflected in the confidence intervals reported.	

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				By limiting the review of the economic literature to two models, the authors have potentially under-represented the degree of uncertainty in the comparative cost-effectiveness. ***Interpretation*** Bayer does not believe that the committee's interpretation of the cost-effectiveness findings fully reflects the full body of available evidence. We note the difference in preference ordering between the 2017 and 2020 versions of the analysis – in 2017, rivaroxaban was rated by the current authors and using the same model, as having the second highest net present value [appendix 6, page 42, lines 20-23]. The change in preference is hard to understand given that the new analysis includes no new clinical data. Bayer suggests that the committee should be more cautious in interpreting the results. If different approaches to modelling been taken according to the evidence found in the SLR, different assumptions and importantly, costs applied, then the committee may have been presented with different results on which to base their recommendations. If RWE had been considered in decision making and cost-effectiveness analyses, then the results would certainly have been different, as evidenced by the published RWE SLR, MA and cost-effectiveness analysis (1-3). Given that other valid approaches to evidence generation and modelling give different results it is inappropriate to limit patient and clinician choice to two DOACs. (1) Briere et al. Real-world clinical evidence on rivaroxaban, dabigatran, and apixaban compared with vitamin K antagonists in patients with nonvalvular	

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				atrial fibrillation: a systematic literature review. Expert Review of Pharmacoeconomics & Outcomes Research 2019. 19:1, 27-36. (2) Coleman C et al. Meta-analysis of real-world evidence comparing non-vitamin K antagonist oral anticoagulants with vitamin K antagonists for the treatment of patients with non-valvular atrial fibrillation. J Mark Access Health Policy. 2019 Feb 4;7(1):1574541 (3) Bowrin K et al. Real-world cost-effectiveness of rivaroxaban and apixaban vs VKA in stroke prevention in non-valvular atrial fibrillation in the UK. J Mark Access Health Policy. 2020 Jun 25;8(1):1782164.	
Bayer PLC	Evidence Review G2	061	001-020	When making indirect comparisons, the analyses and findings are limited by factors such as differences in study design, study size, patient characteristics and study outcome definitions. If all potential sources of heterogeneity and all potential treatment effect modifiers are not considered and adjusted for, then it will limit the reliability of the results. The Evidence Review 6 document states: "*We had planned to use subgroup and meta-regression analyses to examine the extent to which patient-level and study-level characteristics explain between-study heterogeneity. We pre-specified important characteristics to be age, gender, ethnicity/race, body mass index or weight, renal status or creatinine clearance, blood pressure, diabetes mellitus,*	Thank you for your comments. On further discussion the committee agreed that the NMA by Lopez Lopez was probably not able to adequately adjust for the differences between treatment comparisons in terms of population characteristics that could affect outcome. Initially we had felt that the meta-regressions used were adequate, but after consideration of the numbers of studies involved it does seem unlikely that the meta-regression would have been able to make realistic adjustments to effect that were sufficient to negate inter-comparison differences in prognostic characteristics. We have therefore amended the guideline to not recommend any of the 4 DOACs over any other (1.6.3 and 1.6.4).

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				hypertension, previous thrombotic event, liver disease, chronic heart failure, cancer, pregnancy, intervention dose, average time in therapeutic range in the warfarin group and summary assessment of risk of bias for each outcome. Additional factors for AF trials were CHADS2, CHADS2VASC, HAS- BLED, history of previous stroke or transient ischaemic attack and previous myocardial infarction."…… *…… "**Investigation of between-study variation using these characteristics could not be studied in most cases, due to the lack of multiple trials of the same pair-wise comparison**, although we conducted some sensitivity analyses for the review of stroke prevention in AF patients."* Meta-regression should generally not be considered when there are fewer than ten studies in a meta-analysis (1). Arguably one of the most important outcomes is intracranial bleeding and for this network, there were only seven trials included. As a complete investigation of between-study variation of important characteristics could not be studied, Bayer considers there is too much uncertainty in the evidence and subsequent evidence synthesis, to recommend any DOAC over another. The recent ISAR-REACT 5 (2) study illustrates why the conclusions drawn from systematic reviews and meta-analyses are not necessarily borne out when a subsequent independent direct head to head study is undertaken. The hypothesis of the ISAR-REACT study was that "Ticagrelor is superior to prasugrel in patients with acute coronary syndrome (ACS) in terms of clinical outcomes" (3).	

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				An earlier adjusted indirect comparison meta-analysis demonstrated that prasugrel and ticagrelor were both superior to clopidogrel for ACS with similar efficacy and safety (4). A subsequently published Bayesian network meta-analysis of RCTs to compare the efficacy and safety of clopidogrel, prasugrel and ticagrelor in patients with ACS, concluded that ticagrelor has the best net efficacy and safety profile (5). Indeed, for a variety of reasons, including a perceived advantage in early administration and other potential pleiotropic effects, ticagrelor was postulated to be the overall more efficacious choice and this was the rationale behind the ISAR-REACT 5 study (3,6). The results of the ISAR-REACT 5 study were at complete odds with the study hypothesis in that it was prasugrel that was shown to be superior in the primary endpoint with the incidence of major bleeding not significantly different between the two groups (2). As a consequence of ISAR-REACT 5, certain recommendations in clinical guidelines have been amended to reflect the outcomes and now position prasugrel as the preferred choice in NSTE-ACS patients who proceed to PCI (7). This is an example of where the conclusions of meta-analyses, together with clinical hypotheses can be 'overturned' when subsequent direct head to head studies are undertaken. Without head to head studies of the DOACs, it is not possible to make definitive conclusions about their relative efficacy and safety. Bayer considers that in light of the challenges associated with conducting robust NMA, that the evidence presented to the guideline committee is hypothesis generating rather than definitive. The guideline committee could therefore have come to the	

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				alternative conclusion that the analyses are insufficiently robust to recommend one DOAC over another, as not all of the potential treatment effect modifiers had been adjusted for, limiting the reliability of the NMA results. (1) Cochrane Handbook for Systematic Reviews of Interventions. Version 6.1. 2020.https://training.cochrane.org/handbook/current (2) Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes - N Engl J Med 2019; 381:1524-1534 (3) Protocol for: Schüpke S, Neumann F-J, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019;381:1524-34. DOI: 10.1056/NEJMoa1908973 (4) Biondi-Zoccai G, Lotrionte M, Agostoni P, Abbate A, Romagnoli E, Sangiorgi G, et al. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. Int J Cardiol. 2011;150:325–31. (5) Shah et al. Meta-Analysis of the Relative Efficacy and Safety of Oral P2Y12 Inhibitors in Patients With Acute Coronary Syndrome. Am J Cardiol 2017;119:1723e1728 (6) Randomized Comparison of Ticagrelor versus Prasugrel in Patients with Acute Coronary Syndrome and Planned Invasive Strategy—Design and Rationale of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 Trial. J. of Cardiovasc. Trans. Res. (2014) 7:91–100	

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				(7) 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC), European Heart Journal, , ehaa575, https://doi.org/10.1093/eurheartj/ehaa575	
Bayer PLC	Guideline	008 009 010	022 - 024 001 - 028 001 - 021	Bayer considers that each patient should be involved in the choice of treatment after being provided with key information to inform decision making, including dosing frequency. Indeed, theNHS constitution states that patients are at the heart of everything we do and should be involved in decisions around medications (1). Bayer are concerned that the draft guideline gives preference to apixaban and dabigatran which are both dosed twice daily; rivaroxaban is a DOAC that is dosed once daily. 86% of UK AF patients in a European survey expressed a preference for OD daily dosing (2,3), with 43% of patients in another study indicating that dosing frequency is the most important attribute for a patient's choice of DOAC (4). Given that patient preference may influence long term adherence (5) and poor adherence to DOACs is linked with high stroke rates, particularly in those with a CHA2DS2-VASc score ≥2 (6) frequency of dosing	Thank you for your comment. In recommendation 1.6.2 we now refer to shared decision making and cross reference the NICE guideline on patient experience of adults NHS services. Recommendation 1.6.3 and 1.6.4 now recommends that any licensed DOACs should be prescribed. Recommendation 1.6.1 explains that discussion of the risks and benefits of anticoagulation should take into account the person's preferences and clinical risk profiles. The committee's discussion of the evidence in evidence review G1 has been edited to explain that adherence and dosing frequency were considered when making the recommendations.

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				should be considered alongside efficacy and safety when providing a DOAC option to patients with NVAF. To achieve the outcomes reported in the pivotal studies, it is important that patients are dosed appropriately and adhere to their prescribed regimen. It is widely recognised that inappropriate dose reductions are frequent in clinical practice, thus increasing the risks of stroke/systemic embolism, hospitalisation, and death, but without decreasing bleeding risk (7). Rivaroxaban has demonstrated lower levels of inappropriate dosing in UK practice (8). Further, compliance with rivaroxaban dosed once daily has been shown to be higher than that of the DOACs which are dosed twice daily (9). In the Phase IV XANTUS RWE study (10), treatment persistence remained high over the 1-year study period, with 80% of patients remaining on rivaroxaban therapy. A total of 75.1% of rivaroxaban patients (5,096/6,785) reported to their physicians that they were 'very satisfied' or 'satisfied' with their treatment. In light of the increased use of virtual consultations and the importance of patient self-management during the COVID-19 pandemic, patient choice alongside physician preference has never been more important in supporting adherence and persistence. Bayer concludes that in order to optimise adherence and outcomes, once daily treatment options should be offered within the guideline, for all patients, rather than those in whom apixaban and dabigatran are not tolerated.	

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				(1) https://www.gov.uk/government/publications/the-nhs-constitution-for-england/the-nhs-constitution-for-england#patients-and-the-public-your-rights-and-the-nhs-pledges-to-you (2) Zamorano J, et al. Presented at ESC Congress 2012, Paris, France (3) Bakhai et al. Patient perspective on the management of atrial fibrillation in five European countries. BMC Cardiovascular Disorders 2013, 13:108 (4) Wilke T, et al. Patient Preferences for Nonvitamin K Antagonist Oral Anticoagulants in Stroke Prevention: A Multicountry Discrete Choice Experiment. Cardiol Res Pract 2019;2019:5719624 (5) Wilke T, et al. Patient Preferences for Oral Anticoagulation Therapy in Atrial Fibrillation: A Systematic Literature Review. Patient 2017;10:17–37 (6) Yao X, et al. Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation. J Am Heart Assoc 2016 Feb 23;5(2):e003074 (7) Hindricks G, et al. Eur Heart J 2020; Epub ahead of print (8) Rodriguez G, et al. Appropriateness of initial dose of non-vitamin K antagonist oral anticoagulants in patients with non-valvular atrial fibrillation in the UK. BMJ Open 2019 Sep 20;9(9):e031341. (9) Andrade JG, et al. Values and Preferences of Physicians and Patients With Nonvalvular Atrial Fibrillation Who Receive Oral Anticoagulation Therapy for Stroke Prevention. Can J Cardiol 2016 Jun;32(6):747-53.	

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				(10) Camm AJ, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2016; 37: 1145–1153	
Bayer PLC	Guideline	009 010	006-028 001-004	The draft guideline states (section 1.6.2) that apixaban, dabigatran, edoxaban and rivaroxaban are all recommended options, within their marketing authorisation for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation, in line with the criteria specified in the relevant NICE technology appraisal guidance on direct-acting oral anticoagulants (DOACs). Bayer agrees with the recommendation in section 1.6.2 and considers that the sections in the guideline that follow this recommendation (1.6.3, 1.6.4, 1.6.5 and 1.6.7) are not supported by the full body of available evidence, do not take into account clinician and patient preference, which is advocated in section 1.6.1., and are based on incorrect drug acquisition costs, leading to misleading conclusions, with the potential for an inadvertent negative impact on both patients and the NHS. Without head to head randomised controlled trial (RCT) comparisons, there are significant limitations in making indirect comparisons and insufficiently robust evidence is available to distinguish between the DOACs. In our response to the draft guideline, Bayer sets out the limitations of the approach taken and how consideration of different evidence and different costs, including both drug acquisition and health state costs, would have led	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Anticoagulant treatment should be prescribed in the context of shared decision making (1.6.2). The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available

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				to different results and ultimately, different recommendations by the committee. As such, Bayer does not agree with the recommendations in sections 1.6.3, 1.6.4, 1.6.5 and 1.6.7 of the draft guidelines and would advocate that all four DOACs should be options. Recommendations based on drug acquisition costs that are not applicable in general practice are misleading to the NHS and may lead to a waste of valuable NHS resource. It is interesting to note that Thom et al. (1), on which the cost-effectiveness model was based, stated in their discussion that **'*the similarity in net benefits across DOACs suggest the choice be left to physicians for individual patients*'.** Bayer advocates the removal of sections 1.6.3, 1.6.4, 1.6.5 and 1.6.7 from the draft guideline. (1) Thom et al. Directly Acting Oral Anticoagulants for the Prevention of Stroke in Atrial Fibrillation in England and Wales: Cost-Effectiveness Model and Value of Information Analysis. MDM Policy Pract. 2019 Aug 17;4(2):2381468319866828	reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.
BNF Publications	Guideline	008	020	Regarding the statement: "*In 2020 the use of direct-acting oral anticoagulants described in recommendations 1.6.3, 1.6.4 and 1.6.5 was an off-label use in people with atrial fibrillation who do not have specific additional risk factors".*	Thank you for your comment. We have deleted the warning box.

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				As this statement precedes the recommendations 1.6.3-1.6.5, it seems to imply that these recommendations include off-label uses of apixaban, dabigatran, edoxaban and rivaroxaban. However, recommendations 1.6.3–1.6.5 do not recommend use in patients with no additional risk factors, and therefore all of these recommendations as written are within the marketing authorisations. (All of these agents are licensed for use in**non-valvular atrial fibrillation** (NVAF), **with one or more risk factors**, **such as** [lists risk factors from CHADS2 score].) Please could you clarify what is meant by "**specific additional risk factors**" (i.e. is this referring to CHADS2VASC)? The SPCs list specific risk factors but do not provide an exhaustive list, as indicated by use of "such as". Is the purpose of this statement to highlight that these agents have previously been used in patients with AF who have **no risk factors for stroke**, **other than AF?** (which would be inappropriate according to this draft guidance).	
Boehringer Ingelheim	Evidence review G1	005 069	024 031-033	We were concerned that stroke, and particularly ischaemic stroke (which accounts for ~85% of atrial fibrillation-related strokes) was not included as an outcome, given that the aim of treatment with anticoagulants is to prevent complications, particularly stroke. As a cross-sectional survey of 937 patients with AF showed that a large proportion (47.4%) of patients	Thank you for your comment. Stroke was included as an outcome (All stroke or systemic embolism).

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				nominate stroke prevention as the most important factor in their choice of oral anticoagulant, major bleeding was considered to be the second most important factor (14.7%) (Lane DA, et al. Clin Cardiol 2018;41:855-861); these should be weighted accordingly when evaluating options for the national recommendation.	
Boehringer Ingelheim	Evidence review G1	016	General	We are concerned that the NICE evidence review and the network meta-analysis by Lopez-Lopez did not include the updated results of the RE-LY trial (Connolly SJ, et al. N Engl J Med 2014;371:1464-1465). While the additional events identified in this update do not change the overall conclusions of the trial, the effects of the two doses of dabigatran as compared with warfarin on rates of stroke or systemic embolism and major bleeding were minimally changed and this may affect the results of the Lopez-Lopez network meta-analysis.	Thank you for your comment. The committee made a decision to use the Lopez Lopez data to contribute to our decision-making (see committee's discussion of the evidence in evidence review G1), and it was not possible for us to make changes to the data they had used. However, the committee have now decided to amend the recommendation to not recommend one DOAC over another, and so we are confident that the omission of most recent data from the RE-LY trial will not have affected interpretations. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Boehringer Ingelheim	Evidence review G1	046- 053	General	We would like to advise that the direct evidence odds ratios for the comparisons between dabigatran 150mg bd and 110mg bd with warfarin in Tables 18-22 and 24-25, are not consistent with the final results of the RE-LY trial (Connolly SJ, et al. N Engl J Med 2014;371:1464-1465) or the Summary of Product Characteristics, which may impact on the indirect evidence odds ratios for the DOAC comparisons.	Thank you for your comment. The committee made a decision to use the Lopez Lopez data to contribute to our decision-making, and it was not possible for us to make changes to the data they had used. However, the committee have now decided to amend the recommendation to not recommend one DOAC over another, and so we are confident that the omission of most recent data from the RE-LY trial will not have affected interpretations.
Boehringer Ingelheim	Evidence review G1	053 054- 055 056	003- 008	We have concerns regarding the conclusions drawn by Lopez-Lopez et al, which do not accurately reflect the results of the authors' analysis.	Thank you for your comment. We have amended the incorrect statement that apixaban was ranked first for stroke and systemic

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		071	024-032 017-019	The evidence review and Lopez-Lopez et al state that 'apixaban 5mg bd was ranked the best intervention for stroke and systemic embolism'. However, dabigatran 150mg is ranked highest for both stroke or systemic embolism and ischaemic stroke, and has a lower rate of these outcomes in the comparisons versus apixaban 5mg (stroke and systemic embolism: OR 0.82, 95% CI 0.62 to 1.08; ischaemic stroke: OR 0.83, 95% CI 0.59 to 1.16). Section 1.7.1.3 of this evidence review states apixaban 5mg bd had the second lowest odds for stroke/systemic embolism of all the DOACs versus warfarin. We also have concerns around how the rankograms have been derived, as many present results that are not consistent with other elements of the authors' analysis. In Table 24, dabigatran is shown to have the lowest rate of intracranial haemorrhage compared to warfarin. However in the rankograms, dabigatran 150mg bd is ranked at 5 out of 6 for intracranial haemorrhage, while apixaban 5mg bd is ranked first despite having a higher intracranial haemorrhage rate in their comparison versus warfarin, and has a similar intracranial haemorrhage rate in their comparison versus dabigatran 150mg bd. Edoxaban 60mg od and rivaroxaban 20mg od are ranked second and fourth, respectively, despite both having higher intracranial haemorrhage rates in their comparisons versus warfarin and dabigatran 150mg bd. Dabigatran 150mg bd is ranked lowest of the NOACs for all-cause mortality, despite having a similar rate of all-cause mortality in the comparison versus apixaban 5mg (ranked first) (odds ratio 1.00, 95% confidence	embolism. A correct summary of the rankograms has now been added.

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				interval 0.84-1.19); and edoxaban 60mg (ranked second) having a similar rate in their comparison versus warfarin, and a numerically higher rate in the comparison versus dabigatran 150mg (odds ratio 1.03, 95% confidence interval 0.87-1.22).	
Boehringer Ingelheim	Evidence review G1	066 074 188-189	015-016 028 002-006	We would like to highlight the difference in acquisition costs for the specific reversal agents. For idarucizumab, the cost for a course of treatment is £2,400 per patient, based on NHS list price. This is consistent with the cost of reversal using Beriplex®. For andexanet alfa, the average cost of a course of treatment at list price is £15,000 per patient (range £13,875 - £24,975), based on NHS list price.	Thank you for your comment. The cost of idarucizumab in this table was the cost per vial not the cost per course. This has been clarified in the table. The unit cost of andexanet alpha is not available in the NHS drug tariff but is available in the BNF and is £11,100 for 4 x 200mg powder for solution vials = £11,100 using NICE indicative price. This has been clarified in the table.
Boehringer Ingelheim	Evidence review G1	069	008-010	The licensed dose of dabigatran is 150mg bd; we suggest this statement should read: It also found that dabigatran (**150**mg bd) was dominant (less costly and more effective) compared to warfarin (target INR 2-3) and edoxaban (60mg od).	Thank you for your comment. This edit has been made.
Boehringer Ingelheim	Evidence review G1	070	033-037	We would like to highlight that when using warfarin as the common comparator, dabigatran 150mg had the lowest odds for stroke/systemic embolism of all the DOACs, was the only DOAC to demonstrate a statistically significant benefit for ischaemic stroke, had the lowest odds for intracranial bleeding.	Thank you – we have now clarified that dabigatran was ranked first for lowest risk of stroke.
Boehringer Ingelheim	Evidence review G1	071	038-042	There is evidence that upper gastrointestinal side effects with dabigatran can be transient and are effectively managed with measures such as concomitant water and food intake, proton pump inhibitors, H_2-blockers or antacids (Ezekowitz MD, et	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence to the NICE guidelines on

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				al. Europace 2016;18:973-978. O'Dea D, et al. Cardiol Ther 2016;5:187-201). We would also like to highlight that convenience attributes (i.e. dosing frequency, dietary restrictions, storage, administration) are only considered important to patients when efficacy and safety are similar. A systematic literature review of atrial fibrillation patient preference publications found that patients weigh clinical attributes such as stroke and bleeding risk higher than convenience attributes (Wilke T, et al. Patient 2017;10(1):17-37). A cross-sectional survey of 937 patients with AF showed that almost as many patients nominated dietary restrictions as the most important factor in their choice of oral anticoagulant as did dosing frequency (7.0% and 8.2%, respectively) (Lane DA, et al. Clin Cardiol 2018;41:855-861). It should therefore be noted that dabigatran and apixaban have no dietary restrictions, unlike rivaroxaban, which must be taken with food due to decreased oral bioavailability when taken under fasting conditions.	medicine adherence, medicines optimisation and patient experience in adult NHS services which would include taking into account personal preferences such as dose frequency and dietary restrictions.
Boehringer Ingelheim	Evidence review G2	073 178	005-008 015-016	We are concerned that the health economic model included a myocardial infarction switching rule for dabigatran only. This rule was not in place for any of the other DOACs or for the other outcomes, where the probability of switching following an ischaemic stroke, TIA or systemic embolism was 10%, and was 30% following a clinically relevant bleed. Therefore, patients on dabigatran who experienced a myocardial infarction were hypothesized to switch and drop to the lower efficacy of warfarin	Thank you for your comment. In the model patients are assumed to always switch treatment from dabigatran to warfarin if they experience an MI due the clinical evidence suggesting a link between dabigatran and MI risk. The NMA showed that dabigatran was the only one that showed evidence of an increased risk of MI compared to warfarin (except for edoxaban 30mg, however this dose was not included in the model). The point estimate of the risk of MI for all comparators and the uncertainty around these (credible intervals) are used in the economic

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					analysis; data can be found in G2, table 52. Following your comment, the committee agree that the switching rule from dabigatran under MI was not reflective of clinical practice. They updated it so that after MI 50% of patients will switch to apixaban and 50% to rivaroxaban. The results and conclusions are unchanged. See G2 for full results. Note that this was adopted as the base case.
Boehringer Ingelheim	Evidence review G2	080	001-003	We are concerned that the health economic model included an MI switching rule for dabigatran and states: 'Patients are assumed to always switch treatment from dabigatran to warfarin if they experience an MI due to recent findings suggesting a link between dabigatran and MI risk'. There are no recent findings suggesting a link between dabigatran and myocardial infarction risk. In the phase III RE-LY trial there was a non-significant numerical increase in the rate of myocardial infarction with both dabigatran doses compared to warfarin, which has not been replicated in large post-authorisation analyses. In addition the net clinical benefit for dabigatran versus warfarin was maintained and total myocardial ischaemic events were not increased (Hohnloser SH, et al. Circulation 2012;125:669-676), which was further supported by the very large registry follow-up in 134 000 older patients treated with dabigatran or vitamin K antagonists, which did not reveal any increased risk for myocardial infarction (Graham DJ, et al. Circulation 2015;131:157-164).	Thank you for your comment. The Clemens data relating to dabigatran versus enoxaparin or placebo was not applicable to the NMA data because the comparators were different to those used in the NMA (warfarin or the other 3 DOACs). Clemens shows that the risk of MI in dabigatran is similar to that in placebo or enoxaparin (a low molecular weight heparin), but this does not mean the risk of MI in dabigatran is similar to warfarin or the other 3 included DOACs. In support of this, the Clemens data relating to dabigatran versus warfarin shows that dabigatran has a greater risk of MI than warfarin [OR 1.42 (95% CIs:1.07 – 1.88)], based on meta-analysed data from 4 large trials (including RE-LY). Data from RE-LY alone was also presented and this also showed a strong trend towards a greater risk of MI for dabigatran [OR 1.30(95% CIs:0.96 – 1.76)] Following your comment, the committee agree that the switching rule from dabigatran under MI was not reflective of clinical practice. They updated it so that after MI 50% of patients will

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				The results of an analysis of data from fourteen dabigatran clinical trials to assess cardiovascular outcomes (including myocardial infarction) showed that, in more than 10,000 patients, there was no significant difference in myocardial infarction rates with dabigatran and enoxaparin or placebo (Clemens A, et al. Vasc Health Risk Manage 2013;9:599-615).	switch to apixaban and 50% to rivaroxaban. The results and conclusions are unchanged. See G2 for full results. Note that this was adopted as the base case.
Boehringer Ingelheim	Evidence review G2	172	Genera	We are concerned that the data used in the cost-efficacy model (Table 52) is not consistent with the results of the network meta-analysis versus warfarin in Evidence review G1 (Tables 18-25). We are also concerned that the table shows a significantly higher rate of transient ischaemic attack for dabigatran 150mg bd versus warfarin, when this outcome was not reported in the dabigatran trials included in the network meta-analysis, and transient ischaemic attack is not an outcome that was specified in the network meta-analysis in chapter 5.	Thank you for your comment. The network meta-analysis results presented in chapter 5 of G2 and in tables 18-25 of G1 consider each outcome separately and independently. However, for the economic model it is necessary to consider different outcomes jointly. A competing risks network meta-analysis model was used to jointly estimate the log hazard ratios for the different possible events. The competing risks NMA modelled 17 outcomes in total, with a list provided in Appendix 7, as it had to consider all outcomes reported by all trials to correctly account for competing risks. It is correct that no trials report on TIA for dabigatran but note that the hazard ratio relative to warfarin reported in Table 52 is highly uncertain. Although the point estimate is 2.68 the credible interval is 0.062 to 16.1; this reflects the absence of evidence on this treatment effect. The same wide credible intervals are also found for edoxaban, rivaroxaban, and dabigatran 110mg on TIA and apixaban 2.5mg on ICH. However, TIA has little impact on costs and QALYs so this uncertainty is not a serious limitation.
Boehringer Ingelheim	Evidence review G2	188 – 189	General	We would also like to highlight that andexanet alfa has been omitted from the 'Reversal agent dose' section of the table.	Thank you for our comment. This has been added.

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Boehringer Ingelheim	Guideline	008	022-024	Boehringer Ingelheim support NICE's recommendation that when discussing the benefits and risks of anticoagulation use clinical risk profiles and personal preferences to guide treatment choices. A large proportion of patients (47.4%) consider stroke prevention to be the most important factor informing their choice of anticoagulation; major bleeding was considered to be the second most important factor (Lane DA, et al. Clin Cardiol 2018;41:855-861).	Thank you for your comment. Recommendation 1.6.1 states that for most people the benefit of anticoagulation outweighs the bleeding risk.
Bristol Myers Squibb and Pfizer Alliance	Evidence Review G2	230	001-026	We propose making a summary of the 'DOAC cost sensitivity analyses' more visible in the guideline summary • This will be more helpful to commissioners (and could help inform any anticipated procurement decisions).	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC and so it is not considered necessary to include this sensitivity analysis in the guideline summary. Furthermore, this was a sensitivity analysis based on price reductions from baseline. Due to the ongoing NHS England procurement it is not expected that the baseline will remain. Please note following completion of the procurement NICE will consider an update of the guideline.
Bristol Myers Squibb and Pfizer Alliance	Guideline	004	011	We support the recommendation for ECG rhythm recording as the diagnostic criterion for AF, but suggest that evidence supports diagnosis via single-lead ECG as well as 12-lead ECG • 2020 ESC guideline for AF (Hindricks G *et al*, 2020) recommends that irregular rhythm lasting 30 seconds or more is diagnostic for clinical AF. • At the start of the rapidly-progressing COVID-19 epidemic, the NHS made a set of recommendations (NHS Specialist Pharmacy Service, 2020) to reduce patient attendances and associated burden on the NHS. Acceptance of single-lead ECG as	Thank you for your comment. The evidence showed that single lead would miss up to 10% of people with AF detected on 12 lead.

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				diagnostic for AF is likely to support this recommendation. • Additionally, the option of single-lead ECG testing may help to prevent potential delays in initiating anticoagulation in high risk patients, due to the greater availability of single-lead ECG (compared to 12-lead ECG) in care settings other than secondary care, and potential use in remote monitoring.	
Bristol Myers Squibb and Pfizer Alliance	Guideline	006	011	We support the increased emphasis on engaging with patients on key aspects of their care • Discussions with patients and understanding their preferences are particularly important during risk assessment, treatment decisions, follow-up, and assessment of quality of care. • Clear reference is made throughout to the NICE Clinical Guideline (CG138), 'Patient experience in adult NHS services: improving the experience of care for people using adult NHS services'.	Thank you for your comment.
Bristol Myers Squibb and Pfizer Alliance	Guideline	009	011-013	We support the recommendation for apixaban or dabigatran as first-choice DOACs (taking into account the risk of bleeding) *CLINICAL EVIDENCE* Clinical evidence from randomised controlled trials supports the lower bleeding rates associated with apixaban over warfarin and other DOACs: • Apixaban is the only DOAC to demonstrate a significant risk reduction in both stroke/systemic embolism and major bleeding (as well as mortality) compared to warfarin in pivotal RCTs ARISTOTLE,	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost

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				ENGAGE AF, RE-LY, ROCKET (Granger CB *et al*, 2011; Giugliano RP *et al*, 2013; Connolly SJ *et al,* 2009; Patel MR *et al*, 2011). • Only the twice-daily dosed anticoagulants apixaban and dabigatran have demonstrated significant reduction in stroke in pivotal RCTs ARISTOTLE and RE-LY (Granger CB *et al*, 2011; Connolly SJ *et al,* 2009). • Apixaban is the only DOAC that does not increase gastro-intestinal bleeding compared to warfarin in pivotal RCTs ARISTOTLE, ENGAGE AF, RE-LY, ROCKET (Granger CB *et al*, 2011; Giugliano RP *et al*, 2013; Connolly SJ *et al,* 2009; Patel MR *et al*, 2011). Clinical, observational evidence supports the lower bleeding rates associated with apixaban over warfarin and other DOACs: • Apixaban has a more favourable gastro-intestinal safety profile than dabigatran and rivaroxaban (Abraham NS *et al*, 2017). • Apixaban, dabigatran and rivaroxaban appear to have similar effectiveness but different bleeding risks (Noseworthy PA *et al*, 2016). • FDA-sponsored analysis: Apixaban is associated with a 63% reduction in major extracranial bleeding, and a 65% reduction in major gastrointestinal bleeding, compared to rivaroxaban (Graham DJ *et al*, 2019). Adherence and persistence to oral anticoagulants were examined by Banerjee A *et al* (Heart, 2019),	effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC.

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				suggesting highest rates of adherence and persistence with apixaban (and lowest with VKA). The body of evidence comparing apixaban to rivaroxaban (the two most commonly prescribed anticoagulants across England) suggests that apixaban has a lower risk of major bleeding events than rivaroxaban (Hill NH *et al*, 2020). This substantial review of 21 network meta-analyses and 5 observational studies consistently found no differences in efficacy/effectiveness between these two medicines. The latest US observational study (Yao X *et al*, 2020) compared oral anticoagulants in cohorts with differing renal function. Their finding suggested that apixaban and dabigatran were linked to lower rates of major bleeding than rivaroxaban, and that apixaban had lower rates of stroke than dabigatran. Only apixaban is recommended by NICE in preference to warfarin in people with concomitant AF and moderate renal impairment (NICE CG182, 2014). *COST-EFFECTIVENESS EVIDENCE* Cost-effectiveness evidence from a large range of studies across a variety of clinical settings consistently found apixaban to have the highest probability of being the most cost-effective of the DOACs in AF: • The independent, NIHR-sponsored study (López-López JA *et al,* 2017) found that apixaban had the highest probability (60%) of being the most cost-effective medicine for the prevention of stroke in AF, within the usual cost-effectiveness thresholds (ICER of	

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				£20,000-£30,000 per QALY) (also Thom HHZ *et al*, 2019). • A 2016 systematic review of 26 cost-effectiveness analyses (Pinyol C *et al*, 2016) found apixaban to be cost-effective over warfarin and other DOACs. • A 2019 cost-effectiveness evaluation, including both randomised and observational/real-world data, supports the finding that apixaban is cost-effective compared to warfarin and the other DOACs (de Jong L *et al*, 2019). • Apixaban's cost-effectiveness compared to warfarin and other DOACs is supported by a considerable body of additional evidence, from a wide variety of clinical settings across multiple countries. These consistently show apixaban to be more cost-effective than other DOACs in the management of patients with AF. Examples include: o *Austria*: Walter E *et al*, 2020 o *Canada*: CADTH, 2013 o *Denmark*: Poulson PB *et al*, 2017 o *France*:Lanitis T *et al,* 2014 o *Italy*: Bellone M *et al*, 2018 o *Portugal*: Costa J *et al*, 2015 o *Spain*: Oyagüez I *et al*, 2020 o *Taiwan*: Chieh-Yu L *et al*, 2017 o *United Kingdom*: López-López JA *et al,* 2017; Lip GJH *et al*, 2014	

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British Association of Stroke Physicians	Guideline	004	014 - 020	24hr monitor if asymptomatic episodes suspected and less than 24hrs apart ? needs rewording – remove symptomatic / asymptomatic and rewrite as "24hr monitor if clinically suspected episodes and are less than 24hrs apart"? Consider rewording: "Ambulatory ECG monitoring, event recorder or other ECG technology for a period appropriate for AF detection if episodes thought to be more than 24hrs apart"	Thank you for your comment. We have made the edit as suggested.
British Association of Stroke Physicians	Guideline	005	013	ORBIT bleeding risk score Good alternative to HASBLED, will need to be communicated well to change practice from HASBLED	Thank you for your comment.
British Association of Stroke Physicians	Guideline	007	009-013	Assessment of cardiac function No changes from before, fine Differs from ESC guidelines suggesting all AF patients should have an echo but not needed routinely	Thank you for your comment.
British Association of Stroke Physicians	Guideline	009	003	Assessment of bleeding risk – important to monitor bleeding risk and good that it's included	Thank you for your comment.
British Association of Stroke Physicians	Guideline	009	006	Good to see that the DOACS are now first line compared with warfarin. CHADSVASC recommendations follow those in the ESC 2016 guideline	Thank you for your comment.
British Cardiovascular Society	Evidence review G1	071	042	We note that the recommended NOACs are twice a day medications. BCS are concerned that this may result in lower adherence to anticoagulation (Coleman CI, et al. Curr Med Res Opin. 2012;28:669–680; McHorney CA, et al. Curr Med Res Opin. 2015;31:2167–73; Alberts MJ, et al. Int J Cardiol. 2016;215:11-3) and that that could lead to increased risk of events outwith the very controlled trial	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence to the NICE guidelines on medicine adherence, medicines optimisation and patient experience in adult NHS services which

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				environment where these drugs were tested (Shore S, et al. Am Heart J. 2014;167:810-17)	would include taking into account personal preferences such as dose frequency.
British Cardiovascular Society	Guideline	004	020	BCS would ask NICE to provide guidance as to what amount of arrhythmia detected asymptomatically on monitoring should be considered enough to constitute paroxysmal atrial fibrillation. Guidance on how long an episode of AF should be before the diagnosis can be made (and consequently anticoagulation considered) would be very helpful. We note recent ESC guidance that addressed this issue. Similarly, BCS would welcome clarity as to whether atrial flutter and atrial tachycardias should be treated in the same way as atrial fibrillation when detected through monitoring of asymptomatic patients.	Thank you for your comment. We have now referred to the fact that the benefit of anticoagulation for asymptomatic AF that has not been documented on 12 lead ECG is uncertain and that further research is being conducted on this. In the absence of evidence the committee were unable to make a recommendation on this area.
British Cardiovascular Society	Guideline	005	013	The Orbit score is not widely used in the UK for this purpose. It is not clear why UK practitioners would wish to change to using this score system. The ORBIT score is derived from a US population and validated using the ROCKET AF Trial. Subsequent analysis of ORBIT in different patient populations to ROCKET AF have failed to show superiority of the ORBIT score over HAS BLED, (Lip et al. Am J Med 2018 May;131(5):574.e13-574.e27). The link in the guidance to the ORBIT score is to https://www.mdcalc.com/orbit-bleeding-risk-score-atrial-fibrillation. This presents a different version of the score using gender but not reduced haemoglobin in contradistinction to source data (Eur Heart J. 2015 Dec 7; 36(46): 3258–3264.) The requirement for blood testing to generate the ORBIT score has (primary care) resource implications. BCS would wish the guidelines to make it as clear as possible that elevated bleeding risks on *any* score system should not be the reason to deny patients the benefits of anticoagulation. Rather, they should be used to identify patients who might benefit from	Thank you for your comment. The benefits of ORBIT are found mainly in the calibration evidence. Calibration evidence was given priority because of the importance of accurate prediction of absolute risk in the context of using the tools as an aid to the discussion between patient and clinician about the need for risk-modification, rather than as a decision tool about risk modification. In other words, it is envisaged that all patients will be encouraged to risk modify, but that an accurate risk prediction will be helpful in encouraging compliance, particularly in people at higher risk. We have clarified this point in the committee's discussion of the evidence in evidence review E and F. The committee agreed that ORBIT was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk.

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				separate steps to reduce their bleeding risk whilst on anticoagulation. Clinicians would like guidance on how to integrate bleeding scores in to decision making. In the absence of adequate evidence of how that should be done, would like recognition of that evidence gap in the guideline (perhaps as research recommendation)	There may be resource implications due to blood testing, but Hb and haematocrit will normally be drawn automatically before anticoagulation anyway and so wouldn't change practice, because bleeding risk would only be of interest if anticoagulation were already decided upon. We have made it very clear in the review that bleeding risk tools should never be used as a decision aid to deny anticoagulation.
British Cardiovascular Society	Guideline	009	011	This recommendation proved to be the most contentious amongst respondents to the BCS. It is unusual for NICE to prefer specific drugs within a class of agents (no similar recommendations are made for specific beta blockers or ACE inhibitors for heart failure, for example). All agents are widely used in the UK and preferring some over others would require a major change in practice for those areas using the not-preferred drugs. It would therefore be of great importance to be sure of the cost-effectiveness and comparative data upon which such a recommendation could be made. **BCS members had some concerns that the network analysis and cost-effectiveness models used were not robust enough to make such a strong recommendation.** For example, different DOAC trials had quite varied patient populations, both in baseline bleeding and stroke risk profiles. This would make the comparison between trials in the network metanalysis quoted less robust. Cost-effectiveness modelling needs to be done with up to date pricing for the various medications. There have	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case

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				been changes in list price for these drugs and various schemes that reduce the cost to the NHS. Some consideration needs also to be given to the impact of the transition to generic status for some of these medications in the near future. That would seem likely to alter the cost-effectiveness balance. Even if NICE were to set aside these concerns over the validity of preferring one DOAC over another, the way the recommendations are currently laid out is confusing. 1.6.2. seems to be immediately contradicted by 1.6.3. and 1.6.4. **BCS would suggest that 1.6.2.could perhaps go at the *end* of this section, not the beginning**, since it is saying that *if* you are using one of these drugs, you should use them according to the instructions (which of course really goes without saying), and not that they are all equally valid choices.	analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. As all licensed DOACs are now recommended the order of the recommendations is now logical. As we have amended recommendations 1.6.3 and 1.6.4 we have not re-ordered the recommendations.
British Society of Haematology and Royal College of Pathologists (joint response)	Guideline	005	012	We are concerned that the specific issue of severe renal failure has not been addressed. Mavrakanas et al. CJASN Aug 2020, 15 (8) 1146-1154; DOI: 10.2215/CJN.11650919 is the most recent of several articles that show that anticoagulation in patients on dialysis does not reduce the risk of thrombosis but does cause severe bleeding. We made the following comment on the scope: 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 outcome when anticoagulated. Other countries (e.g. US and Canada) recommend against primary prophylaxis with anticoagulation for atrial fibrillation with renal failure.	Thank you for your comment. The committee did not specify renal failure as a factor to subgroup the evidence by in the presence of heterogeneity in the meta-analysis. Only a limited number of subgroups could be specified in order to ensure the data was not too sparse to enable a recommendation to be made. The committee agreed that the guidance in the BNF adequately covered the issues relevant to renal failure when prescribing anticoagulants.

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				Your reply was: 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. We cannot find any evidence that you have considered severe renal failure. If you have what is the explanation for ignoring the evidence that shows that anticoagulation is harmful in this group?	
British Society of Haematology and Royal College of Pathologists (joint response)	Guideline	005	013	We agree that the ORBIT score has advantages over the previously recommended HAS-BLED score.	Thank you for your comment.
College of Paramedics	Guideline	004	003	We appreciate 1.1.1 is in 'grey' but we would recommend healthcare professionals routinely palpate manual pulses, regardless of whether a specific suspicion of AF exists or not. This would promote an increase in early detection of AF occurrence in the community.	Thank you for your comment. Opportunistic screening is outside of the remit of NICE.
College of Paramedics	Guideline	004	011	This appears to contradicts 1.1.1 slightly - which says to only palpate if there is suspicion of AF, which presumably means there would be symptoms, whereas perform ECG… with or without symptoms.	Thank you for your comment. Both 1.1.1 and 1.1.2 are for people suspected of AF, and so do not contradict each other. 1.1.1 refers to those suspected of AF because of symptoms, whereas 1.1.2 refers to those people suspected of AF based on 1) symptoms or 2) history.

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Daiichi Sankyo UK Limited	Evidence Review G1	007	033-039	8.0 METHODOLOGIST REVIEW AND MODEL CRITIQUE DSUK fully respects the work of NICE and the rigorous evidence base that is applied in developing Technology Appraisal Guidance and Clinical Guidelines. However, we would strongly request that the evidence presented to NICE within Evidence Review 6, and all its available data, R Model and WinBUGS models, be reviewed and critiqued by a methodologist with experience across Bayesian statistics and R modelling. This would enable the methodology, findings and models to be independently reviewed and validated as part of the clinical guidelines update. As detailed in response sections 7.0 and 9.0, DSUK have identified potential errors in the model including the implementation of stroke and ICH costs. Section 1.5.2 of the Evidence Review 5, states "*the committee thus agreed that the body of evidence included in Lopez-Lopez was at least as useful as the body of evidence from our review. One member of the committee commented that Lopez-Lopez was an extremely high quality piece of work, and probably the best work published in the area. On this basis, the committee agreed that it was highly unlikely that the resources allocated to performing a new NMA based on our own data would be justified by any gains over Lopez-Lopez, and therefore that using Lopez-Lopez might be preferable to carrying out our own NMA*." As demonstrated above, the study being referred to in this extract is subject to a significant number of flaws, and the Committee failed to take into account numerous considerations that affect its interpretation or the weight that should be placed on it in comparison	Thank you for your comment. This model underwent rigorous validation/peer review by the BMJ group who have expertise in R and Bayesian statistics. The error to the stroke costs has been corrected. Please see full responses to the other comments submitted by DSUK. We have reviewed and re-worded section 1.5.2. We have removed the statement about one member of the committee commenting on the quality of the Lopez-Lopez NMA. This gave the impression that this comment was a prime reason for the use of Lopez-Lopez, which is not the case. The decision to use Lopez-Lopez was based on several reasons other than this comment, as section 1.5.2 now makes clear. The committee did include a range of members with direct experience in the management of atrial fibrillation including the use of DOACs in routine clinical practice. Furthermore, the committee included lay members, who provided a patient perspective throughout the guideline development process. The technical team included a health economist and the model was undertaken by health economists at the NICE technical support unit; furthermore, as stated earlier, external validation of the model was undertaken by experts at the BMJ group.

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				to other relevant factors. The points raised throughout our response show that it within the reasonable range of responses for the Committee to concluded, on the basis of one single Committee member's opinion (which itself is demonstrably flawed), that the Sterne et al. study obviated the need for more rigorous and direct evidence in order to properly assess whether a departure from the established parity between drugs was appropriate. In our view, the Committee has placed undue weight on a single Committee member's viewpoint, and failed to exercise its collective decision-making power in a rational and lawful manner. DSUK has significant concerns related to this statement from a procedural perspective and in the stated confidence in using Sterne et al.'s findings to underpin the recommendations in the guidelines for sequential DOAC use. We would strongly encourage the committee to consider the additional input and validation from methodologists and R modelling experts to determine the quality and appropriateness of Sterne et al.'s methods and findings in the absence of conducting a separate NMA independent of the External Assessment Group who are involved in the original analyses. Furthermore, DSUK would like to note that the Committee may also have benefited from the inclusion of a range of members with direct experience in the management of atrial fibrillation including the use of DOACs in routine clinical practice and also additional health economic expertise to complement an additional critique from a methodologist and experienced R modeller. The patient perspective is another important viewpoint which does not appear to have been captured in arriving at the draft recommendations.	

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Daiichi Sankyo UK Limited	Evidence Review G1	007	033-039	9.0 LACK OF TRANSPARENCY AND REPORTING OF R ECONOMIC MODEL In the limited time available during the consultation period, DSUK has reviewed the model (coded in R) and would like to make the following comments. There are several issues with the model which make it challenging to easily use and critique. With no supplemental directions or outline of the code, it is not intuitive which of the eight R code files should be run first, how the codes relate to each other or build off one another, and the reasoning behind some of the statistical decisions. The R code is not thoroughly annotated for an external audience throughout the script. Overall, the model lacks transparency in its underlying coding, making it hard to use and imposing challenges on any interrogation of its setup, data inputs and generation of results. The hard-coded values within functions makes it difficult to run any sensitivity analyses or change single values except for those that have a scenario analysis pre-specified. Parameter inputs should be read in from a .csv file or listed in a single script (thus keeping all inputs in one place). The cycle transitions are set up in a way that makes it nearly impossible to validate costs and QALYs over time, i.e. per cycle. The formatting of the code is not user-friendly with up to 300 characters in one line and multiple operations being performed at once which makes it very challenging to test changes to the model. An additional major criticism of the model, and subsequently the review process itself, is the length of	Thank you for your comment. We apologise the code was difficult to follow. Stakeholders said "Furthermore, DSUK has identified a potential (and major) error in the way that stroke costs are calculated in the code. Model cycles are of 3 months in duration, thus, the value assigned to the S.cost.mean object within the R script generate.transition.matrix.15.R should be one quarter of annual stroke costs. However, the model currently assigns what we believe to be a full year of costs per cycle (i.e. £4,227 per 3 months rather than annually)." We divided stroke costs by 4 and re-ran with 10,000 samples. No change in conclusions. This correction has been implemented in our basecase. Please see full report G2 for updated results. Finally, please note that this model underwent rigorous validation/peer review by the BMJ group who have expertise in R and Bayesian statistics.

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				time required to run and review the R code. The model takes approximately 19 hours to run the R code in its entirety, making it difficult to fully analyse and interpret the code within the allotted timeline for consultation. Due to the challenges in using and investigating the R model, we have had limited time to evaluate it fully for inaccuracies. However, the aspects we did look at raised major concerns in relation to its accuracy and validity. As mentioned previously, one area was the way in which stroke costs were sourced in the model. Furthermore, DSUK has identified a potential (and major) error in the way that stroke costs are calculated in the code. Model cycles are of 3 months in duration, thus, the value *assigned* to the S.cost.mean *object* within the *Rscript* generate.transition.matrix.15.R should be one quarter of annual stroke costs. However, the model currently assigns what we believe to be a full year of costs per cycle (i.e. £4,227 per 3 months rather than annually). Due to the length and complexity of the R code, it is difficult to verify this error. Stroke costs are amongst the highest value health state costs in the model so a mistake in applying it at full cost value instead of a cycle value would have major implications for the model's validity and therefore cannot be ignored in any review of the draft Guideline. DSUK has run the model using exploratory scenarios with an adaptation that corrects this bug and divides annual stroke state costs by four when assigning to the S.cost.mean *object.* Without performing a full and thorough critique into all aspects of the model, it is not possible to know the extent of all the possible mistakes in the model and their impact in the decision-making process underlying the conclusions is, in DSUK's view, material to the Committee's conclusions, and therefore cannot be	

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				ignored in any review of the draft Guideline. DSUK would encourage the model to be assessed independently by experts in R modelling and NMA methodology within Bayesian frameworks. The fundamental nature of the recommendations that the draft Guideline is seeking to make, in our opinion, calls for additional scrutiny and rigour, particularly in light of any significant reliance on indirect data. Such further input would allow an independent critique of the model and data inputs to enable alternative scenarios to be considered which will improve the transparency and validity of the research that underpins the draft clinical guidance.	
Daiichi Sankyo UK Limited	Evidence Review G1	009	020	2.3 Time in Therapeutic Range for Warfarin in ENGAGE AF-TIMI 48 trial Maximising time within the therapeutic range—i.e.an international normalised ratio (INR) between 2 and 3 has been shown to provide the most benefit for preventing stroke, major haemorrhage, and death. TTR is a commonly used quality measure for anticoagulation therapy with warfarin (Rose et al. 2014). Section 1.5.2 of Evidence Review 5 discusses the committee's consideration on whether subgroups from the clinical trials, based on TTR should be used in the NMA. It states that "*the committee view was that use of whole trial data by Lopez & Lopez was appropriate to produce an evidence based guideline relevant to the NHS.*" The VKA arm in the ENGAGE AF-TIMI 48 study had the highest TTR of all the DOAC phase 3 trials (median 68.4 and mean 64.9). For this reason, the	Thank you for your comment. Thank you for your comments. On further discussion the committee agreed that the NMA by Lopez Lopez was probably not able to adequately adjust for the differences between treatment comparisons in terms of population characteristics that could affect the apparent relative efficacy of the different DOACs, such as TTR in the warfarin arms. Initially the committee agreed that the meta-regressions used to adjust for TTR were adequate, but after consideration of the numbers of studies involved it does seem unlikely that the meta-regression would have been able to make realistic adjustments to effect that were sufficient to negate inter-comparison differences. Given that the original decision to recommend apixaban and dabigatran over rivaroxaban and edoxaban was based on the results of these meta-regressions, the committee's subsequent belief that these meta-regressions are not valid has led to an amendment to not recommend any of the 4 DOACs over any other (1.6.3 and 1.6.4).

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				performance of the warfarin arm can be assumed to be better than that of other trials. In a high-risk population, when comparing the patients with renal dysfunction (CrCl≤50ml/min) from ENGAGE AF-TIMI 48 and ARISTOTLE trials, the populations have different risks (mean $CHADS_2$: 3.1 in ENGAGE AF-TIMI 48 vs 2.6 in ARISTOTLE and mean HAS-BLED 2.8 vs 2.2, respectively). Due to the difference in the risk profile, one would expect higher stroke or systemic embolism (SEE) and higher major bleeding rates in the warfarin arm of the ENGAGE AF-TIMI 48. However, the opposite is true: there are higher rates of major bleeding in the VKA arm of ARISTOTLE vs ENGAGE AF-TIMI 48 (6.44 vs 5.3 %/year) and similar rates of stroke/SEE (2.67 vs 2.7 %/year). The high TTR of ENGAGE AF-TIMI 48 may play a role in this context, however, other (unknown) factors may have contributed as well. As discussed above, the investigation of between-study variations in the warfarin arm could not be studied in most cases. DSUK would advise caution due to the inability of the study to account and adjust for treatment effect modifiers and the approach to proceed with an analysis based on the whole trial data.	
Daiichi Sankyo UK Limited	Evidence Review G1	014	Table row 1	Table shows interventions from ENGAGE AF-TIMI 48 study (reference 64). However, this lists interventions as edoxaban 30 mg bid and 60 mg bid which is inaccurate. These should both be once daily and marked as 'od' or 'qd'.	Thank you for this point – we have amended the error.
Daiichi Sankyo UK Limited	Evidence Review G1	045	010	17.0 SCIENTIFIC ACCURACY OF DATA INCLUDED Further, DSUK has noted a range of mistakes of fact in the scientific data referred to in the documents supporting the consultation.	Thank you for your comment. The NMA gave results for all the different doses of each DOAC versus warfarin, as per protocol (see appendix A in evidence review G1). In the health economic model, although apixaban and

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				In Table 18, edoxaban 30 mg od is included as a comparison with warfarin, however, it is a non-licensed dose. Inclusion of data for non-licensed doses may impact the findings of the analysis that underpins the recommendations in the draft guidance. Furthermore, among the indirect DOAC comparisons in Table 18, dabigatran 110 mg bd is missing. There appears to be consideration of dose selection for dabigatran which does not appear to be the case for the other DOACs, as per strict advice for dose adaptations in the SmPCs of rivaroxaban, apixaban and edoxaban. Additionally, the reduced doses for rivaroxaban, apixaban and edoxaban were part of the standard dose arm in the pivotal trials and not investigated as a separate arm of the trial. The base case analyses by Sterne et al. modelled using data specific to dabigatran 150 mg bd and inform the cost-effective recommendations in the draft guidelines. As discussed previously (response section 5.2), the clinical profile of dabigatran 110 mg bd is considerably different with respect to efficacy and safety from the 150 mg bd dose, thus DSUK would query the applicability of recommendations made for dabigatran when dabigatran 110 mg bd is not included in the analysis, particularly since it is a licensed dose. The impact on the NMA and cost-effectiveness analysis may be substantial since approximately half of AF patients on dabigatran are treated with the 110mg bd dose in UK practice.	dabigatran may be given in lower doses to the elderly, it was assumed that all patients would receive the higher dose, and remain on it, even as they age. However, results were robust to a sensitivity analysis assuming only the lower doses of apixaban (2.5mg bd) and dabigatran (110mg bd) were administered. Where NMA indirect head to head results are not given in Lopez Lopez / Sterne, this is because there was too much uncertainty in the NMA estimates (ratio between interval limits of >9).

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Daiichi Sankyo UK Limited	Evidence Review G1	053	004-005	States: "*The figures below, reproduced from Lopez-Lopez, 2017, show that apixaban 5 mg bd was ranked as the best intervention for stroke or systemic embolism, myocardial infarction, and all-cause mortality.*" This is incorrect. The rankograms produced do not show apixaban is ranked best for any of these endpoints.	Thank you for your comment. We have amended the incorrect statement that apixaban was ranked first for stroke and systemic embolism. A correct summary of the rankograms has now been added.
Daiichi Sankyo UK Limited	Evidence Review G1	070	007	DSUK would like to highlight that the quality of evidence included as part of Sterne et al.'s analysis was of varying quality. Specifically, Evidence Review 5 states that "*The quality of evidence of key outcomes comparing dabigatran and apixaban to warfarin were graded 'low' or 'very low', and the quality of evidence of key outcomes comparing rivaroxaban and edoxaban to warfarin were graded 'medium' or 'high'.*" Such differences in quality of evidence would introduce bias into the analyses if no adjustments are made or justified. This could impact on the estimates of efficacy, safety, economic efficiency and therefore the decision outcomes that underpin the draft recommendations. It is entirely unclear whether any of the identified risks of bias have been taken into account when drafting the recommendations. We would encourage such biases and the quality of the evidence presented to be fully considered. As mentioned above, we do not consider that issuing a 'strong' recommendation complies with NICE's own published guidance (at paragraph 9.1 of its Manual), in light of the acknowledged low quality of the evidence, and in any event, do not consider that NICE could rationally derive any recommendation of particular	Thank you for your comment. Study quality was not chosen, pre-hoc, as a variable for investigating effect modification, and so it would not be correct to investigate it as a factor after results have been observed. However, the committee considered quality ratings in their discussion of the evidence and did not consider that it would have a significant effect on overall interpretations. It should be noted that because the interpretations have been altered to allow for the uncertainty related to an inadequate meta-regression, we have not recommended any of the 4 DOACs over any other (1.6.3 and 1.6.4).

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				DOACs in preference to others on the basis of the evidence available.	
Daiichi Sankyo UK Limited	Evidence Review G1	072	006	2.4 Use of unequivocal statement appears to disregard uncertainty Regarding the following statement cited within Evidence Review 5: "*Although the NMA evidence was clear that apixaban and dabigatran were superior to the other DOACs, the committee were aware that there were circumstances where the other DOACs might be the only ones available, or where patients might express a wish not to use apixaban or dabigatran.*" (Note: emphasis added) DSUK is concerned by the use of an unequivocal statement to describe the Sterne et al. results where there are well-documented challenges with heterogeneity and uncertainty. In addition, the Sterne et al. analysis includes many clinical endpoints for which the point estimates were similar and the credible intervals in the NMA overlapped across the four DOACs. We would advise caution in the interpretation of these findings and the wording used is misleading for the reader.	Thank you for your comment. This paragraph has been deleted as we now recommend any licensed DOAC (1.6.3 and 1.6.4).
Daiichi Sankyo UK Limited	Evidence Review G2	061	017 - 022	2.2 Meta-regression methods explored Evidence Review 6 acknowledges the importance of ad[illegible] to determine the influence of a range of potential effect modifiers by adjusting for CHA2DS2-VASc score and sparsity of data in the network of treatment comparisons, meta-regression methods [illegible] detection of differences in treatment effect modifiers. Section 3.8.1 discusses [illegible] states that "*Investigation of between-study variation using meta-regression [illegible] multiple trials of the same pair-wise comparison, although [illegible] patients. Specifically, we performed several meta-regressions [illegible] covariate.*"	Thank you for your comment. On further discussion the committee agreed that the NMA [illegible] meta-regression would have been able to make

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				With regards to the meta-regression models to assess the influence of treatment effect modifiers (where data a concluded no evidence of effect modification. However, given the sparsity of data in terms of the treatment co and the distribution of potential treatment effect modifiers across trials, we do not believe the meta-regression detect differences in potential treatment effect modifiers. A subgroup analysis, if data allowed, would possibly l investigators to explore the robustness of the NMA results in a more homogenous population, and perhaps be into whether there was evidence to suggest treatment effect modification where meta-regression methods wer detect a difference. However, subgroup analyses were not conducted by the authors. DSUK has concerns that, despite the importance of assessing and adjusting for treatment effect modifiers, Ste thoroughly address this issue using meta-regression, and no subgroup analyses were attempted to assess the findings. Again, these variables appear to have been disregarded, or at least not considered, by NICE in makir recommendations.	realistic adjustments to effect that were sufficient to negate inter-comparison differences in prognostic characteristics. We have therefore amended the guideline to not recommend any of the 4 DOACs over any other (1.6.3 and 1.6.4).
Daiichi Sankyo UK Limited	Evidence Review G2	072- 073	Table 4	Edoxaban 60 mg od has been excluded as an intervention from the table	Thank you for your comment. This has been edited.
Daiichi Sankyo UK Limited	Evidence Review G2	097	Table 13	7.0 POTENTIAL ERRORS IN MODEL COSTS FOR ISCHAEMIC STROKE AND INTRACRANIAL HAEMORRHAGE 7.1 Ischaemic stroke costs The healthcare costs used by Sterne et al. for ischaemic stroke (IS), sourced from Luengo-Fernandez R et al. (2013), are not considered by DSUK to be reflective of current routine UK practice in 2020 and include substantial costs attributed to an acute event and post-IS management. The Luengo-Fernandez data, used within the model, is based on a population-based study (Oxford Vascular study) where stroke patients recruited between 1 April 2002 to 31 March 2007 were included in the analyses. As part of the stroke analyses, 153 patients were investigated, of whom 60% had a $CHADS_2$ risk score	Thank you for your comment. We re-ran our model with acute event for stroke £5506 and annual management cost £6613 from Bakhai (with no uncertainty) and 10,000 samples. This has been added as a sensitivity analysis to our report. Under this analysis dabigatran (150mg bd) has greatest expected net benefit at willingness-to-pay £20,000 and apixaban (5mg bd) at £30,000. We didn't model death from ICH directly as it was included in the all-cause mortality from the trials. We judged that including it again after ICH would be double counting this source of death. However, the ICH year 1 event cost (£13400) includes the cost of fatal events. Table 2 of Luengo-Hernandez 2013 explains that of the 17 haemorrhagic strokes, 8 (47%) were fatal. Table

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				of 3 or more. It is important to highlight that the management of these patients, who were more severe than the patient population being modelled by Sterne et al., would be more challenging and thus incur greater costs than we would expect to see if a more recent study was utilised to reflect current management approaches and in a less severe patient population. DSUK has validated this with clinical experts in the UK who agree that improvements in stroke outcomes since 2014 has reduced the morbidity of strokes and thus the costs associated with stroke should be reflected in this update of CG180. Clinical experts have stated that the introduction and increased usage of DOACs, which were not available at the time of the Luengo-Fernandez analysis, have reduced both the number and severity of strokes in AF patients. Bakhai A et al. (2020) is a recently published paper based on real-world NVAF patients in England. Bakhai et al. estimated total NHS costs for 42,966 NVAF patients 12 months from diagnosis. AF patients experiencing an ischaemic stroke event were associated with mean total annual NHS cost of £9,167. This estimate includes both the acute event cost element and the subsequent management costs. These costs, and the 2018/19 NHS reference costs for stroke non-elective long stay episodes (Table 4 below), suggest that the acute event costs applied in the Sterne et al. model for stroke (£13,603.37) are substantially overestimated and do not reflect current NHS costs. Table 4: 2018/19 NHS reference costs for stroke Currency description | Non-e Stroke with CC score 16+	3 indicates the cost for fatal ICH was £1592 (SD=1886) and these were included in the "all strokes" cost £10683, which we inflated to £13400.

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				Stroke with CC score 13-15 £5,822 Stroke with CC score 10-12 £4,424 Stroke with CC score 7-9 £3,586 Stroke with CC score 4-6 £3,097 Stroke with CC score 0-3 £2,723 (Abbreviation: CC = critical care) A midpoint on the range of costs for stroke episodes according to NHS reference costs, is £5,320.50 which would appear much more in line with the evidence from Bakhai A et al. (2020) compared to the older data from Luengo-Fernandez. DSUK has run the Sterne et al. R model with an exploratory scenario that includes updating stroke costs to more accurately reflect the present day value. Using acute event costs (first 3 months) and post-acute (2nd, 3rd and 4th quarter costs, adjusted to annual cost) from Bakhai et al, (2020), then inflating to 2019/2020 values using an ONS Consumer Price Inflation Index for medical services, produces an updated acute event cost for stroke (£5,506) and a post-stroke management cost (£6,613). Updating stroke costs for these more accurate figures has an impact on the cost-effectiveness results. This is covered in the exploratory scenario section 11.0 below. In addition to acute costs for stroke, the model also modelled post-stroke management costs as an input based on the annual figure of £4,227.51 (Luengo-Fernandez et al., 2013, as stated in Table 13 of Evidence Review 6). During our review of the model, we have identified a potential error with the model code for this post-stroke management cost. This is	

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				covered further in response section 9.0below when we discuss potential model errors and limitations. 7.2 Intracranial haemorrhage (ICH) costs implementation On reviewing the parameters included in the model, DSUK has identified another potential error in the way that ICH costs have been implemented in the model. We understand the authors have implemented the Year 1 costs for ICH as an event cost. However, this appears to be allocated to all patients irrespective of survival. Thus, the Year 1 post-ICH management cost doesnot appear to be adjusted for mortality, which is a mistake as to the facts underlying the analysis.	
Daiichi Sankyo UK Limited	Evidence Review G2	175	Table 52	6.0 EXCLUSION OF PUBLISHED TIA DATA FOR EDOXABAN According to Evidence Review 6 (Table 22, page 131), apixaban is the only DOAC for which evidence on TIA has been identified in the systematic review. This evidence is taken from a small, 12-week, open-label, Phase 2 trial conducted entirely in a Japanese population (ARISTOTLE-J, n=222) raising questions on its reliability and validity to UK clinical practice. Treatment effect estimates for DOACs other than apixaban appear to be informed by the application of a vague prior distribution (which may be more informative than intended), resulting in similar estimates across the remaining three DOAC with wide credible intervals. There is no explanation anywhere in the report about how this was handled – about whether evidence for other DOACs in respect of TIA was sought, and about how treatment effect estimates for the model were derived for edoxaban in the apparent	Thank you for your comment. The Aristotle J study was included based on a a priori decision by the committee to not exclude data based on geographical origin. It had been envisaged that the meta-regression would be able to adjust for any effect modification. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne, particularly in terms of the ability of the meta-regression to sufficiently adjust for such covariates. This made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals were wider and

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				absence of evidence. While NICE is an expert decision-maker, it is still required to explain reasons for ignoring material factors affecting its final decision. This is of particular concern since the mean hazard ratios used in the model (listed in Evidence Review 6, Table 52) have very wide confidence intervals, highlighting uncertainty, and the treatment effect point estimates for the DOACs (other than apixaban) are notably high compared to warfarin. For example, the hazard ratio assumed (vs. warfarin) for edoxaban 60 mg od is 2.76 (0.06, 15.8) compared to 0.74 (0.041, 3.26) for apixaban. Notably, published TIA evidence from the pivotal RCT ENGAGE AF-TIMI 48 (n=21, 105) exists for edoxaban and should have been included as part of the cost-effectiveness model. Giugliano RP et al. (2014) reports 106 TIA events for edoxaban 60 mg and 95 TIA events for warfarin, resulting in a HR of 1.11 (CI: 0.843, 1.468). A review of the R model shows that the TIA treatment effect parameter is an important determinant of cost-effectiveness estimates for edoxaban. The use of published TIA data for edoxaban, rather than the application of vague priors, is essential to this analysis and we would advise that published data be used as part of the cost-effectiveness analyses for the NICE review of these guidelines. DSUK has run the model using exploratory scenarios that include replacing the TIA HR based on the published evidence by Giugliano RP et al. (2014). The cost-effectiveness results derived from this exploratory analysis are presented in this response document.	the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore were no longer confident to recommend a specific DOAC or DOACs. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.

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Daiichi Sankyo UK Limited	Evidence Review G2	197	001-002 Figure 25	11.0 EXLORATORY ALTERNATIVE MODELLED SCENARIOS In order to illustrate that NICE would be more likely to reach a different conclusion when taking into account the additional relevant factors we have identified in this document, DSUK has used the R model to test alternative exploratory scenarios that attempt to address some of the limitations in Sterne et al. These scenarios can be summarised as follows: • Updated NMA (clinical outcomes): replacing the clinical outcomes hazard ratios with data from the Leicester University NMA (where available) which attempt to explore heterogeneity across trials ($CHADS_2$ >=2) • Published TIA hazard ratios (clinical outcome): estimated TIA hazard ratio for edoxaban from published source (Giugliano et al., 2014) • Amended stroke model coding error: correcting the code to divide stroke costings by four (to reflect 3-month cycle duration) Updated stroke costs: replacing the acute event cost of stroke and management cost post-stroke with inflated costs derived from Bakhai et al. (2020) The results for the alternative scenarios are presented below. It should be noted that NHS List prices are used for all scenarios: Table 6: Scenario 1 - Updated clinical outcomes (NMA HR & published TIA HR) with amended potential stroke cost coding error	Thank you for your comment. Below are responses to the specific comments: • DSUK suggest considering an unpublished "Leicester University" NMA. DSUK do not provide results or data from this unpublished NMA. It is impossible to assess whether its inclusion/exclusion criteria aligned with the NICE scope or what other differences in NMA methodology there might be (e.g. class effects on DOACs or informative priors on regression coefficients). In the absence of a publication, we cannot use it in the NICE model. The analysis may be similar to that published in Batson 2016.[4] This analysis was exploratory and only considered stroke. However, they found "None of the covariates explored impacted relative treatment effects relative to placebo". This is aligned with our exploration of meta-regressions on each of the outcomes separately, where we found there was not sufficient data to run the models (Section 3.8.1). Conclusion should be that there is no justification to use covariate adjusted analyses. These analyses are limited by only aggregate data being available. DSUK is encouraged to make its trial data available and thus allow for individual level regression analyses to be explored. • DSUK suggest "Published TIA hazard ratios (clinical outcome): estimated TIA hazard ratio for edoxaban from

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	Coumarin INR.2.3	Apixaban 5mg	Dabigatran 150 mg	Edoxaban 60 mg	Riv
Costs	19,440 (11,363; 36,432)	18,639 (12,795; 29,339)	18,318 (11,972; 30,693)	18,733 (12,791; 29,116)	21,2
Incremental Costs	- (-, -)	-801 (-8,941; 3,340)	-1,123 (-9,492; 2,982)	-707 (-8,916; 2,942)	-1,8
QALYs	5.365 (4.479; 6.261)	5.873 (4.978; 6.762)	5.638 (4.740; 6.536)	5.739 (4.884; 6.599)	5.7
Incremental QALYs	- (-, -)	0.508 (0.139; 0.882)	0.273 (-0.121; 0.652)	0.374 (0.005; 0.698)	0.4
INB 20,000 GBP	- (-, -)	10,959 (3,795; 21,046)	8,591 (-1,938; 16,502)	8,191 (2,312; 17,091)	6,7
INB 30,000 GBP	- (-, -)	16,038 (5,639; 28,939)	9,324 (-2,637; 22,476)	11,933 (3,448; 23,154)	11,0

(Abbreviation: GBP = British Pound)

From our exploratory analysis, we found that the effect of correcting the code to divide stroke costings by four has a large effect on the cost-effectiveness outcomes. In this scenario which also updates the clinical outcomes used in the model, edoxaban 60 mg od has a higher net benefit than rivaroxaban 20 mg od and dabigatran 150 mg bd at both the £20,000 and £30,000 thresholds. Additionally, the lower range of the INB credible intervals of edoxaban and apixaban are positive whilst those of dabigatran and rivaroxaban are negative.

Table 7: Scenario 2 - Updated clinical outcomes (NMA HR & published TIA HR) with amended potential stroke cost coding error and updated acute and management costs of stroke (derived from Bakhai et al. 2020)

Developer's response

- DSUK suggest "Amended stroke model coding error: correcting the code to divide stroke costings by four (to reflect 3-month cycle duration)"

Thank you for spotting this error. This has been amended. Please note the conclusions of the model do not change.

- They finally suggest using Bakhai et al 2020 as an alternative stroke cost

We have included this sensitivity analysis in response to ID112 above. Under this analysis dabigatran (150mg bd) has greatest expected net benefit at willingness-to-pay £20,000 and apixaban (5mg bd) at £30,000. Also, comparing DSUK's scenario 1 to scenario 2 indicates that little changes when switching to Bakhai 2020 costs. The primary reasons that scenario 1&2 differ so much from our base case is (as explained above) the selection of TIA hazard ratios and unjustified use of an alternative NMA.

This study (ENGAGE AF-TIMI) was included in the NMA of TIA-3 as was analysed consistently with other included studies using a method that was peer reviewed and published in RSM and the NIHR report[1,2]. It would be biased to choose just this hazard ratio from this paper (other outcomes are analysed) and only do this for this treatment.

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				Overall	**Overall**

	Coumarin INR 2.3	Apixaban 5 mg	Dabigatran 150 mg	Edoxaban 60 mg
Costs	19,305 (10,987; 35,847)	18,830 (12,800; 29,563)	18,334 (11,932; 30,362)	18,824 (12,743; 30,116)
Incremental costs	- (-, -)	-476 (-8,326; 3,799)	-970 (-8,198; 3,176)	-481 (-7,762; 3,562)
QALYs	5.399 (4.494; 6.304)	5.913 (5.011; 6.817)	5.878 (4.789; 6.587)	5.779 (4.904; 6.646)
Incremental QALYs	- (-, -)	0.514 (0.147; 0.901)	0.279 (-0.107; 0.666)	0.381 (0.063; 0.696)
INB 20,000 GBP	- (-, -)	10,763 (3,554; 20,854)	6,534 (-1,879; 16,268)	7,992 (2,237; 16,741)
INB 30,000 INB	- (-, -)	15,907 (5,528; 29,014)	9,343 (-2,622; 22,058)	11,798 (3,442; 22,825)

This is the same scenario as scenario 1 but with the acute and management cost of stroke amended based on Bakhai et al. (2020). As with scenario 1 above, the results of this scenario show that edoxaban 60 mg od has a higher net benefit than rivaroxaban 20 mg od and dabigatran 150 mg bd at both the £20,000 and £30,000 thresholds. Again, the lower range of the INB credible intervals of edoxaban and apixaban are positive whilst those of dabigatran and rivaroxaban are negative.

11.1 Interpretation of exploratory findings

These results show that adjusting for the differences in clinical outcomes, stroke acute and management costs, and correcting the potential stroke cost modelling error have a significant impact on the cost-effectiveness results. In the alternative scenarios presented, all DOAC interventions have a positive mean INB versus warfarin at a £20,000 and £30,000

On further discussion the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne, particularly in terms of the ability of the meta-regression to sufficiently adjust for such covariates. This made it difficult to be confident of the validity of precision of the NMA estimates (see the committee's discussion of the evidence in evidence review C1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals were wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore were no longer confident to recommend a specific DOAC or DOACs. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.

References:

4. Batson S, Sutton A, Abrams K. Exploratory Network Meta Regression Analysis of Stroke Prevention in Atrial Fibrillation Fails to Identify Any Interactions with Treatment Effect. PLoS One 2016; 11(8): e0161864.

5. Giugliano RP, Ruff CT, Rost NS, et al. Cerebrovascular events in 21 105 patients with atrial fibrillation randomized to edoxaban versus warfarin: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48. Stroke 2014; 45(8): 2372-8.

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				threshold. This suggests that all DOACs are a cost-effective use of NHS resources based on conventional NICE thresholds. Only apixaban and edoxaban have 95% credible interval around the INB which do not cross zero versus warfarin. In scenario 1, where the HRs for clinical outcomes are adjusted and the stroke cost model code is corrected, the incremental net benefit (INB) figures demonstrate that edoxaban is superior to both dabigatran and rivaroxaban at £20,000 and £30,000. When an updated acute cost for stroke is applied, in scenario 2, the cost effectiveness findings are similar to scenario 1. It should be noted that these alternative scenarios should be considered as exploratory and do not represent a fully comparable analyses as not all baseline characteristics across DOAC trial populations could be taken into account. Furthermore, the $CHADS_2$ >=2 subgroup data was not available for all clinical endpoints required in the model thus assumptions had to be made to impute data from all patients which is an additional limitation. Specifically, published data for the subgroup were not available for apixaban for TIA, SEE, and other clinically relevant bleeding. For dabigatran, data were not available for ischaemic stroke, TIA, SEE, other clinically relevant bleeding and MI. For these missing data, Sterne et al. inputs were used. That said, through these exploratory scenarios, DSUK has demonstrated that by attempting to adjust for heterogeneity in stroke risk across trials and correcting and using updated model input data has a significant	6. Thom H, Lopez-Lopez JA, Welton NJ. Shared parameter model for competing risks and different data summaries in meta-analysis: Implications for common and rare outcomes. Res Synth Methods 2019. 7. Sterne JA, Bodalia PN, Bryden PA, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess 2017; 21(9): 1-386.

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				impact on the cost-effectiveness results and conclusions presented by Sterne et al. These outputs demonstrate the significance of the failures identified throughout this document, and the evident effect that they have had on the conclusions informing the draft Guideline.	
Daiichi Sankyo UK Limited	Evidence Review G2	197	1-2 Figure 25	10.0 INAPPROPRIATE USE OF CEACS TO COMPARE MULTIPLE INTERVENTIONS DSUK does not consider that the use of Cost Effectiveness Acceptability Curves (CEACs) is an appropriate way to present the cost-effectiveness results between multiple treatment options in order to decide on the optimal intervention and consider that a reasonable decision-maker would exercise caution in the interpretation of the results in particular for a non-technical audience. To illustrate this point, we use the following example. The incremental net benefit (INB) in the table is a mean. It therefore takes into account the cardinal distance between treatments. The CEAC uses an ordinal measure, only accounting for the order of the treatments. The table below, from Fenwick E et al. (2001) shows how the 'best' treatment can have a lower probability of being optimal. This is more likely the more treatments exist. Table 5: Expected net benefits and probability of optimality - three interventions (Fenwick E et al., 2001) | | Treatment A | | Iteration 1 | 11 |	Thank you for your comment. We did not use the CEACs to choose optimal treatment; the optimal treatment was that with highest expected net benefit. We believe this comment is referring to the sensitivity analyses where only the CEACs are presented for most analyses as the conclusion that apixaban (5mg bd) had highest expected net benefit was unchanged. In response, we have clarified our interpretation at the beginning of section 6.9: "Our conclusion that apixaban (5mg bd) and dabigatran (150mg bd) have the highest incremental net benefits at willingness-to-pay thresholds in the range £20,000-30,000 was changed only by the sensitivity using Bakhai 2020 for the acute and management stroke costs, in which dabigatran (150mg bd) has highest net benefit. For all scenarios where apixaban still has greatest expected net benefit at £20,000-30,000, we provide only the CEACs; these quantify the probability that a treatment has highest net benefit, rather than indicating which treatment has highest expected net benefit." Note that we have included results tables (not just CEACs) for the three additional sensitivity analyses conducted in response to stakeholder comments.

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				Iteration 2 | 12 | 10 | 9 Iteration 3 | 13 | 18 | 15 Iteration 4 | 14 | 16 | 17 Iteration 5 | 15 | 14 | 11 Expected NB | 13 | 14 | 13 The table gives five iterations from a Monte Carlo simulation involving three treatments (A, B and C). The treatment with the highest expected net benefit (B) has only a 20% probability of being optimal. DSUK would like to advise caution in using CEACs to compare and rank multiple treatment options to determine an optimal intervention. It is possible for an intervention to have a higher probability of being optimal, but have a lower INB than the same intervention. Pairwise analysis should be undertaken for treatment interventions of interest. The CEAC for pairwise comparisons can look very different to the CEAC for multiple treatments and thus pairwise CEAC analyses should be used instead to provide accurate comparisons. These findings are further confirmed by Barton et al. (2008) who concluded that CEACs can represent decision uncertainty, but should not be used to determine the optimal decision.	
Daiichi Sankyo UK Limited (contains conf comments	Evidence Review G1	071	038	12.0 LACK OF CONSIDERATION OF PRACTICAL FACTORS AND PATIENT PREFERENCE Beyond efficacy and safety parameters, DSUK would like to highlight the practical benefits that edoxaban adds to the anticoagulation treatment paradigm.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence to the NICE guidelines on medicine adherence, medicines optimisation and patient experience in adult NHS services which

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				Published literature has shown improved adherence and compliance with once-daily treatment regimens compared with twice-daily regimens in patients with AF (Laliberté F et al., 2012). Furthermore, the European Patient Survey in Atrial Fibrillation found that 80.7% (n = 918) of patients expressed a preference for taking anticoagulation medication once daily compared with only 7.6% (n = 87) who preferred a twice-daily regimen (Bakhai A et al., 2013). A recent study by Toorop MMA et al. (2020) analysed 1,399 questionnaires completed by patients receiving DOACs in the Netherlands. Several statistically significant predictors of non-adherence were identified, including being on DOACs with twice-daily dosing regimens [OR 1.9, 95% CI (1.3-2.6)]. It should be noted that edoxaban is the only once-daily DOAC with superior reduction in major bleeding versus well-managed warfarin (Giugliano RP et al., 2013). Figure 5: [redacted] (Academic in confidence) *REDACTED* Figure 5 demonstrates adherence rates for the four DOACs after 12 months according to a study by Smits E et al. (academic in confidence) with marked improvements for AF patients on once-daily regimens. High persistence rates are also supported for edoxaban from the ETNA-AF-Europe study (De Groot JR et al., 2020). Overall, 1191 of 13092 patients (9.1%) permanently discontinued from edoxaban treatment, and 11901 of 13092 patients (90.9%) were still receiving edoxaban at the end of one-year follow-up.	would include taking into account personal preferences such as dose frequency.

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				The European Heart Rhythm Association (EHRA) Practical Guide (2018) highlights that "once-daily regimen generally results in greater adherence vs. BID regimens in cardiovascular patients. Most, but not all studies evaluating adherence for NOACs indicate that an OD dosing regimen is superior from a total tablet count perspective." (Steffel J et al., 2018). In Evidence Review 5, *"the committee discussed the patient experience of using apixaban and dabigatran, and described how dabigatran may lead to more upper GI side effects, and also possibly less compliance because of the greater number of doses per day. The NMA and pairwise data did not provide information to substantiate this and so the committee decided that these issues should not influence the recommendation."* DSUK are concerned that practical benefits, which have a considerable impact on patient compliance and the patient experience, have been overlooked as part of the draft guidelines. Guidelines suggest that the choice of DOAC should take into account patient preferences (Steffel J et al., 2018). Patients should have the right to receive care and treatment that meets their needs and reflects their preferences according to the NHS Constitution (2015). Specifically, Section 1.3 from the NICE clinical guidelines 'Patient experience in adult NHS services: improving the experience of care for people using adult NHS services' (CG138), highlights the importance of patient's views and encourages an individualised approach to patient services, for which the draft CG180 recommendations currently run contrary to.	

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				The Sterne et al. analysis, that forms Evidence Review 6, does not model patient and practical factors of DOAC treatments such as dosing frequency, patient compliance, option to include in Monitored Dosage Boxes and with/without food requirements. Edoxaban offers these practical benefits for patients: once-daily dosing with or without food, limited drug-drug interactions, and lactose free presentations. DSUK is concerned that these have not been considered by these clinical guidelines despite their impact on the patient experience. DSUK encourages NICE to consider the importance of individualised decision making which examines patient factors and clinical need. The impact of patient choice and preferences is not currently included in the economic model and the committee appear to have disregarded this important aspect in its decision-making thus far.	
Daiichi Sankyo UK Limited (contains conf comments)	Evidence Review G1	070	011	5.0 DOSING OF APIXABAN AND DABIGATRAN IN UK CLINICAL PRACTICE DSUK considers that NICE erred in its consideration of the dosage for The NMA separated out the different doses of the DOACs as separate comparators. In the health economic model the cohort of patients were modelled using the dosing as per the drug SPC, that is their dosing was reduced as they reached the age stated in the SPC. The costs and effectiveness data (from NMA) for the appropriate dose was then used in the model.apixaban and dabigatran, failing to account for the clinical reality described below, in which the real dosages used in practice are bound to affect the real use of the drug if the draft Guideline is finalised in its current form.	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (recommendation 1.6.2). The NMA separated out the different doses of the DOACs as separate comparators. In the health economic model the cohort of patients were modelled using the dosing as per the drug SPC, that is their dosing was reduced as they reached the age stated in the SPC. The costs and effectiveness data (from NMA) for the appropriate dose was then used in the model.

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				5.1 Unlicensed low-dose 2.5 mg bd apixaban usage The cost-effectiveness analyses conducted by Sterne et al. did not consider any scenarios on the unlicensed usage of low-dose (2.5 mg bd) apixaban. We are aware that unlicensed low dose apixaban is widely used as part of routine NHS practice, however, the modelling does not include any sensitivity analysis on this as part of the analysis. Rather, the analysis was limited to those that were appropriately given 2.5 mg bd as per licensed dose-reduction in ARISTOTLE. Evidence Review 5 states that "*The committee highlighted that the description of the dose for the main apixaban trial (5 mg) might be misleading as a small number of participants with additional risk factors were allowed to use 2.5 mg. However over 95% used 5 mg so it was agreed that it was acceptable to categorise the dose as 5 mg.*" DSUK has concerns about this point as published data suggests that low dose apixaban usage in the UK is significantly higher than what was observed in ARISTOTLE. ARISTOTLE included 4.7% of patients dosed with apixaban 2.5 mg bd. A recent study in the UK suggested this proportion of patients on apixaban 2.5 mg is 36.3%, many of whom are inappropriately under dosed (Fay et al. 2016). [redacted] The significance of appropriate dosing has been highlighted by Yao X et al.(2017) 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 patients with AF treated with apixaban, dabigatran, or rivaroxaban	

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				between 1/10/10–30/9/15. 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. The authors concluded that *"Potential underdosing (using reduced dose NOACs in patients without severe renal impairment) was associated with a nearly 5-fold increased risk of stroke in apixaban-treated patients. This outcome suggests that the tendency to prescribe reduced dose apixaban comes at the cost of reduced effectiveness of stroke prevention."* This study highlights concerns with underdosing and it has been commented in the most recent ESC AF guidelines (2020) and also in the EHRA Practical guide (2018) on the use of DOACs (Steffel J et al., 2018). The EMA Pharmacovigilance Risk Assessment Committee (PRAC) has requested the marketing authorisation holder 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 provision of the results should expedited if the results warrant an update of the product information. DSUK is concerned that usage of unlicensed low dose apixaban, which is linked to worse outcomes, is not taken into consideration in the model. [redacted]	

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				Again, as a result, we consider that NICE has failed to take into account matters which are bound to be considered by any rational decision-maker in drafting the Guideline.	
Daiichi Sankyo UK Limited (contains conf comments)	Evidence Review G2	175	Table 52	5.2 Dabigatran 110 mg bd usage Fay M et al. (2016) highlights that amongst dabigatran treated patients, the dabigatran 110 mg bd regimen is widely used in UK clinical practice (55.5% of all dabigatran treated patients). . [redacted] The draft NICE recommendations in section 1.6 for dabigatran are based on the clinical and cost-effectiveness results for the dabigatran 150 mg bd intervention and cannot be generalised across both licensed doses. As stated in Table 52 in Evidence Review 6, dabigatran 110 mg is associated with prevention of ischaemic stroke that is no better than warfarin [mean hazard ratio (HR) 1.13 (0.89, 1.42)] and when comparing the HRs of dabigatran 150 mg bd against dabigatran 110 mg bd, the lower dose performs worse than the higher dose across ischaemic stroke, TIA and systemic embolism which will have an impact on the accuracy of the findings if dosage is not accounted for. Low-dose dabigatran 110 mg bd is explored as a scenario in the Sterne et al. cost-effectiveness analysis but with limited results presented to inform judgements on cost-effectiveness impact on the DOACs. The recommendation in section 1.6 is for dabigatran but the basis is the clinical and cost effectiveness of	Thank you for this comment. The committee agreed that if a large proportion of people are receiving 110mg dabigatran, most are actually receiving the inappropriate dose, and that correct doses should be used. We now refer to the BNF when deciding on dosing (1.6.2) We recognise that the lower dose of 110mg may be appropriate for some people, although this will be a considerably lower proportion of people than the 55% cited, and we have allowed for this small proportion in our economic model.

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				the 150mg bd dose. Again, as a result, we consider that NICE has failed to take into account matters which are bound to be considered by any rational decision-maker in making the draft recommendations.	
Department of Cardiology, Northumbria Healthcare NHS Foundation Trust	Guideline	004	013 - 020	There seems to be acceptance that event recorders/ambulatory monitors or "appropriate technology" can diagnose paroxysmal AF (Atrial Fibrillation). Therefore it seems odd that there is not acceptance that an ALIVOCOR (for instance) may be able to diagnose persistent AF in the setting of an irregular pulse. In current COVID based practice (and before), many use ALIVCOR to catch/prove episodes due to challenges with timely 12 lead ECG. All will need a 12 lead in due course but not necessarily to detect AF. We feel that it should be acceptable to diagnose an irregular pulse as AF using validated devices such as KARDIA and the evidence supports this.	Thank you for this comment. For persistent AF, there was evidence from our review that lead I devices would not be sensitive or specific enough to replace the gold standard 12 lead ECG as the definitive method of detection. Although 12 lead is not as feasible to use as the lead I devices (which is, of course, why adequately accurate index tests needed to be sought), clinically adequate accuracy is a more important consideration, and so the feasible but inadequately accurate devices could not be recommended over 12 -lead ECG. For paroxysmal AF the situation was rather different, because the committee did not think that any of the longer-term gold standards used in any of the studies were adequate, thus prohibiting any meaningful evaluation of the index tests. This meant there were no options to select any feasible index tests with adequate accuracy, and also no options to suggest the use of an assumedly less feasible gold standard method. The committee therefore made a pragmatic recommendation that in the absence of evidence of the optimum form of paroxysmal AF detection, but in the knowledge that longer duration testing is more accurate, testing for suspected paroxysmal AF should be continued for as long as possible using any form of continuous or loop monitoring. A research recommendation has been made to cover this gap in knowledge.

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Department of Cardiology, Northumbria Healthcare NHS Foundation Trust	Guideline	009	011	Guidance has referred to "dabigatran or apixaban" without specifying which dose they refer to. For individuals who could be eligible for the larger or the smaller dose there will be clear differences in the cost effectiveness balance depending on which is chosen. This is highly relevant if dabigatran is being favoured over the other NOAC options such as edoxaban and rivaroxaban. Similarly this guidance asserts that apixaban is superiorly cost effective. If this is the case it should follow that this is suggested as first line and the inclusion of dabigatran on an equal footing is not appropriate. The Sterne and Lopez publications quoted in the guidance, do have differences in their results reflecting the challenging nature of these complex analyses and urging caution when applying their results. The Sterne publication is more favourable for edoxaban clinical efficacy than the Lopez. The guidance is heavily reliant on these analyses. These are relatively old, pre-existing and unadjusted network analysis. Similarly they include patient groups (e.g. Asian) which are not relevant to the UK and phase 2 studies which use doses not licenced for current use. These complex analyses are very vulnerable to small errors in data inclusion and methodology. There is a large amount of subgroup data from the large NOAC RCTs and therefore individual groups may have very different magnitudes of benefit from different agents and this will also markedly affect the cost effectiveness analysis. Grouping all patients together whilst simple will mean some patients may not get the most cost effective/clinically effective option for individual patients. The stroke risk profile in the various NOAC trials was not the same. There are significant methodological differences in the trials including study	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only nationally reductions can be included in the reference case analysis. In the case of DOACs we have used

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				design and outcome definitions. Therefore the conclusions for this networked metanalysis are not based on similar patient groups. The price estimates on which these analyses are made are not up to date. There have been changes in the list price for these drugs and various schemes that reduce the cost to the NHS. We accept it is difficult to build these into a model but important if cost is being considered ahead of/equally alongside efficacy. For significant decisions such as these we need our own analysis with UK pricing and populations/doses appropriate to UK practice. Real world data has not been included in the decision making process. This can support the clinical data from RCTs. I understand the desire to use randomised control trials over real world data but in a situation such as this without head to head studies and with very different study designs/populations/proportions on reduced dose, it could have been helpful. Tolerability including tablet size/side effects/dosette box/once v twice daily has a relevance in terms of patient preference, QALY issues and a degree of cost effectiveness relevance (if patients end up being switched to alternate NOACs). This has not apparently been taken into account. This guidance does not give a first line choice for patients who need a once daily drug for practical drug adherence reasons. The proposals in this guidance are inconsistent with other international well recognised guidance.	the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making. Tolerability and adherence should be taken into consideration in the context of shared decision making (1.6.2).
Guildford and Waverley ICP	Evidence Review G2	010	007	Warfarin is cheap but therapeutic monitoring increases treatment costs.	Thank you for your comment. The costs of monitoring were included in the health economic

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				The cost of monitoring warfarin has been substantially reduced in able patients due to the availability and access to patient self- monitoring. The initial cost models for DOACs indicated that the costs of those DOACs were justified by the fact that these agents did not require monitoring. Because of the widespread message that DOACs are safe, we found that junior doctors were prescribing the DOACs without suitable counselling, and we are therefore funding initiation reviews in primary care (even when started in secondary care) and yearly reviews. There is good evidence that without sufficient time for clinician training, and patient assessment and counselling, there are poor dosing decisions, for example: Inappropriate non-vitamin K antagonist oral anticoagulants prescriptions: be cautious with dose reductions, Neth Heart J. 2019 Jul; 27(7-8): 371–377. In our experience, there is insufficient patient counselling on the precautions required due to increased bleeding risk when treatment initiated in secondary care.	model. Patient assessment (recommendation 1.6.1) and counselling should form part of the discussion on choosing anticoagulant treatment in the context of shared decision making (recommendation 1.6.2).
Guildford and Waverley ICP	Evidence Review G2	010	008	Novel oral anticoagulants (NOACs) have more rapid onset and offset of action than warfarin and more predictable dosing requirements. We recognise that for patients, the ease of taking DOACs without needing careful dietary control required by warfarin results in frequent patient preference however, warfarin should remain an option for the following reasons: • In your evidence abstract you state that: Novel oral anticoagulants (NOACs) have more rapid onset and offset of action than warfarin and more predictable dosing	Thank you for your comment. Recommendation 1.6.1 refers to clinical risks profiles and personal preferences when deciding on anticoagulant treatment. The committee discussed the TTR in the included trials (see Evidence Review G1 committee's discussion of the evidence). Trial data stratified by TTR in five studies was discussed. The sub-group analyses in these studies suggested a possible association between lower mean centre TTR and increased relative efficacy of DOACs relative to warfarin in some of the outcomes, which would fit with the premise that lower TTR would impair warfarin

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				requirements. It is true that dosing requirements are more predictable in the average patient, however there are many patients who are not average: • Creatinine clearance calculations are inaccurate in a large number of patients making it difficult to identify the correct dose of DOAC, especially at the borderline values: Reference: Which estimate of renal function should be used when dosing patients with renal impairment? Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals • Time in therapeutic range (TTR): The warfarin arms of the DOAC trials had TTR in the range from 58-68, the local, audited TTR in Surrey Heartlands is in the order of 74. There is a clear relationship between TTR and bleeding risk: Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control Thromb Res . 2009 May;124(1):37-41 • As well as the original patients found to be insufficiently anticoagulated with DOACs, o Metallic heart valve, Moderate or severe mitral stenosis, • Warfarin is an option in severe renal dysfunction, CrCl< 15ml/min • Warfarin is preferred in Antiphospholipid Syndrome: MHRA: Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome	performance. The committee noted that although the subgroup analyses may indicate a lower efficacy of DOACs with higher TTRs, they were very concerned that the use of subgroups to fit with a mean UK TTR would inevitably result in underrepresentation of patients with poor INR control typically seen in UK clinical practice. Hence, the committee view was that use of whole trial data by Lopez & Lopez was appropriate to produce an evidence based guideline relevant to the NHS. Warfarin remains an option for people in whom DOACs are not suitable, not tolerated or contraindicated (1.6.5). The DOACs should be prescribed in accordance with the guidance in the BNF (1.6.2).

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				• Consider warfarin for patients weighing more than 120Kg, or BMI > 40kg/m2 By placing warfarin so low down in the selection of anticoagulation it is even more likely than now to be overlooked as an option by junior doctors even when appropriate. Some very experienced general practitioners with very good warfarin management systems are also aware of emerging DOAC failures compared to the well established warfarin control.	
Guildford and Waverley ICP	Evidence Review G2	042	009	We are concerned about your conclusions: For stroke prevention in AF, apixaban (5mg bd) was ranked as being among the best interventions for a wide range of the outcomes evaluated including stroke or systemic embolism, MI, major bleeding, and all-cause mortality. Edoxaban (60mg od) was ranked second for major bleeding and all cause mortality. Except for all-cause mortality, outcomes for rivaroxaban (20mg od) were ranked less highly than several other NOACs. The non-NOAC interventions (warfarin (INR 2-3) and antiplatelet therapy (aspirin/clopidogrel≥150mg od)) were ranked worst for stroke or systemic embolism and were not among the best three interventions for any of the outcomes.	Thank you for your comment we have amended this error (apixaban best for bleeding but not stroke as stated).
Guildford and Waverley ICP	Guideline	005	008	Use the CHA2DS2-VASc stroke risk score to assess stroke risk in people with…. a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm Although there is a 90% success rate for cardioversion, only around 35% of patients are still in sinus rhythm after 1 year, ref: https://academic.oup.com/europace/article/22/8/1149/5825418 . The wording in the above statement is not sufficient to inform consistent decision making: It would	Thank you for your comment. The committee agreed that there is no evidence to inform the recognised time when a review decision can safely determine that risk of AF recurrence is so low that anticoagulation can be stopped. The committee were therefore unable to make a recommendation in this area.

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				be better to recommend a specific duration and review of patients which a sufficient CHA2DS2-VASc stroke risk score to require anticoagulation where there is no specific known cause for the original presentation.	
Guildford and Waverley ICP	Guideline	009	011	Offer anticoagulation with either apixaban or dabigatran to people with atrial fibrillation and a CHA2DS2-VASc score of 2 or above, taking into account the risk of bleeding We are concerned that the options to use edoxaban, rivaroxaban and warfarin have been removed on the basis of the evidence discussed in the evidence review G-6. We do not agree that the evidence used supports a specific preference of one DOAC over another and over warfarin based on reasons and evidence described below: • No placebo controlled or head-to-head clinical trials have been carried out since the NICE technology appraisals: o Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation Technology appraisal guidance [TA249]Published date: 15 March 2012 o Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation Technology appraisal guidance [TA256]Published date: 23 May 2012 o Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation Technology appraisal guidance [TA275]Published date: 27 February 2013	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model was revised to an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2). The DOACs were recommended over vitamin k antagonists because the committee were confident in the results of the health economic model showing that they were more clinically and cost effective across all outcomes. However, recommendation 1.6.5 recommends a vitamin K antagonist if DOACs are contraindicated, not tolerated or are not suitable. Intracranial bleeding was specified as an outcome in the review protocol (see appendix A

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				○ Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation ○ Technology appraisal guidance [TA355]Published date: 23 September 2015 • In those appraisals, the committees accepted an equal place in therapy for all DOACs and warfarin. In 2017 and reviewed again in 2019, the Surrey and North West Sussex reviewed the relevant trials and issued to following policy statement : APC 420-2019 (replaces PCN 269-2017). • The APC accepted that in the absence of head-to-head trials between the direct oral anticoagulants (DOACs), the differences between the trials with respect to patient selection, concurrent medication, warfarin arm time in therapeutic range (TTR), and relative duration of treatments, invalidates claimed benefits for one DOAC over another: • On this basis, the APC agreed that, as originally indicated by NICE, all oral anticoagulants should continue to be considered equal and that selection of treatment should be based on patient choice between warfarin and a DOAC. • On current evidence, should the other DOACs reduce their cost to the health economy sufficiently to be similar or better than that for edoxaban, they would be considered for addition to the selection tool, https://surreyccg.res-systems.net/PAD//Content/Documents/2/FINAL%20DOAC%20Selection%20tool%20October2019V3.pdf • Audits find that the TTR for warfarin in the Area Prescribing Committee collaborative is much higher	evidence review G1). The intracranial bleeding evidence from the NMA showed that all DOACs were superior to warfarin. In addition, indirect estimates suggested strong trends for superiority of apixaban and dabigatran (and to a lesser extent edoxaban) over rivaroxaban. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Recommendations 1.6.3 and 1.6.4 have therefore been amended and now refer to all licensed DOACs. DOACs were shown to be more clinically and cost effective than warfarin across all outcomes critical to decision making. Warfarin remains an option if DOACs are not suitable, not tolerated or contraindicated (1.6.5). The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.

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				than that in the DOAC trials, and therefore conclusions that DOACs are safer than warfarin under these circumstances has not been demonstrated. Warfarin should continue to be a treatment option in the local health economy. Patients who are well controlled on warfarin should not be switched to a DOAC unless the prescriber and patient have a full discussion of benefits and risks of the alternative treatment. • When carefully considering the lack of good evidence describing differences between benefits and risks of DOACs due to the lack of head-to-head trials between these treatments, it is important to consider the cost to the health economy. • Due to a rebate, the cost of edoxaban is significantly lower to the health economy than the other competitor agents and therefore should be the preferred choice of DOAC. • Dabigatran and warfarin are also included in the selection tool, recommended instead of edoxaban in specific indications, because of their pharmacokinetics, availability of an antidote, and, in the case of warfarin, for patients where a higher dose of anticoagulant is required and can be measured such as patients with mechanical valves and patients with obesity>40kg/m2 • In June 2019, the APC reviewed new evidence published in a BMJ paper, July 2018 titled, 'Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care' which concluded that apixaban was safer than other DOACs. The APC did not accept that the type of research, a cohort study, is powered to make those conclusions. The APC members concurred with the previous recommendation made in 2017 and confirmed that edoxoban is still the preferred DOAC. *BMJ paper, July 2018 titled, 'Risks and benefits of direct oral	

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				anticoagulants versus warfarin in a real world setting: cohort study in primary care' **Warfarin:** We recognise that for patients, the ease of taking DOACs without needing careful dietary control required by warfarin results in frequent patient preference for DOACs however, warfarin should remain an option for the following reasons: • In your evidence abstract you state that: Novel oral anticoagulants (NOACs) have more rapid onset and offset of action than warfarin and more predictable dosing requirements. It is true that dosing requirements are more predictable in the average patient, however there are many patients who are not average: • Creatinine clearance calculations are inaccurate in a large number of patients making it difficult to identify the correct dose of DOAC, especially at the borderline values: Reference: Which estimate of renal function should be used when dosing patients with renal impairment? Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals • Time in therapeutic range (TTR): The warfarin arms of the DOAC trials had TTR in the range from 58-68, the local, audited TTR in Surrey Heartlands is in the order of 74. There is a clear relationship between TTR and bleeding risk: Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control Thromb Res . 2009 May;124(1):37-41	

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				• As well as the original patients found to be insufficiently anticoagulated with DOACs,
				  ○ Metallic heart valve,
				  ○ Moderate or severe mitral stenosis,
				• Warfarin is an option in severe renal dysfunction, CrCl< 15ml/min
				• Warfarin is preferred in Antiphospholipid Syndrome: MHRA: Direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events in patients with antiphospholipid syndrome
				• Consider warfarin for patients weighing more than 120Kg, or BMI > 40kg/m2
				By placing warfarin so low down in the selection of anticoagulation it is even more likely than now to be overlooked as an option by junior doctors even when appropriate.
				Some very experienced general practitioners with very good warfarin management systems are also concerned about of emerging DOAC failures compared to the well established warfarin control.
				
				Comparative safety of DOACs:
				Initial marketing of apixaban promoted the superior safety of apixaban with regards to intracranial bleeds. These claims have been withdrawn, however the message bias still persists in both clinicians perception and in meta-analyses: Evaluation of the Inclusion of Studies Identified by the FDA as Having Falsified Data in the Results of Meta-analyses The Example of the Apixaban Trials, JAMA Intern Med. 2019 Apr; 179(4): 582–584.
				In addition it is important to note very different populations between the trials, for example, when looking at the CHADS2 Score between the trials, you	

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				will find that these range from 2.1 for RE-LY and Aristotle (dabigatran and apixaban respectively), 2.8 for Engage AF (edoxaban) and 3.6 for Rocket AF (rivaroxaban) it is clear that there are very big differences between the patient populations in the trials, especially considering that each CHADS2 Score denotes a co-morbidity, all of which in the score (except female vs male) contribute to an increased risk of adverse events. Another clear evidence for the difference between trials involves looking at the warfarin arm of those trials: Stroke Prevention in Atrial Fibrillation: A Clinical Perspective on Trials of the Novel Oral Anticoagulants, Cardiovasc Drugs Ther. 2016; 30: 201–214, Published online 2016 Jan 18. It is therefore not appropriate to suggest that any one DOAC is safer than another. **Price of DOACs:** "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". The costs of the DOACs currently on the market are very different from those at the time of the economic modelling, especially when considering costs to the local health economy as a result of long term rebates which wholly comply with the PRESQIPP ethical framework. The committee also did not take into consideration the probable patent expiry for dabigatranin 2023, rivaroxaban in 2026, edoxaban and apixaban in 2027, We therefore request that the Guidance should limit	

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				itself to recommend the DOAC of the lowest acquisition costs as the first line treatment. Switching to apixaban in our ICP (pop approx. 210,000) as described in the draft consultation would cost in excess of £400K per annum. The cost of the actual switching process will require a prescriber to search the databases, identify patients, redo creatinine clearance calculations, possibly including additional blood test, contacting the patients to inform them of the switch, switching patients, and ensuring that any remaining 'old' prescriptions are discarded. This will cost in excess of £50 per patient (pilot data available), an additional £150,000 costs, all this before switching patients currently on warfarin. Patients on warfarin are usually those excellent time in therapeutic range (TTR) otherwise they would have already been changed. In order to invest over £600K in the first year, just in our population would need a very good justification and these numbers included in the cost models.	
Icentia	Evidence Review A	007	010 - 022	The following study should have been included within the evidence review: Nault I, et al., Validation of a novel single lead ambulatory ECG monitor - Cardiostat™ - Compared to a standard ECG Holter monitoring. J Electrocardiol. 2019 Mar-Apr;53:57-63. doi: 10.1016/j.jelectrocard.2018.12.011. Epub 2018 Dec 19.	Thank you for your comment. This non-randomised study was not eligible for this review (see Appendix A evidence review A). At the protocol stage it was decided that this review A should include randomised trials only as they are associated with the least risk of bias.
Icentia	Evidence Review A	030	012	Alternative unit prices for 1 lead, single-use ambulatory ECG monitors are not included which may prove cost effective versus current standard of care	Thank you for your comment. We provided the unit costs for a number of lead-I devices, it was not possible for us to report every single device. Some very low cost devices were included in the list. The committee noted that although the lead-

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					I devices do not appear particularly costly per use they may add a significant resource burden in terms of the need for expert interpretation. This would either require training of GPs or would necessitate sending lead-I results to cardiologists for guidance and advice. The committee considered the published health economic analysis alongside the clinical evidence and concluded that there was insufficient direct evidence to support replacing the current methods of detecting AF.
Icentia	Evidence Review B	006	007-009	The following study should have been included within the evidence review: Nault I, et al., Validation of a novel single lead ambulatory ECG monitor - Cardiostat™ - Compared to a standard ECG Holter monitoring. J Electrocardiol. 2019 Mar-Apr;53:57-63. doi: 10.1016/j.jelectrocard.2018.12.011. Epub 2018 Dec 19.	Thank you for this suggestion. This study was considered for the review, but excluded because it did not comply with the review protocol (please see excluded studies list).
Icentia	Guideline	004	018-200	Since EMBRACE study (Dr. Gladstone et al.) showed that non-invasive ambulatory ECG monitoring for a target of 30 days significantly improved the detection of atrial fibrillation by a factor of more than five and nearly doubled the rate of anticoagulant treatment, as compared with the standard practice of short-duration ECG monitoring. With this in mind, should long term 'continuous' ECG recorder technology be favoured over event recorders? During a Pandemic like COVID-19, reducing unnecessary patient visits to clinics/ hospitals is a priority. Therefore, ambulatory ECG monitoring technologies which enable patients to be able to fit the monitors in the comfort and safety of their own homes	Thank you for your comments. Our recommendation was that testing for AF that may include paroxysmal AF should be continued for as long as possible by any form of continuous or loop monitoring. This very general recommendation was made because the evidence was not strong enough to suggest that any specific test or device should be recommended but did suggest that the accuracy of detection increased with the duration of testing. The GC did not agree that there was sufficient evidence to recommend long term ECG recorder technology rather than event recorders. We agree with your suggestions that the ideal long term device should be easily removable or MRI-safe, and that ambulatory

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				would help reduce virus transmission rates whilst maintaining current standard of care. As MRI scans are used for TIA and stroke diagnosis and follow-up, they can be needed while the patient is already wearing an ambulatory ECG monitoring device. For long term ECG recordings, using an MRI safe recorder or one which can be removed then reinstalled after the scan would represent an advantage.	monitoring is particularly important during the current pandemic.
Johnson & Johnson Medical Limited	Comments Form Question 2	N/A	N/A	**Would implementation of any of the draft recommendations have significant cost implications?** The inclusion of laser ablation in 1.7.19 - The cost of ablation equipment is a key driver of the outcomes of the cost-effectiveness analysis. It is important to ensure the products included in the analysis are representative of a standard paroxysmal atrial fibrillation ablation procedure, and that the associated costs are reflective of costs in the current healthcare system. Underestimating or overestimating the cost of AF ablation equipment included in the assessment (please see comment 21 for details) could potentially lead to increased costs per procedure, which would have consequent impact on NHS expenditure. - The purchase of the capital equipment and software required to perform laser ablation procedures would increase total cost as the technology is not currently available in the majority of hospitals in the UK. There would	Thank you for your comment. Following stakeholder consultation some omissions were identified, new data provided, and issues raised that led to amendments to the economic model. These included: -Edits to some of the equipment costs further to stakeholder comments -30% uplift for laser equipment costs from local source used as the base case rather than sensitivity analysis - Reduction in cardiac tamponade risk for cryoballoon (from 1% to 0.4%) -Addition of persistent Phrenic Nerve Palsy risk for laser (1% as with cryoballoon) - Sensitivity analysis on procedural costs for catheter ablation where 'elective' case HRG cost used for RFPP, 'day case' cost used for cryoballoon and 'total HRG' used for all other catheter ablation. -Threshold analysis to see what reduction in procedure cost is needed for cryoballoon to become most cost effective. This saving was then compared narratively to savings associated with not having general anaesthesia, savings in staff costs from shorter procedure duration and savings from same day discharge.

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				also be additional training required for clinicians to gain competency in its use. The inclusion of RF PP ablation in 1.7.19 Once the suggestions in comment 21 are implemented, greater use of RF PP could provide further value for the NHS. In addition, as demonstrated by the evidence used in the cost-effectiveness analysis, the reduction in AF recurrence for RF PP would lead to long-term cost reductions due to the need for fewer repeat ablation procedures.	The latter two sensitivity analyses were considered extreme scenarios as the committee noted that laser and RFPP may also be associated with some of these savings and they are not exclusive to cryoballoon ablation. Please note capital equipment was not included in the costing as the committee stated that in most cases this is provided free of charge by manufacturers as part of a contractual agreement in exchange for the purchase of a minimum volume of equipment. Overall, the results indicate RFPP is the most cost effective option. The sensitivity analyses around costs do not change the conclusions, although the probability of RFPP being most cost effective does reduce. The threshold analysis for cryoballoon indicates a reduction of £2,913 is required. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge, this equated to £1,289 in savings which is not enough for cryoballoon to become more cost effective than RFPP. A 'consider' recommendation was chosen due to the uncertainty regarding the cross over rate from AAD to ablation, to which the model was sensitive to. Furthermore, the volume and quality of the clinical evidence upon which the model was based was not deemed high enough to make an offer recommendation. The committee made a further 'consider' recommendation for either cryoballoon or laser ablation for people who are unsuitable for RFPP. The committee considered these people to include those for whom a short procedure time or reduced risk of fluid overload from saline

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					irrigated RF catheters was preferred, for example those with a recent history of decompensated heart failure.
Johnson & Johnson Medical Limited	Comments Form Question 3	N/A	N/A	**What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)** The inclusion of RF PP ablation in 1.7.19 - Johnson & Johnson Medical do not believe there will be challenges switching from cryoballoon ablation to RF PP, as RF PP is widely used in all arrythmias and the majority of clinicians are trained on the technology and use it regularly. - User of RF PP also creates efficiencies in technology usage, as it means the time between procedures is not wasted whilst swapping technologies. Ablation procedures have become increasingly shorter as the technology has evolved; however, turnaround time between cases may still reduce overall procedure efficiency. - Due to the reduction in AF recurrence rates associated with the use of RF PP ablation, the number of patients requiring repeat ablation procedures could diminish, thereby reducing waiting list numbers and/or increasing capacity in the system. Johnson & Johnson offers extensive medical education programs to ensure safe and effective use of RF PP ablation products for all levels of clinician expertise. In addition to our medical education offerings, we also have a skilled team of technical	Thank you for your comment.

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				specialists to support the use of our technology during the procedure and train the hospital team to use the products safely and effectively.	
Johnson & Johnson Medical Limited	Comments Form Question 4	N/A	N/A	**The recommendations in this guideline were developed before the coronavirus pandemic. Please tell us if there are any particular issues relating to COVID-19 that we should take into account when finalising the guideline for publication.** COVID-19 has led to challenges in patient access to timely and effective treatment. Urgent patients are being prioritised for treatment; however, for patients not classified as urgent, there is risk of disease progression whilst waiting for treatment. The recommendation for use of RF PP will provide clinicians with flexibility and allow them to treat different arrythmias without wasting time changing technology between procedures. In response to COVID-19, hospitals have had to consider approaches to improve patient throughput, including same day discharge and the use of conscious sedation (to avoid general anaesthetic) for RF PP patients. As mentioned in comment 4, ablation with RF PP technology under conscious sedation is safe and effective as demonstrated by the RF PP studies selected by NICE for the analysis.	Thank you for your comment. The decision whether to perform RF point-by-point ablation under conscious sedation or general anaesthesia will take place in the context of shared decision making.
Johnson & Johnson Medical Limited	Evidence Review J1	070	002	We believe that the specified list of products used for a laser procedure is not comprehensive. To perform a laser ablation procedure for a paroxysmal atrial fibrillation patient in accordance with the standard of care, additional products not listed by NICE would likely be required. We suggest that NICE consult with additional physician users of laser ablation technology to ensure that all products required for a standard paroxysmal atrial fibrillation ablation with laser are included in the costing. As stated in the NICE laser	Thank you for your comment. We have reviewed the list of products and IPG563. Two items have been added to the laser ablation base case costs: a circular mapping catheter and cable. When discussing with the laser user who provided the list of kit, he noted that this was not required and that he does not use it (500+ case experience). As a result, a sensitivity analysis was conducted excluding this additional kit.

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				balloon Interventional Procedures Guidance (IPG653), a circular mapping catheter is required, however, it is not currently included in the costing analysis. NICE, 2016. Percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation. Interventional procedures guidance	
Johnson & Johnson Medical Limited	Evidence Review J1	071	014	We suggest a revision to the base case analysis based on updated laser ablation equipment costs.	Thank you for your comment. Given the likelihood of local negotiations, the committee have agreed to increase the local costs by 30% in the basecase analysis rather than only in a sensitivity analysis, to ensure a fair assessment of different ablation techniques. Please note as well as the above edit, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this.
Johnson & Johnson Medical Limited	Evidence Review J1	071	042	We support the committee's decision to increase laser ablation equipment costs by 30% due to local negotiated cost reductions and suggest that this is a more accurate reflection of the true costs of the equipment used in the procedure, and should therefore be used in the main cost-effectiveness analysis.	Thank you for your comment. Given the likelihood of local negotiations, the committee have agreed to increase the local costs by 30% in the basecase analysis rather than only in a sensitivity analysis, to ensure a fair assessment of different ablation techniques. Please note as well as the above edit, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this.
Johnson & Johnson	Evidence Review J1	072	001	The exploratory analysis where the cost of all types of catheter ablation technology were equivalent confirms	Thank you for your comment. As this exploratory analysis was not evidence based it could not be

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Medical Limited				that the use of RF PP provides the most cost-effective procedure. This analysis should be given more weight in informing the recommendations given the current limitations around the collection of accurate ablation equipment cost data for laser ablation.	used to support a recommendation. Please note that given the likelihood of local negotiations, the committee have agreed to increase the local costs by 30% in the basecase analysis rather than only in a sensitivity analysis, to ensure a fair assessment of different ablation techniques. Please note as well as the above edit, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this.
Johnson & Johnson Medical Limited	Evidence Review J1	077	007	We agree with the assessment of the evidence and the conclusion that ablation is superior to medical therapy for first line patients.	Thank you for your comment.
Johnson & Johnson Medical Limited	Evidence Review J1	077	050	The committee acknowledged that the decision to use a 'consider' rather than 'offer' recommendation for ablation was based on the small evidence base currently available for laser ablation (4 studies), which is not comparable to the large evidence base that currently exists for RF PP (56 studies). We suggest updating 1.7.19 to '*offer radiofrequency point-by-point ablation for people with symptomatic paroxysmal or persistent atrial fibrillation if drug treatment is unsuccessful, unsuitable or not tolerated*' as this is supported by the evidence base and the European Society of Cardiology (ESC) 2020 guidelines, which "recommend" ablation as second line treatment and "consider" ablation for first line treatment. Updating to 'offer' may also help to increase patient choice. Recommendation 1.7.20 will ensure that patients have all the information on risks and benefits	Thank you for your comment. It is true that the number of RF PP studies in the pairwise reviews was relatively high (61 across the 4 strata). In the NMA, upon which the model was based, the evidence base for RF PP was smaller. For the outcome of recurrence for RF PP studies there were 16 studies in the NMA (RF PP vs RF ME = 4 studies; RF PP vs cryo = 6 studies; RF PP vs hybrid = 1 study; RF PP vs laser = 1 study; RF PP vs medical = 4 studies). A 'consider' recommendation was chosen due to the uncertainty regarding the cross over rate from AAD to ablation, to which the model was sensitive to. Furthermore, the volume and quality of the clinical evidence upon which the model was based was not deemed high enough to make an 'offer' recommendation.

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				before deciding whether ablation is an appropriate treatment option.	The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP. The committee considered these people to include those for whom a short procedure time or reduced risk of fluid overload from saline irrigated RF catheters was preferred, for example those with a recent history of decompensated heart failure.
Johnson & Johnson Medical Limited	Evidence Review J1	081	006	Due to the low penetration of laser in the UK, widespread adoption of the technology would lead to a significant change in current practice. This change would require large investments in capital equipment, software and training that are not included in the current cost-effectiveness analysis. In comparison, RF PP is widely adopted within the UK; if the additional costs associated with adoption of laser technology were taken into consideration, this would affect laser ablation's overall cost-effectiveness.	Thank you for your comment. Capital equipment was not included in the costing as the committee stated that in most cases this is provided free of charge by manufacturers as part of a contractual agreement in exchange for the purchase of a minimum volume of equipment. Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP. The committee considered these people to include those for whom a short procedure time or reduced risk of fluid overload from saline irrigated RF catheters

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					was preferred, for example those with a recent history of decompensated heart failure.
Johnson & Johnson Medical Limited	Evidence Review J1	081	010	We support the statement that RF PP is more widely available as it can be used for arrhythmias other than atrial fibrillation. The fact that RF PP is more versatile than other ablation technologies leads to potential costs savings by avoiding the purchase of multiple platforms of ablation technology to perform all procedures. Use of RF PP for AF procedures also helps physicians maintain their proficiency with the technology, which will likely translate to the best possible outcomes across arrhythmias.	Thank you for your comment.
Johnson & Johnson Medical Limited	Evidence Review J1	081	020	Patient preference is an important factor in the decision of the type of sedation used in an AF ablation procedure. However, choice of sedation is also dependent on the hospital resources available, clinical judgement and clinician preference. One factor that should not influence choice of sedation is the type of ablation technology used in the procedure. When evaluating patient and clinician preferences, it is important to consider the importance of limiting exposure to fluoroscopy. Many clinicians and patients prefer not to be exposed to excess radiation when avoidable. RF PP technology is used in conjunction with 3D mapping systems, that allow for real-time imaging of the heart, which reduce dependency on fluoroscopy for imaging. This is demonstrated in several studies included in the NICE systematic literature review (Andrade 2020, Bin Waleed 2019, Giannopoulos 2018, Gunawardene 2018, Hunter 2015 and Kuck 2016).	Thank you for your comment. Choice of sedation should be discussed with the patient in the context of shared decision making. This is referred to in the committee's discussion of the evidence in evidence review J1.
Johnson & Johnson Medical Limited	Evidence Review J2	015	35	The AF recurrence for laser ablation is likely underestimated, leading to a conservative model, as the only study providing recurrence data for laser ablation (Dukkipati 2015) provided a different measure	Thank you for this comment. Our protocol definition of AF recurrence did not specify the duration of AF, and so we have included any duration of testing. We cannot change our

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				of AF recurrence, using a 60 second episode of AF rather than 30 seconds which is used in the other studies. The 2017 expert consensus statement from global heart rhythm societies including the European Heart Rhythm Association defines AF recurrence as any recurrence of AF longer than 30 seconds (2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation). Studies included in the NICE systematic literature review that use 30 seconds include: Andrade 2019, Bin Waleed 2019, Hunter 2015, Gunawardene 2018, Kuck 2016, Morillo 2014, McCready 2014	review inclusion/exclusion criteria post-hoc as this would increase the risk of bias. However, this issue would not have affected the NMA estimates greatly. This is largely because the longer duration will have underestimated recurrence for the comparator of RF PP to an equal degree as well, partially eliminating this artefact.
Johnson & Johnson Medical Limited	Evidence Review J3	016	Table	The network meta-analysis (NMA) demonstrates that RF PP has the lowest AF recurrence rate compared to other catheter ablation technologies. The RF PP technology used in several of the studies in the NMA is no longer standard of care in the UK (non-contact force catheters). A recent NMA (Gupta 2020) using randomized and non-randomized prospective comparative studies of ablation technology found a greater difference between 12 month recurrence for RF PP technology used today in the UK, as compared to the currently used cryoballoon technology. Dhiraj Gupta, Tom De Potter, Tim Disher et al. Comparative Effectiveness of Catheter Ablation Devices in the Treatment of Atrial Fibrillation: A Network Meta-analysis of Patients in Prospective Studies. Journal of Comparative Effectiveness Research (2020) PMID:31913063 DOI: 10.2217/cer-2019-0165.	Thank you for your comment. The committee agreed that the protocol definition of RF PP did not need to specify the sub-types for inclusion and therefore non-contact force catheters were included.
Johnson & Johnson Medical Limited	Evidence Review J3	019	Table	One of the main drivers in the cost-effectiveness model is the intervention cost. Therefore we request that the committee seek advice from additional electrophysiologists, specifically those who routinely use RF PP, cryoballoon and laser, to provide guidance	Thank you for your comment. Committee members as well as some of their colleagues had provided input on the equipment. Some errors/omissions to the equipment were identified as a result of the stakeholder

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				on the products required to perform an paroxysmal atrial fibrillation ablation procedure in accordance with the standard of care for each technology type.	consultation. As a result of these comments and further discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.
Johnson & Johnson Medical Limited	Evidence Review J3	037	023	The committee noted that the cost of laser ablation technology may include locally negotiated discounts, however these discounts were not included in the equipment cost of other ablation technologies. The NICE guidelines manual state public list prices for technologies should be used in reference case analysis. If list price is not available for laser, as an alternative we suggest the sensitivity analysis SA21 where laser is increased by 30%, would be the next best alternative.	Thank you for your comment. Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.
Johnson & Johnson Medical Limited	Evidence Review J3	037	026	It was noted by the committee that cables for RF PP can be sterilized and reused up to 4 times. However, this is inaccurate as it underestimates the number of times that they can be reused. The instructions for use recommend that the cables can be sterilized and reused up to 20 times. The costing in the model should be updated to reflect this.	Thank you for your comment. The reuse of the cable has been changed to 10 times. Although the manufacturer instructions suggest this can be done up to 20 times, based on committee experience this is not done in practice and the sterilising companies will only allow 10 times.

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Johnson & Johnson Medical Limited	Evidence Review J3	083	024	As the committee have noted, the results of the cost effectiveness analysis are sensitive to the cost of laser ablation. Given the challenges highlighted within the comments, we suggest that the committee revisits their recommendations regarding laser ablation.	Thank you for your comment. Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.
Johnson & Johnson Medical Limited	Evidence Review J3	097	Table	As the economic model is sensitive to cost, we suggest that electrophysiologists familiar with RF PP, laser and cryoballoon review the ablation equipment identified for each modality to ensure it is representative of products used for a paroxysmal atrial fibrillation procedure, and that the associated costs are reflective of costs they have seen in their practice. Below is our suggestion on the ablation equipment used in RF PP, laser ablation and cryoballoon ablation that should be included in the analysis to be reflective of current clinical practice: • For RF PP, the Decanav diagnostic catheter is currently not used as the standard of care in the UK for paroxysmal atrial fibrillation procedures. The Decanav catheter can create high-resolution, high-density maps and is predominantly used in ventricular tachycardia procedures. To accurately reflect current practice an alternative diagnostic catheter should be used in the model. For example, use of the Webster CS catheter would more accurately reflect	Thank you for your comment. Committee members as well as some of their colleagues had provided input on the equipment. We have reviewed your suggestions and made the following changes. RFPP: - changed Decanav diagnostic catheter to Webster CS as well as changing associated cables. - The reuse of the cable has been changed to 10 times. Although the manufacturer instructions suggest this can be done up to 20 times, based on committee experience this is not done in practice and the sterilising companies will only allow 10 times. Cryoballoon: added diagnostic catheter and cable. The committee said gas would be included as part of procedural NHS reference costs.

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				current practice in the UK for paroxysmal atrial fibrillation procedures, and costs significantly less than the Decanav catheter. • For RF PP, the 3 cables that have been identified as necessary to perform the procedure have been reused 4 times each in the model. The instructions for use indicate that the cables can be reused up to 20 times, and therefore, this should be reflected in the model. • For cryoballoon ablation, it should be considered whether a diagnostic catheter for phrenic nerve pacing, cables and gas should be also be included in the model. We believe including these additional products would be more reflective of the current standard of care. • For laser ablation, a circular mapping catheter should be included within the model, as stated in the NICE interventional procedures guidance. (NICE, 2016. Percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation. Interventional procedures guidance) For laser ablation, the reuse of an endoscope 50 times may not be reflective of current practice. There is no evidence supporting the number of times an endoscope can be reused and there have been calls for further research to be done to validate appropriate reuse for these products. (Petersen, 2016). From discussions with clinical experts, it is our understanding that the current standard of care is to reuse an endoscope approximately 10 times, given decreasing image quality of the camera after multiple sterilizations. Petersen BT, Cohen J,Hambrick RD, Buttar N, Greenwald DA, Buscaglia JM, Collins J,	Laser: added circular mapping catheter and cable. Reduced endoscope reuse to 10 times in line with current practice and manufacturer recommendation. In addition, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.

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				Eisen G. Multisociety guideline on reprocessing flexible GI endoscopes: 2016 update.	
Johnson & Johnson Medical Limited	Evidence Review J3 analysis	037	027	For laser ablation procedures, the use of an endoscope 50 times may not be reflective of current practice. There is no evidence supporting the number of times an endoscope can be reused and there have been calls for further research to be done to validate appropriate reuse for these products (Petersen, 2016). From discussions with clinical experts, it is our understanding that the current standard of care is to reuse an endoscope approximately 10 times, given decreasing image quality of the camera after multiple sterilizations. We would recommend that NICE validates the current standard of care for endoscope use with additional clinical experts. Petersen BT, Cohen J,Hambrick RD, Buttar N, Greenwald DA, Buscaglia JM, Collins J, Eisen G. Multisociety guideline on reprocessing flexible GI endoscopes: 2016 update.	Thank you for your comment. We have reduced endoscope reuse to 10 times in line with current practice and manufacturer recommendation.
Johnson & Johnson Medical Limited (Contains conf comments)	Comments Form Question 1	N/A	N/A	**Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.** The inclusion of laser ablation in 1.7.19 - Due to the current very low penetration of laser ablation in the UK, widespread adoption of the technology would lead to a significant change in current practice. This change would require large investments in capital equipment, software and training that are not included in the current cost-effectiveness analysis. - In contrast to laser, RF PP technology is widely available in UK, with clinicians trained	Thank you for your comment. Following stakeholder consultation some omissions were identified, new data provided, and issues raised that led to amendments to the economic model. These included: -Edits to some of the equipment costs further to stakeholder comments -30% uplift for laser equipment costs from local source used as the base case rather than sensitivity analysis - Reduction in cardiac tamponade risk for cryoballoon (from 1% to 0.4%) -Addition of persistent Phrenic Nerve Palsy risk for laser (1% as with cryoballoon) -Sensitivity analysis on procedural costs for catheter ablation where 'elective' case HRG cost used for RFPP, 'day case' cost used for

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				to use it to ablate other arrythmias in addition to atrial fibrillation. In addition, Johnson & Johnson offer an extensive medical education program to ensure safe and effective use of our RF ablation technology for clinicians with varying skills and experience. Also of note, RF PP ablation has become increasingly simpler to perform with the availability of newer technologies, such as the VISITAG SURPOINT module, due to a reduction in learning curve to effectively use the technology. The use of 'consider' in 1.7.19 The use of 'consider' rather than 'offer' RF PP ablation could impact patient access to ablation as it could discourage primary care physicians from referring patients to specialists. This may result in increased use of anti-arrhythmic drugs for longer durations of time despite the availability of RF PP ablation that may reduce symptom burden and improve quality of life. Information cited in the recent NHS England consultation of catheter ablation highlights that there is huge variation in ablation access across England and these recommendations could exacerbate inequality of access in these areas. Please see comment 11 in the document above for further rationale on changing 'consider'.	cryoballoon and 'total HRG' used for all other catheter ablation. -Threshold analysis to see what reduction in procedure cost is needed for cryoballoon to become most cost effective. This saving was then compared narratively to savings associated with not having general anaesthesia, savings in staff costs from shorter procedure duration and savings from same day discharge. The latter two sensitivity analyses were considered extreme scenarios as the committee noted that laser and RFPP may also be associated with some of these savings and they are not exclusive to cryoballoon ablation. Overall, the results indicate RFPP is the most cost effective option. The sensitivity analyses around costs do not change the conclusions, although the probability of RFPP being most cost effective does reduce. The threshold analysis for cryoballoon indicates a reduction of £2,913 is required. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge, this equated to £1,289 in savings which is not enough for cryoballoon to become more cost effective than RFPP. A 'consider' recommendation was chosen due to the uncertainty regarding the cross over rate from AAD to ablation, to which the model was sensitive to. Furthermore, the volume and quality of the clinical evidence upon which the model was based was not deemed high enough to make an 'offer' recommendation. The committee made a further 'consider' recommendation for either cryoballoon or laser ablation for people who are unsuitable for RFPP.

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					The committee considered these people to include those for whom a short procedure time or reduced risk of fluid overload from saline irrigated RF catheters was preferred, for example those with a recent history of decompensated heart failure.
Kent Surrey Sussex Academic Health Science Network	Evidence Review G1	070	011	The committee refers to the possible misleading claim that the dose of Apixaban was 5mg twice daily but fails to refer to the very small percentage of people in the study on the 2.5mg twice daily dose. This should have been an important part of the decision process as many patients on apixaban are over 80 years of age and either are under 60Kg or have a creatinine over 133mmol/L and therefore would be prescribed 2.5mg twice daily. The trial population do not therefore reflect the real-world use of the drug.	Thank you for your comment. The NMA separated out the different doses of the DOACs as separate comparators. In the health economic model, although apixaban and dabigatran may be given in lower doses to the elderly, it was assumed that all patients would receive the higher dose, and remain on it, even as they age. However, results were robust to a sensitivity analysis assuming only the lower doses of apixaban (2.5mg bd) and dabigatran (110mg bd) were administered.
Kent Surrey Sussex Academic Health Science Network	Evidence Review G1	071	001	The decision to recommend apixaban or dabigatran appears to be based on a meta-analysis by Lopez-Lopez. The trials used in this analysis had significantly different stroke risk and bleeding risk. The drugs preferred in this guideline have a lower stroke risk, whereas the trials involving edoxaban and rivaroxaban had higher stroke risk and more closely reflect real life experience of primary care who will initiate these drugs.	Thank you for your comment. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Recommendation 1.6.3 and 1.6.4 now recommend any licensed DOAC.
Kent Surrey Sussex Academic Health Science Network	Evidence Review G1	071	039	The importance of once a day drug versus twice daily was dismissed by the committee but the evidence to support this dismissal appears inadequate. Many GPs have used Rivaroxaban and when patients are asked reasons for choosing a specific DOAC using the NICE patient decision support tool, they will say the once a day regime is more convenient. It is seems	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence to the NICE guidelines on medicine adherence, medicines optimisation and

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				inappropriate fir NICE, having designed a patient decision support tool, to now deny patient choice that is implicit in that tool. NICE should provide further evidence to dismiss frequency of dosing when patients consider it is so important. Not only is patient choice important in a decision about drug initiation but also because of the risks of inappropriate dosing for multiple daily dose drugs.	patient experience in adult NHS services which would include taking into account personal preferences such as dose frequency.
Kent Surrey Sussex Academic Health Science Network	Guideline	009	011	Earlier in the guideline on page 9, NICE state that all four direct oral anticoagulants are recommended as options within their marketing authorisation but then contradicts this by advising clinicians to offer apixaban or dabigatran. There have been no head to head trials between the four drugs and therefore we believe that there is inadequate evidence to recommend apixaban and dabigatran over edoxaban or rivaroxaban. Dabigatran cannot be used in standard medicines compliance aids because the capsules are sensitive to moisture. Because Dabigatran is contraindicated in patients with a creatinine clearance less than 30mL/min if effectively means that patients and clinicians have no choice for first line therapy and can only be offered edoxaban or rivaroxaban if they cannot tolerate apixaban. In a class of four drugs, licensed and recommended by NICE, it is wholly inappropriate for NICE to then reduce their first line options to one drug.	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs (1.6.3 and 1.6.4). When deciding on what DOACs to offer, the formulation on the medication should be taken into account in the context of shared decision making.
Kettering General Hospital NHS Foundation Trust	Guideline	004	006 - 010	*manual pulse palpation ... Breathlessness, palpitations, syncope or dizziness, chest discomfort, stroke or transient ischaemic attack*	Thank you for your comment. Opportunistic screening is outside of the remit of NICE.

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				Also screen with manual pulse palpation if ≥ 65years (especially male) with hypertension, diabetes mellitus, heart failure, coronary artery disease, chronic kidney disease obesity, and obstructive sleep apnoea Cadby G et al Chest 2015;148:945_952. Boriani G, et al Europace 2015;17:1169_1196. Lip G, et al Europace 2017;19:891_911 Hobbelt, et al Europace 2017;19:226_232. 25. Aune D, et al J Diabetes Complications 2018;32:501_511. Nalliah CJ, et al. Curr Cardiol Rep 2018;20:137.	
Kettering General Hospital NHS Foundation Trust	Guideline	004	011 - 013	*Perform 12-lead ECG if irregular pulse detected* or a screening tool with single-lead ECG tracing ≥ 30 s showing heart rhythm (usually repeated recordings). Steinberg JS, et al Circ Arrhythm Electrophysiol 2018;11:e006274 Svennberg E, et al Circulation 2015;131:2176_2184. Halcox JPJ, et al Circulation 2017;136:1784_1794. EHJ (2020) 00, 1_125 doi:10.1093/eurheartj/ehaa612	Thank you for your comment. The evidence showed that single lead would miss up to 10% of people with AF detected on 12 lead.
King's College Hospital NHS Foundation Trust –	General	General	General	We thank NICE for the opportunity to comment on the draft guidance for AF.	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be

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Thrombosis Centre				Our team represents a clinical academic group at King's College Hospital, comprising of doctors, nurses and pharmacists that provide anticoagulation care for a sizable population of South East London. We have a specialist interest and expertise in the field of anticoagulation and provide national leadership in this discipline. The focus of our feedback on the draft NICE AF guidance is on the choice of oral anticoagulants in AF and the following recommendations: 1.6.3 Offer anticoagulation with either apixaban or dabigatran to people with atrial fibrillation and a CHA2DS2-VASc score of 2 or above, taking into account the risk of bleeding. [2020] 1.6.4 Consider anticoagulation with either apixaban or dabigatran for men with atrial fibrillation and a CHA2DS2-VASc score of 1, taking into account the risk of bleeding. [2020] 1.6.5 If apixaban and dabigatran are not tolerated in people with atrial fibrillation, offer anticoagulation with either edoxaban or rivaroxaban. [2020] We are concerned with dabigatran being suggested as a first line option, for the following reasons: ***Indirect evidence comparisons*** The comprehensive review of evidence undertaken by NICE is interesting. However, we are concerned that this recommendation is made, anchored on *indirect* evidence.	confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs (1.6.3 and 1.6.4). The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence in the NICE guidelines on medicine adherence, medicines optimisation and patient experience in adult NHS services which would include taking into account personal preferences such as dose frequency as well as factors such as swallowing difficulties, naso-gastric tubes and dosette boxes. The DOACs should be prescribed in accordance with the guidance provided in the BNF (see recommendation 1.6.2).

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<tr><td></td><td></td><td></td><td></td><td>The populations studied in the landmark studies on which the draft guidance analysis is based on, were not the same, as illustrated in the following table:

<table>
<tr><th colspan="2"></th><th>ARISTOTLE</th></tr>
<tr><td colspan="2">TTR (INR 2.0-3.0)</td><td>66% (median)
62.2% (mean)</td></tr>
<tr><td colspan="2">Mean $CHADS_2$ Score</td><td>2.1</td></tr>
<tr><td>C</td><td>CHF</td><td>36%</td></tr>
<tr><td>H</td><td>HTN</td><td>87%</td></tr>
<tr><td>A</td><td>Age ≥ 75</td><td>31%</td></tr>
<tr><td>D</td><td>Diabetes</td><td>25%</td></tr>
<tr><td>S_2</td><td>Prior stroke or TIA</td><td>19%</td></tr>
<tr><td colspan="2">Patients with HASBLED score ≥ 3</td><td>23%</td></tr>
</table>

Important clinical differences between the populations studied will have impacted on the outcomes from these trials. The baseline stroke risk of patients in the ENGAGE AF and ROCKET AF studies were much higher than in ARISTOTLE and RE-LY. Furthermore, the proportion of patients in the trials had differing levels of bleeding risk, again will have impacted on the clinical outcomes.

In our view, however sophisticated the statistical analysis, the only way of truly knowing if one DOAC is superior to another, is through a head to head study. As the overall benefits suggested by the NICE analysis are very small through indirect evidence, we do not feel it is appropriate to recommend dabigatran a first line agent in the UK.</td><td>Monitoring was outside of the scope of this guideline.

We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.</td></tr>
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				Indeed the authors of the comprehensive network meta-analysis by Lopez and colleagues[1], which NICE have leaned on in their analysis, states ***that a trial directly comparing DOACs would overcome the need for indirect comparisons to be made through network meta-analysis*** – suggesting that the authors themselves of this comprehensive review are wary of such analysis and the conclusions that can be drawn from them. ***Medication adherence*** The guidance has not considered medication adherence in the decision. It is well documented that medication adherence with chronic medications can be sub-optimal.[2] Patients prescribed anticoagulants are not exempt from this and research has been conducted looking at this specific issue with different DOACs. The findings from this work suggest that although this can be a problem for all DOACs, compared to direct Xa inhibitors, dabigatran adherence in the *real-world* is worse. Several studies have shown that adherence to all DOACs wanes significantly over time.[3-8] In a study from the US, Brown and colleagues found that over the 9-month study period looking at proportion of days covered (PDC) of those newly initiated on anticoagulation, only 45% of AF patients were adherent with a PDC >80%. Patients prescribed either apixaban or rivaroxaban had a mean PDC of 82% and 83% respectively at 3-months. Dabigatran adherence was found to be worse with mean PDC of 76% falling to 57% at 3 and 9-months respectively.[3] Borne and colleagues also report a similar finding, in that dabigatran adherence is significantly worse than rivaroxaban and apixaban.[8] Furthermore, amongst AF patients in Zhou and colleagues' database analysis, a similar picture is reported. On average patients took	

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				only 69% of dabigatran doses over the first 9-months of treatment, failing to take 65% of doses at 12-months. Here 49% of patients were non-adherent at 12-months with 49% of patients having treatment gaps totalling more than 60-days over that period.[9] Although the clinical trial data for dabigatran might provide a marginal benefit in a clinical trial setting, real-world data demonstrates that there is a high non-adherence and discontinuation rates with dabigatran, which could be avoided, in part, by having an alternative DOAC suggested as a first line. In RE-LY, 348 pts (5.8%) in the warfarin group and in 707 patients (11.8%) and 688 patients (11.3%) in the 110-mg and 150-mg dabigatran groups respectively experienced dyspepsia, and then approximately 2.2 and 2.1% stop therapy as a result of GI symptoms compared with 0.6% warfarin. Our experience suggests that when a patient has a *bad* experience or perceives a *bad* experience with an anticoagulant, the chances of them taking an alternative agent is significantly reduced. Therefore, getting it right from the start is much better for long term persistence. In addition, there is some debate that adherence to the once daily regimens of rivaroxaban and edoxaban will be superior to the twice daily regimens of apixaban and dabigatran. Alberts and colleagues have tested this hypothesis by comparing adherence to rivaroxaban with adherence to either apixaban or dabigatran according to prescription claims (edoxaban was not licensed at that time). Overall, on average 30% of DOAC patients were non-adherent to treatment. More patients were adherent to the once daily rivaroxaban versus the twice daily apixaban or dabigatran.[10] A comparative database analysis from the US comparing rivaroxaban adherence with dabigatran adherence (i.e. once versus twice daily) revealed that in that cohort of patients the mean PDC	

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				with rivaroxaban was superior to that of dabigatran at 3, 6, 12 and 24-months. [11] As a team, we are not convinced that there is sufficient research published which clearly demonstrates that once daily DOAC is better than twice a day. However, during our consultations, if it's clear that a patient takes all their other chronic medications once a day (e.g. ramipril and bisoprolol), then our practice would be to prioritise a once daily DOAC in such a patient to make the routine of medication taking easier; where there is clear evidence that routine behaviour does lead to better adherence and persistence rates long-term. ***Current UK prescribing practice*** Data from UK prescribing practice suggests that the direct Xa inhibitors are overwhelmingly prescribed across the UK.[12] This is based on clinicians themselves judging the evidence and their clinical experience in *real-world* practice. Any clinical benefits dabigatran provides over rivaroxaban and edoxaban are small, in our group's view. The experience of using DOACs in the UK has gradually increased, along with how to deal with any problems that might arise. We are concerned that by suggesting the dabigatran as a first line agent, where little clinical experience exists in the UK, will be confusing for many clinicians. Our experience suggests that having apixaban along with a once daily DOAC would be a safer recommendation and be in line with UK clinical practice. Familiarity in our opinion, is important, particularly from a patient safety point of view with anticoagulants. ***Swallowing difficulties, naso-gastric tubes, dossette boxes*** Our centre houses 2 hyper acute stroke units. Strokes patients can have swallowing difficulties post stroke, which can persist for a significant period of time and	

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				require their tablets to be crushed before they can be swallowed or flushed down a NG tube. With apixaban, edoxaban and rivaroxaban, this is possible. However, with dabigatran the capsules cannot be opened and swallowed or flushed down an NG tube. The dabigatran capsules also cannot be taken out of their original blister pack and placed in a dossette box, which for many older adults is a mechanism they use to manage their medications on a daily basis. Given dabigatran's inferiority in this sizable population setting, it being recommended as first line agent does not seem appropriate. ***Practicalities for primary care*** There is a growing number of patients in primary care who require carers attending to their needs, including medication needs. If all their medications can be taken as once daily preparations, then to send stretched services into a patient's home to administer a second tablet / capsule is not cost-effective or practical. It would therefore be sensible for NICE to have a once daily DOAC recommended as a first line agent, in addition to apixaban. ***Obesity*** In clinic, we are increasingly being charged with looking after over-weight and obese patients. Dabigatran has renal clearance reported ~80%. It is well documented that the absolute clearance of drugs increases with weight, when drugs are highly renally cleared.[13] The number of patients who were obese in RE-LY were not significant, so how the efficacy data translates to this growing sub-population is questionable. Data in this sub-population has emerged over the last few years, with direct Xa inhibitors, particularly with	

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				rivaroxaban.[14-19] The published research suggests that rivaroxaban does not lose efficacy in this sub-group and our own pharmacokinetic work provides the basis for why that might be the case.[20] Anecdotally, our experience with apixaban and edoxaban is also good in this population, although we prioritise rivaroxaban in this setting. The likely reasons for this are due to the different clearance mechanisms that direct Xa inhibitors undergo. Therefore, having an alternative agent in place of dabigatran as first line would remove any issues from this perspective. ***Renal function and Acute Kidney Injury*** A significant advantage that direct Xa inhibitors hold over dabigatran is the extent of renal clearance they undergo; significantly less in comparison to dabigatran. In the AF setting, where older adults are typically being prescribed these agents, this becomes an important issue. Our group believes, that a key reason why many UK clinicians have not been prescribing dabigatran is due to its significant renal clearance. Dabigatran is contra-indicated in patients with a CrCl <30 mL/min. The 3 direct Xa inhibitors can be safely used in patients down to a CrCl of 15 mL/min. This in our view is a significant benefit with this class of medicines and provides a *safety-net,* should the patient experience acute kidney injury (AKI), which can commonly occur in the very old. Exposing patients unnecessarily to dabigatran does not seem sensible, in our view. ***Monitoring dabigatran and the very old*** A paper published by the BMJ in 2014 has investigated the role of plasma concentration monitoring with dabigatran and how internal documents from the manufacturers of dabigatran suggested that there is a role to monitor the plasma concentration of dabigatran, where in some patient	

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				groups a 5 fold difference in plasma concentrations were observed. These internal documents also defined the optimal range for dabigatran, but this monitoring aspect was down-played by the manufacturers, as the practical aspects of DOACs would be lost.[21] It should not be ignored that in those over 80 years old, even the 110 mg had a unfavourable trend compared to warfarin (major bleeding 80 years: hazard ratio 1.12 (95% confidence interval 0.84, 1.49). Indeed, the negative experience of dabigatran in the frail, elderly population is eloquently illustrated by Harper and colleagues and their early experience with dabigatran in New Zealand.[22] The DOACs are making anticoagulants available to patients that historically we would not have anticoagulated with warfarin. This is particularly true for patients who are in the frail / elderly category, who are also vulnerable to the adverse effects of DOACs. The draft NICE guidance has not taken this into account, particularly with respect to dabigatran, in our opinion. Our centre has a lot of experience with DOACs and with their plasma concentration monitoring, where the assays are available in our laboratory. This is not the case, for many UK centres, making the safe use of dabigatran very difficult. Based on these reasons, our team challenge NICE's recommendation of dabigatran as a first line recommendation in this draft AF guidance and urge a reconsideration of this. Apixaban, along with edoxaban or rivaroxaban would be a safer recommendation. Dabigatran is best reserved as a second line option. **References**	

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Lancashire and South Cumbria NHS Foundation Trust	Guideline	009	006	Only recommending NOACs as effectively first line choices for anticoagulation removes the option of warfarin, which is a cheaper option, is easily and cheaply reversible in cases where INR is too high and already part of the established management of atrial fibrillation. TTR values may vary across regions however this should not preclude having warfarin as an option as local systems can control INR to within acceptable ranges. A switch to NOACs will place significant pressure on prescribing budgets. Local admitted patient care data shows that costs are around twice as much for NOACs compared to warfarin. A&E costs are also approximately double for NOACs suggesting more likely admission to hospital. Outpatient costs also appear to be higher for NOACs. European Medicines Agency and local data both show that NOACs may frequently be prescribed outside of licence, at incorrect dose or with interacting medicines. They appear to be frequently prescribed without regular monitoring of renal function.	Thank you for your comment. The results of the health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. Recommendation 1.6.5 recommends a vitamin K antagonist if DOACs are contraindicated, not tolerated or not suitable. In recommendation 1.6.6 we refer to taking into account time in therapeutic range when discussing switching from a vitamin k antagonist to a DOAC. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2).
Lancashire and South	Guideline	009	011	Apixaban and dabigatran are prioritised among the four available DOACs. This does not take into account	Thank you for your comment.

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Cumbria NHS Foundation Trust				regional procurement discounts that may influence the placing of either edoxaban or dabigatran as first line choices. Locally edoxaban is first line NOAC choice and this choice is listed in our atrial fibrillation guideline and has been incorporated into the primary care EMIS template.	Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available.
Liverpool Health Partners	Evidence review E and F	008	014	There are errors in Table 2: ▪ $HEMORR_2HAGES$ requires genetic testing to calculate so the 'None' in the 'Additional tests required to complete risk tool' is incorrect. ▪ 'H' in HAS-BLED is uncontrolled hypertension NOT hypertension per se ▪ Definitions of the 'D' criteria need to be corrected as 'alcohol use' is incorrect and 'medication usage predisposing to bleeding' is incorrect. It should just state 'alcohol excess/abuse' and 'concomitant antiplatelets or NSAIDs, respectively.	Thank you for your comment. This has been amended in Table 2 evidence review E and F.
Liverpool Health Partners	Evidence review E and F	082	037	"*Meanwhile, the NRI evidence was fairly equivocal, suggesting similarities between ORBIT and HAS-BLED, and the committee felt that it did not negate the calibration evidence that ORBIT was the most appropriate tool*" The reason for these tools is to highlight patients at high-risk of bleeding and to identify modifiable risk factors that may be addressed. The ORBIT score includes mostly risk factors that are non-modifiable.	Thank you for your comment. The committee agreed that the first priority of a tool is to make an accurate prediction. Our committee agreed that ORBIT was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk. These absolute risks can be used to accurately inform the discussions between

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				Furthermore, if as stated above, there is no clinical evidence of superiority of one bleeding risk tool over the other, surely the more practical tool for healthcare professionals should be recommended.	clinician and patient about risk-factor modification. The question is whether this advantage is sufficient to warrant the apparent disadvantages of ORBIT incorporating less modifiable risk factors. Whilst it is true that ORBIT does not involve measurement of some of the important modifiable risk factors, such as labile INR, such modifiable risk factors can be measured in other ways, and may already be available on the patient's data. Furthermore, whether ORBIT or HAS-BLED are used does not actually change the amount of modifiable risk factor investigations that need to be carried out by the investigating clinician. For example, measurement of haemoglobin, labile INR, blood pressure, liver function tests and renal function tests will need to be carried out in both cases to evaluate whether current bleeding, increased blood pressure or treatable liver or renal disorders are present, each of which can be treated if needed to reduce bleeding risk. The only difference is that the results of labile INR, blood pressure, liver function tests and renal function tests will feed into informing the HAS-BLED score whereas haemoglobin and renal function results (GFR) will feed into the ORBIT score. This does not make ORBIT any more costly in terms of clinician time and resources, as other variables in ORBIT do not require invasive investigations. In addition, the notion that if the modifiable risk factors are not part of the tool then clinicians will not be prompted to discuss their modification is not a real disadvantage. This is because checking the modifiable risk factors of bleeding forms part of

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					routine assessment for any clinician dealing with AF patients. We would therefore argue that the real benefits of the greater absolute risk prediction accuracy from ORBIT outweigh the disadvantages of ORBIT not incorporating some of the modifiable risk factors, because the advantages are very real but the disadvantages are surmountable.
Liverpool Health Partners	Evidence review E and F	General	General	Comparing components of ORBIT *vs.* HAS-BLED The ORBIT bleeding risk score[3] is comprised of age over 74 years (1 point), anaemia (2 points), bleeding history (2 points), eGFR <60mL/min/1.73m^2 (1 point), and concurrent antiplatelet use (1 point). The points for each component is not immediately obvious and perhaps this score should be called OR$_2$B$_2$IT. Most notably, the ORBIT score has little consideration for reversible bleeding risk factors unlike the HAS-BLED score. Most of the components within he ORBIT score are already within the HAS-BLED score which is simple and may be used for NOAC/warfarin. In the latter, the HAS-BLED score also includes labile INR to draw focus on this as an important determinant of bleeding.	Thank you for your comment. The first priority of a tool is to make an accurate prediction. Our committee agreed that ORBIT was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk. These absolute risks can be used to accurately inform the discussions between clinician and patient about risk-factor modification. The question is whether this advantage is sufficient to warrant the apparent disadvantages of ORBIT incorporating less modifiable risk factors. Whilst it is true that ORBIT does not involve measurement of some of the important modifiable risk factors, such as labile INR, such modifiable risk factors can be measured in other ways, and may already be available on the patient's data. Furthermore, whether ORBIT or HAS-BLED are used does not actually change the amount of modifiable risk factor investigations that need to be carried out by the investigating clinician. For example, measurement of haemoglobin, labile INR, blood pressure, liver function tests and renal function tests will need to be carried out in both cases to

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					evaluate whether current bleeding, increased blood pressure or treatable liver or renal disorders are present, each of which can be treated if needed to reduce bleeding risk. The only difference is that the results of labile INR, blood pressure, liver function tests and renal function tests will feed into informing the HAS-BLED score whereas haemoglobin and renal function results (GFR) will feed into the ORBIT score. This does not make ORBIT any more costly in terms of clinician time and resources, as other variables in ORBIT do not require invasive investigations. In addition, the notion that if the modifiable risk factors are not part of the tool then clinicians will not be prompted to discuss their modification is not a real disadvantage. This is because checking the modifiable risk factors of bleeding forms part of routine assessment for any clinician dealing with AF patients . We would therefore argue that the real benefits of the greater absolute risk prediction accuracy from ORBIT outweigh the disadvantages of ORBIT not incorporating some of the modifiable risk factors, because the advantages are very real but the disadvantages are surmountable.
Liverpool Health Partners	Evidence review E and F	General	General	This fails to consider that bleeding risk is dynamic[1]. In terms of calibration, this is of more relevance when determining prognosis. The point is that the focus on calibration is appreciable since they highlight that absolute risk of events when using a prediction model is of highest clinical interest. "*The committee reiterated the importance of using a bleeding risk tool to inform plans to reduce reversible*	Thank you for the important point that bleeding risk is dynamic (meaning that the bleeding risk assessed at baseline is not necessarily the same bleeding risk that exists years later at the point where the bleeding event occurs) and the difficulties in capturing this with risk tools. This limitation applies to all tools and to both calibration and discrimination. This is probably captured in the tendency of tools to underestimate risk (at time of bleeding the risk

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				causes of bleeding and to maintain appropriate levels of vigilance, rather than as a threshold based tool to determine if anticoagulation should take place". From this statement, it can be inferred that it is most important to have accurate risk prediction rather than good discrimination tools. However, the draft NICE guidelines do not recommend to actually use the accurate risk predictions to make any clinical decisions based on these risk predictions. Moreover, it references many modifiable risk factors (e.g., uncontrolled BP) that are not actually in the ORBIT score, though they do appear in the HAS-BLED score. For discrimination, this is frequently of interest when looking for accurate diagnostic testing, i.e., does a patient have the disease at X level of predicted risk / above prespecified cut-points on a score.Good discrimination gives the opportunity to identify certain characteristics of the model parameters (i.e. risk factors) that can accurately discriminate. Indeed, it is acknowledged that bleeding risk tools should be used to identify and treat modifiable risk factors. Therefore, the performance of a prediction model cannot be measured solely on either calibration or discrimination.	was probably much higher than when risk was measured 3 years previously). The decisions were made on a combination of calibration and discrimination. However, calibration was given priority because of the importance of accurate prediction of absolute risk in the context of using the tools as an aid to the discussion between patient and clinician about the need for risk-modification, rather than as a decision tool about risk modification. In other words, it is envisaged that all patients will be encouraged to risk modify, but that an accurate risk prediction will be helpful in encouraging compliance, particularly in people at higher risk. We have clarified this point in the discussion. Addressing the point that we should have used a different tool that contains more information on risk factors to modify, it should be remembered that the first priority of a tool is to make an accurate prediction. Our committee agreed that ORBIT was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk. The question is whether this advantage is sufficient to warrant the apparent disadvantages of ORBIT incorporating less modifiable risk factors. Whilst it is true that ORBIT does not involve measurement of some of the important modifiable risk factors, such as labile INR, such modifiable risk factors can be measured in other ways, and may already be available on the patient's data. Furthermore, whether ORBIT or HAS-BLED are used does not actually change the amount of modifiable risk

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					factor investigations that need to be carried out by the investigating clinician. For example, measurement of haemoglobin, labile INR, blood pressure, liver function tests and renal function tests will need to be carried out in both cases to evaluate whether current bleeding, increased blood pressure or treatable liver or renal disorders are present, each of which can be treated if needed to reduce bleeding risk. The only difference is that the results of labile INR, blood pressure, liver function tests and renal function tests will feed into informing the HAS-BLED score whereas haemoglobin and renal function results (GFR) will feed into the ORBIT score. This does not make ORBIT any more costly in terms of clinician time and resources, as other variables in ORBIT do not require invasive investigations. In addition, the notion that if the modifiable risk factors are not part of the tool then clinicians will not be prompted to discuss their modification is not a real disadvantage. This is because checking the modifiable risk factors of bleeding forms part of routine assessment for any clinician dealing with AF patients . We would therefore argue that the real benefits of the greater absolute risk prediction accuracy from ORBIT outweigh the disadvantages of ORBIT not incorporating some of the modifiable risk factors, because the advantages are very real but the disadvantages are surmountable.
Liverpool Health Partners	Evidence review E and F	General	General	The HAS-BLED score has been validated in wide variety of clinical scenarios and may be used to predict bleeding risk in AF whilst on OAC (both VKA and non-VKA anticoagulants), aspirin, or without any	Thank you for your comment. Our systematic review looked at the validation of all tools (by being measured up against the gold standard of later bleeding), and ORBIT was found to have

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				antithrombotic therapy[4, 5]. In fact, theHAS-BLED is also the only score shown to be predictive of intracranial haemorrhage (ICH), the most serious form of bleeding[6]. Furthermore, the HAS-BLED score has also been validated in non-AF populations, including those with venous thrombo-embolism,acute coronary syndrome, or percutaneous coronary interventions,or those undergoing bridging therapy, as well as in venous thromboembolism (VTE)[4, 7, 8]. It is important to standardise risk tools if possible for practical reasons.	the best picture of overall predictive capacity in major bleeding, clinically relevant bleeding and ICH in the relevant population of people with AF on anticoagulants. In the context of this guideline, the validity of the tool in other populations is less important than the validity of the tool to the AF population. To use a tool because it can be used for a variety of conditions at the same time may reduce resource use, but it will not improve clinical outcomes if it is not the optimally accurate tool for all conditions.
Liverpool Health Partners	Evidence review E and F	General	General	In the 2020 NICE VTE guidelines (https://www.nice.org.uk/guidance/ng158), the HAS-BLED score is recommended. In this setting, the ORBIT score has not been studied. Introducing various bleeding risk scores for various conditions seems impractical when this can be done using a single tool (HAS-BLED score).	Thank you for the point that recommended bleeding risk evaluation for other conditions, such as VTE, does not use ORBIT. This means that if ORBIT is used for AF, another tool (such as HAS-BLED) has to be used for other conditions. The committee highlighted that the first priority of a tool is to make an accurate prediction. Our committee agreed that ORBIT was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk for AF. The question is whether this advantage is sufficient to warrant the apparent disadvantages of ORBIT not being able to be used for other conditions. We would argue that if other tools need to be used for other conditions this does not really constitute a major hurdle for clinicians, particularly after an initial transition period when new practices are being learned. The use of these tools is not difficult, and access to the online versions is very simple. Thus, needing to use an extra tool does not constitute a difficult problem for clinicians. Therefore, we would argue that the real benefits of the greater

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					absolute risk prediction accuracy from ORBIT outweigh the disadvantages of not being able to use the same tool across different conditions. The resource and impact section has been updated to note that: Another challenge in implementing ORBIT is that HAS-BLED has been recommended as a bleeding tool for people with VTE. Overall, however, the committee considered that these implementation challenges were worth overcoming for the greater accuracy and usefulness gained from using the ORBIT score in people with atrial fibrillation.
Liverpool Health Partners	Evidence review E and F	General	General	Evidence for ORBIT vs. HASBLED We would like to highlight that the implication that there are no relevant clinical studies comparing bleeding risk tools with HAS-BLED is simply NOT true. In a study of nationwide Danish registries[9], the HAS-BLED, ATRIA, and ORBIT bleeding scores were compared in AF patients on NOACs. At 1-year, the c-indexes were approximately 0.59, with only minor differences between scores. Furthermore, the HAS-BLED score had higher sensitivity (62.8%) compared with ATRIA (29.7%) and ORBIT (37.1%). HAS-BLED classified the least number of patients at low risk and achieved the highest benefit if applying a major bleeding intervention threshold of approximately 2%, whereas benefit from using either ATRIA score or ORBIT score was only evident using higher intervention thresholds. Guo et al[10] compared bleeding risk prediction that focused on modifiable bleeding risk factors (as recommended in the 2016 European guidelines, i.e. 'European score') versus other published bleeding risk scores that have been derived and validated in AF	Thank you for your comment. When stating the lack of comparative studies in section 1.5 the committee were specifically referring to the lack of any randomised trials comparing outcomes of the use of different tools. In part E the developer initially looked for randomised prediction tool studies [where people are randomised to one tool or another and the groups are prospectively compared for patient-centred health-related outcomes such as quality of life] as they are considered the best evidence for the efficacy and cost effectiveness of prediction tools, though none were found. These are not studies primarily designed to evaluate accuracy directly, which were looked at in evidence review F. In our prediction section F the review included many studies (including Lip 2018 and Guo 2018, which you have mentioned) where the different tools were compared for prediction accuracy. Chao, 2018 was considered but excluded because it had a non-anticoagulated cohort (see exclusion list).

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				subjects (HEMORR $_2$HAGES, HAS-BLED, ATRIA, and ORBIT) in a large hospital-based AF cohort. The HAS-BLED score was superior to predict bleeding events compared with the European score, with the differences between c-indexes of 0.10-0.12 (Delong test, all P < .05), NRI values of 13.0%-34.5% (all P < .05), and IDI values of 0.7%- 1.4% (all P < .05). The European score had similar predictive ability to other bleeding risk schemes (HEMORR$_2$HAGES, ATRIA, and ORBIT) for major bleeding and ICH, as reflected by non-significant differences in c-indexes, NRI, and IDI (all P > .05). Decision curve analysis showed that HAS- BLED had better net benefit of predicting major bleeding compared with the European score. Other comparisons of HAS-BLED vs ORBIT that have been published, also appears to be ignored by the NICE GDG. Chao et al[11]compared a risk assessment strategy for major bleeding and intracranial haemorrhage (ICH) based on modifiable bleeding risk factors against established bleeding risk stratification scores (HEMORR$_2$HAGES, HAS-BLED, ATRIA, ORBIT). All contemporary bleeding risk scores had modest predictive value for predicting major bleeding but the best predictive value and NRI was found for the HAS-BLED score.	The committee did consider the head to head discrimination evidence that you cited during committee discussion, but felt that the head to head calibration data was the most important to consider, because it gave the best indication of which tool had the best absolute risk accuracy. These calibration data suggested that ORBIT was a better tool in terms of predicting absolute risk. Importantly, this held at all risk levels, including the higher risk levels where it is particularly important to be aware of the risks.
Liverpool Health Partners	Evidence review E and F	General	General	In a systematic review and meta-analysis[12] of 7 studies comparing the ORBIT and HAS-BLED scores in anticoagulated AF patients, the pooled C- statistic of continuous variables for major bleeding was 0.65 (0.60,0.69) for ORBIT and 0.63 (0.60,0.66) for HAS-BLED. Compared with HAS-BLED, more anticoagulated AF patients (88.5% vs 32.6%) and major bleeding events (75.6% vs 25.6%) were categorized as low risk using ORBIT. The ORBIT score had a 1.21,	Thank you for your comments. The 7 studies you cite were all considered amongst the other papers we cited. 5 of these were included but the studies by Caro and Abumaileq were letters, which we do not include because letters are unlikely to be subject to stringent peer-review (they are not in our excluded list because they would have been excluded on the initial sift i.e. on the basis of the abstract. Our systematic

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				1.73 and 1.44-fold elevated risk of major bleeding in the low, intermediate and high risk strata, respectively. Calibration analysis demonstrated that the ORBIT score under-predicted major bleeding in the low, intermediate, and high risk stratifications, where an odds ratio of 0.64 (0.37-1.10), 0.63 (0.38-1.05) and 0.64 (0.38-1.06), respectively. Overall, the evidence does not appear to suggest that the ORBIT score performs better than the HAS-BLED score in predicting major bleeding events among AF patients who are anticoagulated. In fact, an independent Patient-Centered Outcomes Research Institute (PCORI) systematic review and evidence appraisal concluded that the HAS-BLED score had the best evidence for predicting bleeding risk (moderate strength of evidence)[13, 14]. This review only compared the HAS-BLED score, HEMORR2HAGES score, ATRIA score, Bleeding Risk Index (BRI) and ABC bleeding risk score, although they state they were aware of other tools, such as ORBIT score, but their scope was focused on the scores used most frequently in clinical settings and prioritised through the stakeholder panel and topic refinement process with PCORI. This highlights again the lack of use of the ORBIT score. Additionally, the PCORI review concluded that *"Clinical risk scores must take into account the balance between simplicity and practicality versus accurate prediction, especially in a high-capacity clinical environment. While clinical risk scores are necessarily reductionist and cannot feasibly consider all patient parameters, our results here show moderate predictive ability of risk scores that can be calculated relatively easily from patient history and demographics."*	review has included all other relevant studies in this area as well. Therefore, in spite of the conclusions in the cited sources, the results of our evidence review of more extensive data showed that ORBIT is the most accurate predictor of absolute bleeding risk. The primary task of a bleeding risk score is to make an accurate prediction of bleeding risk, to facilitate patient and clinician discussion of modification of risk factors. In this respect we believe our data supports the use of ORBIT. ORBIT may be less commonly used at present, but this is a function of its recent introduction. It is true that ORBIT does not involve measurement of some of the important modifiable risk factors, such as labile INR, but such modifiable risk factors can be measured in other ways, and may already be available on the patient's data.

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Liverpool Health Partners	Evidence review E and F	General	General	It should be noted that other international guidelines that have evaluated the latest evidence recommend the use of the HAS-BLED score, for example the 2018 CHEST expert panel guidelines from the American College of Chest Physicians[15], which was based on systematic review and GRADE methodology and the recent 2020 European Society of Cardiology (ESC) AF guidelines on AF management[16]. A European Heart Rhythm Association survey found that HAS-BLED was the most commonly used bleeding score (>75%) amongst European cardiology centres[17]. It general, it is important that new published guidelines are in harmony with one another unless there is new evidence or incorrect recommendations. Having a drastically different set of recommendations as presented in the draft version of this document only serves to cause confusion and uncertainty which can have a negative impact to patient care.	Thank you for your comments. The systematic review has included all relevant studies in this area. Therefore, in spite of the conclusions in the cited sources, the results of the evidence review on more extensive data showed that ORBIT is the most accurate predictor of absolute bleeding risk, based on our more extensive data.
Liverpool Health Partners	Evidence review E and F	General	General	The ORBIT score is subject to several methodological limitations[3]. Firstly, it was derived from an observational registry (ORBIT-AF) and validated using the ROCKET-AF trial[18]. The ROCKET-AF trial comprised of a highly selected patient cohort that only included high risk patients with AF (i.e. $CHADS_2$score of ≥2, with those with $CHADS_2$ score 2 being capped at 10%) and excluded patients with significant renal impairment (creatinine clearance <30 mL/min). Furthermore, patients in the warfarin arm had poor anticoagulation control with a TTR of 55%. In the study by O'Brien et al[3], patients supposedly categorised as low-risk using the ORBIT score are still subject to a risk of 2.4 bleeds per 100 patient-years, whilst a 'medium risk' patient has a bleeding risk of 4.7 per 100 patient-years.In contrast, patients with a low-	Thank you for your comment. The derivation methodology of a tool is not crucial if it is still able, despite this setback, to achieve better predictive capacity than other tools. The committee agreed that the calibration data demonstrated that ORBIT was best placed to predict absolute bleeding risk in relevant patient populations. Thank you for the important point that bleeding risk is dynamic (meaning that the bleeding risk assessed at baseline is not necessarily the same bleeding risk that exists years later at the point where the bleeding event occurs) and the difficulties in capturing this with risk tools. This limitation applies to all tools and to both calibration and discrimination.

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				risk of bleeding by HAS-BLED have indeed a low bleeding rate of ~1 per 100 patient-years. Overall, an overemphasis on statistical significance with c-statistics and recalibration ignores the fact that bleeding risk assessment is not a static phenomenon and many risk factors that increase the risk of bleeding are potential modifiable. Furthermore, it neglects consideration of the clinical utility of these tools. A useful prediction model may inform public health (e.g. screening) or patient care (prognosis or decision support). Discrimination may have higher research interests relative to calibration, but it really comes down to how a score is applied. Calibration is very important if a score is used to inform patients or if used in making clinical decisions; however, this is apparently not the case, since in the assessment of ORBIT vs HAS-BLED, the GDG mentions that it should NOT be used for decision making.	
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Liverpool Health Partners	Guideline	005	008	The stroke risk in AF is not dependent on the success of cardioversion. Furthermore, if this statement is kept, it should also comment on catheter ablation.	Thank you for your comment. The committee agree that stroke risk is not dependent on the success of cardioversion and that the recommendation reflects this point. We now mention catheter ablation in the recommendation (1.2.1).
Liverpool Health Partners	Guideline	005	013	We are concerned that the drastic change to the ORBIT score is not supported by sufficient evidence. Moreover, this is a tool that many clinicians will be unfamiliar with. Therefore, we strongly urge the GDG to continue recommending the HAS-BLED score which has been proven to provide a good balance of accuracy and practicality.	Thank you for your comment. All of the evidence that met the review protocol criteria was included in the review (see Appendix A in evidence review E and F). Calibration evidence was given priority because of the importance of accurate prediction of absolute risk in the context of using the tools as an aid to the discussion between patient and clinician about the need for risk-modification, rather than as a decision tool about risk modification. In other words, it is envisaged that all patients will be encouraged to risk modify, but that an accurate risk prediction will be helpful in encouraging compliance, particularly in people at higher risk. This has been clarified in the committee's discussion of the evidence in evidence review E and F. Based on the calibration evidence, our committee agreed that ORBIT was the best-calibrated tool, and

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					therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk. The committee were confident that the benefits of ORBIT will outweigh any disadvantages from the need for some degree of initial adaptation on the part of new users.
Liverpool Health Partners	Guideline	005	015	Bleeding risk assessment should be undertaken not only when taking oral anticoagulant (OAC), but also when first diagnosed (i.e. on no antithrombotic therapy), on aspirin (perhaps when the AF patient with vascular disease is first diagnosed) and while on OAC. Thus, the bleeding risk assessment tool needs to be applicable at all steps of the patient pathway. The ORBIT score has not been validated in non-OAC treated patients, whereas HAS-BLED has been validated in non-OAC (nothing, aspirin) and OAC (warfarin, NOAC)	Thank you for your comment. This recommendation has been made with specific reference to people with AF who are taking, or about to take, anticoagulants. Since bleeding risk is of principal interest for those on anticoagulants the committee agreed that it was appropriate that ORBIT has been validated only in OAC cohorts.
Liverpool Health Partners	Guideline	006	001-010	In the management of AF, there is a need to address modifiable bleeding risk factors. However, the ORBIT score ignores bleeding risks such as uncontrolled hypertension and prior stroke. Indeed, an AF patient with a previous haemorrhagic stroke would score zero points on the ORBIT score (so considered 'low risk') when indeed it should be evident that these patients are at a high-risk of further bleeding. In contrast, this same patient would score a minimum of 2 points on the HAS-BLED score. Arguably, the use of NOACs are increasing but we still need a well validated bleeding risk tool that is applicable to any type of anticoagulation.	Thank you for your comment. The evidence shows that overall ORBIT is more accurate at prediction of absolute risk of bleeding than other tools. We did not design the review to cover different patient groups (apart from those categorised by type of OAC use and antiplatelet/aspirin/NSAID use) and so cannot make separate recommendations for different groups (defined by characteristics other than the medication criteria described). Although there may be some patient groups that might be more suited to other tools, the recommendations are relevant to the majority of patients where ORBIT will be most accurate. ORBIT was validated in both VKAs and NOACs.

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Liverpool Health Partners	Guideline	006	003	There should be clarification provided on what poor INR control means, ideally TTR <70%. Otherwise this is left to the interpretation of the reader and there will be differences in practice.	Thank you for your comment. This is covered by the recommendations in section 6 on assessing anticoagulation control with vitamin K antagonists.
Liverpool Heart and Chest Hospital NHS Foundation Trust	Evidence Review J1	070	Table 28	The cost effectiveness of ablation for AF is highly sensitive to the up-front costs of the ablation procedure. This is comprised of the HRG for ablation plus the tariff-excluded device costs. The committee have considered NHS supply chain catalogue for pass through (equipment) costs for point-by-point RF and cryoballoon ablation. We consider this reasonable and equitable. However, to then use a single centre's costs from a single user for the Laser balloon (especially when this technology is not widely used or quoted on NHS supply chain) and use these costs for the cost-effectiveness analysis is fundamentally flawed. All hospitals in the UK performing AF ablation do so at high volumes as guided by the Clinical Reference Group (CRG) guidelines initially published in 2009. Hospitals can therefore individually negotiate pricing reductions on tariff excluded devices, and these savings can be passed through to NHS England for the total price of ablation. LHCH is a major centre performing a high volume of point by point RF and cryoballoon ablations for AF and we have negotiated bulk buy discounts with suppliers. We are able to disclose (confidentially) our costs for tariff excluded devices. We have included the standard HRG for ablation (codes EY30A & EY30B - £4118) within these costs. These are compared to the values from Table 28 (P70) below.	Thank you for your comment. Although there may be local negotiations for the equipment, as part of the NICE methods manual, we include nationally available costs where available, and in the case of devices these are the costs listed in the NHS supply chain catalogue. For laser ablation the equipment is not listed in the NHS supply chain catalogue which is why we used a local cost. Given the likelihood of local negotiations, the committee have agreed to increase the local costs by 30% in the basecase analysis rather than only in a sensitivity analysis, to ensure a fair assessment of different ablation techniques. Please note as well as the above edit, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.

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				Technology **NHS Supply Chain Cost** **LHCH cost** RF PP (point by point) £9,286 £6,740 (inc Agilis sheath and Lasso) RF ME (multielectrode) ablation £9,991 n/a Cryoballoon ablation £10,951 £6,368 Laser ablation £8,510 It can clearly be seen that the costs of HCTED available to major centres is considerably cheaper than that quoted on NHS supply chain. It would be inequitable to use single centre costs for the Laser balloon in a cost-effectiveness analysis and not consider that this single centre (negotiated) price is not genuinely comparable to those for other ablation technologies.	
Liverpool Heart and Chest Hospital NHS Foundation Trust	Evidence Review J1	075	045-051	The cost efficacy analysis of ablation is a concern to us. Within this analysis the clinical effectiveness of ablation technologies is considered to approximately equivalent. This can be accepted for point by point RF and for cryoballoon, but there is a lack of comparative evidence for the laser balloon in the literature. It should also be evident to the committee that laser balloon ablation is not the technique of choice for most operators in the UK (or elsewhere in Europe of North America). .	Thank you for your comment. There was evidence comparing laser ablation to radiofrequency point by point included in the NMA conducted for the clinical review (Dukkipati, 2015). Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The

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					recommendations 1.7.19 and 1.7.20 have been changed to reflect this.
Liverpool Heart and Chest Hospital NHS Foundation Trust	Guideline	005	013	A new recommendation is the use of the ORBIT score to replace the HASBLED score. We urge the GDG to very seriously reconsider this recommendation, and to retain the use of the HASBLED score. The ORBIT has essentially the same variables as HAS-BLED with some glaring *omissions* such as labile INR, alcohol and liver disease. Otherwise the ORBIT score components are already within the HASBLED score. The latter also offers simplicity, and can be used in patients on DOAC as well as warfarin where the L criteria ('labile INR') draws attention to the quality of anticoagulation control, which is a powerful determinant of bleeding risk if time in therapeutic range is low.	Thank you for your comment. The committee agreed that ORBIT was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk. Whilst it is true that ORBIT does not involve measurement of some of the important modifiable risk factors, such as labile INR, such modifiable risk factors can be measured in other ways, and may already be available on the patient's data. Furthermore, whether ORBIT or HAS-BLED are used does not actually change the amount of modifiable risk factor investigations that need to be carried out by the investigating clinician. For example, measurement of haemoglobin, labile INR, blood pressure, liver function tests and renal function tests will need to be carried out in both cases to evaluate whether current bleeding, increased blood pressure or treatable liver or renal disorders are present, each of which can be treated if needed to reduce bleeding risk. The only difference is that the results of labile INR, blood pressure, liver function tests and renal function tests will feed into informing the HAS-BLED score whereas haemoglobin and renal function results (GFR) will feed into the ORBIT score. This does not make ORBIT any more costly in terms of clinician time and resources, as other variables in ORBIT do not require invasive investigations. In addition, the notion that if the modifiable risk factors are not part of the tool then clinicians will not be prompted to discuss their modification is not a real

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					disadvantage. This is because enquiring about modifiable risk factors of bleeding forms part of routine clinical assessment. We would therefore argue that the real benefits of the greater absolute risk prediction accuracy from ORBIT outweigh the disadvantages of ORBIT not incorporating some of the modifiable risk factors, because the advantages are very real but the disadvantages are surmountable.
Medtronic	Evidence Review J1	077	050-053	It is noted in the draft guidance that the recommendations for left atrial ablation are likely to reinforce current practice, which is relatively restricted – approximately 1% to 2% of all people with atrial fibrillation currently have ablation. We believe this is inappropriate considering the proven benefits of this therapy. We believe the draft clinical guideline does not fully represent the health outcomes benefits of ablation which would be evident from a meta-analysis that combines the similar ablation modalities in comparison to drug therapy – to quantify the "class effect" benefits in terms of mortality, stroke, quality of life, and so on. It appears that the Committee considered the benefits of ablation per se already to be well established, however, we do not accept this view given that only 1-2% of all people with atrial fibrillation (AF) currently receive ablation. We respectfully ask the Committee to consider how to rectify this, in order to communicate a comprehensive evidence-based summary of the benefits of ablation to general cardiologists and general practitioners, who currently may not be referring enough patients for this specialist treatment. In respect to this, we recall that multiple stakeholders requested guidance on ablation per se during Scoping. We note the following specific mentions on this topic	Thank you for your comment. The draft question in the scope was What is the clinical and cost effectiveness of different ablative and non-ablative therapies in people with atrial fibrillation? And this was revised by the committee to 'Clinical and cost effectiveness of different ablative therapies in people with atrial fibrillation'. This question was included in the scope in response to new evidence identified by the surveillance review which was to compare the different ablation techniques https://www.nice.org.uk/guidance/cg180/resources/surveillance-report-2017-atrial-fibrillation-management-2014-nice-guideline-cg180-pdf-5958229444837. We have given a detailed explanation of the rationale for our approach in section 1.7.3 of the ablation review document. The committee agreed that the best way to frame the question would be to compare ablation treatments separately against each other and also medical treatment. This would allow important differences between ablation treatments to be discerned, and, crucially, would allow a health economic evaluation of the most cost-effective ablation treatment. In addition, it allows the

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				from the consultation comments and responses document • BHRS requested "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.". In this case, the response from NICE was "*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*." • The Association of British HealthTech Industries commented: "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." The response from NICE was: "*Thank you for your comment. We have now amended the two questions of rate and*	separate ablation treatments to be compared to medical care, thus providing the most comprehensive data possible from a review. Comparing pooled methods of ablation to medical care would be unable to discern the most cost-effective ablation treatment. The committee agreed that the data shows clearly that ablation is clinically and economically superior to medical treatment if medical treatment is unsuccessful, unsuitable, or not tolerated Although CABANA was not included in the review when the health economic model was done, a number of sensitivity analyses were undertaken to explore whether or not our model reflected the EQ5D data from CABANA. These analyses indicated that we may have underestimated the benefit of ablation, but our results are within the confidence intervals reported by CABANA and when the utility decrement for AF symptoms is increased, the model conclusions are unchanged.

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				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).” • An identical comment was submitted by Johnson & Johnson Medical Ltd., with an identical response from NICE. Unfortunately, a single, narrower research question was specified by the Committee, which was “What is the clinical and cost effectiveness of different ablative and non-ablative therapies in people with atrial fibrillation?”. It was not clear at the outset of the guideline development that this would lead to the exclusion from the systematic review and meta-analysis of randomized trials of ablation versus drugs which permitted investigators to choose their own preferred ablation technology in the intervention arm. Furthermore, it was not clear that a meta-analysis would not be performed to examine the “class effect” of similar ablation technologies versus drugs. As a consequence, important studies have been excluded from the review (CABANA, Packer et al. (2019) and Mark et al. (2019); CAPTAF, Blomstrom-Lundqvist C et al. (2019); CASTLE AF, Marrouche et al. (2018)), and an overall estimate of the treatment effects of ablation has not been made. This is not without consequence: in the Evidence Review 11 ablation cost-effectiveness	

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				analysis report, it was noted (page 84) that "There was uncertainty regarding the following areas: (1) impact of ablation on stroke and mortality in the short term as denoted by the wide credible intervals from the network meta-analysis (NMA) data". The uncertainty presumably was increased more than necessary because the NMA had only compared each of the ablative therapies to each other, and never made an estimate of the "class effect". The Committee had a documented discussion showing they were aware of some of the limitations of this approach, which was prompted specifically by the exclusion of the CABANA study from the network meta-analysis (Evidence Review Report 9 Ablation, pages 81-83). Overall, the committee felt that the case for not having the additional question [What is the clinical and cost effectiveness of catheter ablation versus medical care?] was stronger than the case for including it. We respectfully disagree, because although the NMA established that medical care is inferior to ablation technologies in terms of preventing AF recurrence, the economic analyses for catheter ablation technologies assumed **zero improvement** for other important endpoints when the technologies were considered only individually versus drugs: • The risk ratios for mortality from the NMA shows that **mortality risk was the same for catheter ablation techniques as antiarrhythmic drugs (AAD)**, except for Thoracoscopy and Hybrid ablation (Evidence Review 11 Ablation Cost Effectiveness, Table 8 on page 25). It is reported that "*Upon discussion of the results of the NMA, the committee expressed concern with the uncertainty demonstrated by the credible*	

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				intervals which were all crossing 1 when comparing the different techniques to AADs." • it was assumed that the **stroke risk was the same for all catheter ablation techniques as AADs**, with the exception of RF ME where it was assumed to be double that of AADs. • To recap, the reason for raising the above concerns is that it may be as a result of this approach that the draft clinical guideline has opted for the weaker recommendation to "Consider" rather than "Offer" ablation. Furthermore, the draft guideline does not communicate strongly about the health benefits of ablation, which is important to communicate to the wide clinical community and payers this guideline will reach. If the "class effect" of ablation (versus drugs) would include a mortality benefit, for instance, that is important to communicate. **References** • Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kenneback G et al. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. JAMA. 2019; 321(11):1059-1068 . • Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L et al. Catheter ablation for atrial fibrillation with	

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				heart failure. New England Journal of Medicine. 2018; 378(5):417-427 . • Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH et al. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA. 2019; 321(13):1275-1285. • Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: The CABANA randomized clinical trial. JAMA. 2019; 321(13):1261-1274.	
Medtronic	Evidence Review J3	036	005	We believe there is an omission regarding capital equipment costs in the economic model, for instance the costs for a radiofrequency (RF) generator or Cryo console. While these represent 'sunk costs' by and large because centres who perform AF ablation already have invested in the necessary capital equipment, the limited install base of the laser balloon system means there would be significant budget implications for wider spread adoption of this technology.	Thank you for your comment. Capital equipment was not included in the costing as the committee stated that in most cases this is provided free of charge by manufacturers as part of a contractual agreement in exchange for the purchase of a minimum volume of equipment. Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.

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Medtronic (contains conf comments)	Evidence Review J1	080	022-026	We would courteously ask that NICE consider the key clinical and operational benefits the Arctic Front Cardiac Cryoablation Catheter Family (Arctic Front Advance™ and Arctic Front Advance Pro™), generally referred to as cryoballoon ablation regarding its cost and resource efficiencies in clinical practice compared to other ablation modalities. **Sedation use savings** Conscious or moderate sedation used during cryoablation procedures have been demonstrated to result in shorter procedure times, similar safety and efficacy of the cryoablation, and similar patient satisfaction as cryoablation performed under general anaesthesia (GA) (Miśkowiec et al., 2018; Wasserlauf et al., 2016; Wasserlauf et al., 2020). Besides, the use of conscious sedation results in direct savings to the health system by avoiding an anaesthetist and an Operating Department Practitioner (ODP) intervention, without impacting patient reported outcomes (Wasserlauf et al., 2020). With the average procedure time for a catheter ablation (range of 96 - 236 minutes, according to the studies included in Kukendrajah et al., [2020] meta-analysis that compared different ablation types), the use of GA would cost the NHS an additional £174 to £429 for a consultant anaesthetist and £56 to £138 for an ODP to support a catheter ablation procedure (NHS PSSRU 2018/19 for a consultant physician and for a Hospital-based scientific and professional staff/Band 5). With cryoballoon ablation not requiring GA, this would not only provide additional savings to the NHS but would also free up the anaesthetist and ODP time to support other elective or non-elective procedures.	Thank you for your comment. Following stakeholder consultation some omissions were identified, new data provided, and issues raised that led to amends to economic model. These included: -Edits to some of the equipment costs further to stakeholder comments -30% uplift for laser equipment costs from local source used as the base case rather than sensitivity analysis - Reduction in cardiac tamponade risk for cryoballoon (from 1% to 0.4%) -Addition of persistent Phrenic Nerve Palsy risk for laser (1% as with cryoballoon) - Sensitivity analysis on procedural costs for catheter ablation where 'elective' case HRG cost used for RFPP, 'day case' cost used for cryoballoon and 'total HRG' used for all other catheter ablation. -Threshold analysis to see what reduction in procedure cost is needed for cryoballoon to become most cost effective. This saving was then compared narratively to savings associated with not having general anaesthesia, savings in staff costs from shorter procedure duration and savings from same day discharge. The latter two sensitivity analyses were considered extreme scenarios as the committee noted that laser and RFPP may also be associated with some of these savings and they are not exclusive to cryoballoon ablation. Overall, the results indicate RFPP is the most cost effective option. The sensitivity analyses around costs do not change the conclusions,

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				Same-day discharge Alongside direct savings and more flexibility in staff management, a reduction in general anaesthesia supports a faster patient recovery and enables facilitation of a same-day discharge (SDD) approach to patients undergoing catheter ablation for their atrial fibrillation (AF). Analysis with NHS Digital Hospital Episode Statistics (HES) included all the spells with patients undergoing percutaneous transluminal ablation of pulmonary vein to left atrium conducting system (OPCS Code: K621, "Ablation") between March 2019 and February 2020, with information of the energy source for cryoballoon ablation (OPCS Code: Y112) or radiofrequency (RF) point-by-point ablation (OPCS Code: Y114). The results showed that 53% of spells with patients undergoing an ablation were discharged the same day with cryoballoon ablation (N=1,320/2,495), whereas only 18% were discharged on the same day with RF point-by-point (N=540/3,015). This analysis highlights the positive impact cryoballoon ablation can provide to facilitate SDD, helping to free up beds for other procedures. The safety, efficacy, and economic value attributed to SDD have been evaluated in different cohort analyses in the UK: • Opel et al., (2018) compared the safety and efficacy of cryoballoon ablation procedures performed as a day case at a non-cardiac centre (Whipps Cross Hospital) to that of a regional cardiac centre (St Bartholomew's Hospital) where AF ablation patients were kept overnight post-procedure. Overall, 276	although the probability of RFPP being most cost effective does reduce. The threshold analysis for cryoballoon indicates a reduction of £2,913 is required. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge, this equated to £1,289 in savings which is not enough to for cryoballoon to become more cost effective than RFPP. A 'consider' recommendation was chosen due to the uncertainty regarding the cross over rate from AAD to ablation, to which the model was sensitive to. Furthermore, the volume and quality of the clinical evidence upon which the model was based was not deemed high enough to make an 'offer' recommendation. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP. The committee considered these people to include those for whom a short procedure time or reduced risk of fluid overload from saline irrigated RF catheters was preferred, for example those with a recent history of decompensated heart failure. Please see the edits in the model write up and ablation chapter for full details.

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				patients were recruited from the local hospital, and were matched to those attending for cryoablation at the regional cardiac centre for this analysis. The results demonstrated that when performed by appropriately trained clinicians, cryoballoon ablation can be performed as a day case procedure safely, effectively, and efficiently: ○ Procedure time was one third shorter at the local centre compared to the regional centre (63.5 ±1.1 min vs. 101.7 ±2.9 min, p<0.0001) and fluoroscopy time was halved (5.5±0.2 min vs. 12.6±0.6 min, p<0.0001); ○ The overall complication rate was low for the local centre day case service (5.4% vs. 6.3% in the regional centre, p = not significant); ○ 91% of patients from the local centre were in sinus rhythm at 3 months post-procedure vs. 80% of patients from the regional cardiac centre. • Arujuna et al., (2018) assessed the safety and associated costs of day case procedures in paroxysmal and persistent AF patients, at Royal Wolverhampton NHS Trust where 161 consecutive cryoballoon ablations were performed, including 40-day case and 121 overnight. Procedure time was significantly shorter for day cases compared	

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				to cryoablations with overnight (152±37 vs. 181±47 min respectively, p=0.001). A low overall complication rate was observed for day case procedures (1.8%), with no readmissions in the day case group and 2 in the overnight group. Moreover, £12,000 savings were estimated at 4.5 years with day case. • Reddy et al., (2020) assessed a day case service for AF catheter ablation at the Royal Papworth Hospital, Cambridge. The authors demonstrated an overall low complication rate at 6 months follow up (3.3%) with no significant difference between the day case group (n = 168) and overnight group (n = 284). Day case procedures were significantly shorter (mean 139.6 vs. 160.7 min), less likely to require general anaesthesia (29.2% use vs. 60.1%) and led to £67,200 savings over the 13 month period (an overnight stay in a ward bed was estimated between £140 and over £700, and thus at £400 in average). • Bartoletti, et al. (2019) assessed a day case service for AF catheter ablation at the Liverpool Heart and Chest Hospital. The retrospective analysis included 642 ablations with overnight and 143 day cases and concluded there was no difference in peri-procedural complications between day cases and overnight cases (1/143, 0.7% vs. 10/642, 1.6%; p=0.430). Procedure duration was significantly shorter for day cases compared	

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				to ablations with overnight (120±29 vs. 153±43 min respectively, p<0.001). • In a retrospective analysis of AF ablation cases performed at Barts Heart Centre and Whipps Cross university Hospital, Creta, et al. (2020) reported that 79.2% of AF ablation day cases were performed with cryoballoon. The overall complication rate was 3.1% and was significantly lower in the day case cohort compared to overnight cohort, as acute complications commonly precluded same-day discharge (1.6% vs. 3.8%; p=0.005). In total, 13 (1.8%) day case patients were readmitted within the 48-hours following discharge for non-life-threatening complications. After accounting for the cost savings associated with same-day discharge (overnight cost estimated at £400) and the costs of accident and emergency department attendance (£106), the annual net savings of same-day discharge to the hospital was £83,927. • He, et al. (2020) retrospectively studied all consecutive complex elective left-atrial ablation procedures performed at University Hospital Coventry, Rugby St-Cross Hospital and Worcester Royal Hospital. Left-atrial ablation procedures included ablations of AF, left atrial tachycardia and combined AF and other procedures. Overall, 967 patients with complex ablation were assessed, including 347 patients with a cryoballoon ablation for which over 90% had the procedure as a day case (n=313 same day, n=35 overnight) and	

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				489 with a RF ablation and 3D mapping for which less than 18% had the procedure as a day case (n=88 same day, n=401 overnight). None of the patients discharged on the same day (n=88 with RF/3D mapping, n=313 with cryoballoon and n=13 with cryo and 3D mapping) developed complications within 24 hours that would otherwise have been detected by overnight stay. The authors estimated that an overnight-stay, excluding any other procedures, costs £350 and that a same-day ablation policy over this period would have saved £310,450. Additionally, the authors highlighted that many centres admitting patients overnight, have inherent cost-implications and are associated with significant risk given the COVID-19 pandemic (Bonalumi et al., 2020). Authors concluded that same-day left atrial catheter ablation is safe and associated to savings, with significant benefits for patients and healthcare providers, and can help mitigate the risk of COVID-19 transmission. • The AVATAR-AF randomized controlled trial, which was recently conducted in 13 centres in the UK, tested a 'streamlined' AF cryoballoon ablation procedure compared to a conventional cryoablation procedure (Mann I et al, 2019). Streamlined procedures were performed without adjunctive pulmonary vein (PV) mapping to verify PV electrical isolation and with a SDD protocol. When the procedure is done without PV mapping, multiple cost savings include the PV mapping	

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				catheter, electrophysiology (EP) recording equipment, fewer specialist staff, and a day case protocol reduces bed occupancy. The total equipment cost for a cryoballoon procedure [in Table 28 of the Evidence Review J3 – ablation cost effectiveness analysis report] and the total ablation procedure cost [in Table 29 of the Evidence Review J3 - ablation cost effectiveness analysis report] appropriately could be revised in a scenario analysis. The 12-month freedom from hospital-based arrythmia episodes was not different between patients treated with a streamlined cryoablation approach and those that underwent a conventional cryoablation procedures (Late Breaking Clinical Trials session, EHRA 2019). **Procedure efficiency: procedure duration and predictability, EP lab efficiency** There is an increasing demand for electrophysiology services, which has been further exacerbated as a result of COVID-19. An ageing population with numerous comorbidities (sleep apnoea, heart failure) and patients acquiring commercially available smart watches with the ability to detect AF are contributing to the increasing levels of concerned patients focused on AF examinations. Studies and meta analyses have shown cryoballoon ablation to be a shorter and more efficient procedure, with a predictable procedure time compared with other modalities of ablation (e.g. radiofrequency point-by-point catheter	

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				ablation). Efficient procedures have a lower procedure associated cost and allow operators to perform more procedures within an electrophysiology (EP) lab day with less associated overtime (Monnickendam 2018 and Kowalski 2016), along with the studies in the NHS setting illustrated above. • A systematic review and meta-analysis (Ravi et al., 2020) to evaluate the efficacy and safety of the second generation of Medtronic cryoballoon (CBA-2G) in comparison to radiofrequency ablation-contact force (RFA-CF) in patients with paroxysmal or persistent AF. The procedure time for cryoballoon was found to be shorter (mean difference: −31.32 min; 95% CI: −40.73 to −21.92; p<0.001) compared with RFA-CF. • A meta-analysis comparing the efficacy, safety, and procedural characteristics of cryoballoon and radio frequency (RF) ablation in women and men undergoing their first PVI procedure found a significantly shorter procedure time for both genders with cryoballoon (22.5 minutes shorter in women and 27.1 minutes shorter in men) (du Fay de Lavallaz et al., 2020). • A randomised controlled trial (RCT) assigned 346 patients with drug-refractory paroxysmal AF to contact force–guided radiofrequency ablation (CF-RF; n=115), 4-minute cryoballoon ablation (Cryo-4; n=115), or 2-minute cryoballoon ablation (Cryo-2; n=116). Follow-up was 12 months. The CF-	

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				RF group had a significantly longer procedure time compared with the cryoballoon group (164.5min for CF-RF, 143.0 min for Cryo-4 and 130.5 for Cryo-2) (Andrade et al., 2019) • Kowalski et al, in preparation. (Data in Confidence) ○ Increased procedural efficiency demonstrated with cryoballoon ablation enables [redacted] AF ablation cases per lab day with minimal overtime days. Additionally, there was time for an additional non-ablation EP procedure [redacted]% of days in which [redacted] cryoballoon ablations were performed. **Learning curve and reproducibility** Cryoablation results in consistent outcomes across centres and is less dependent on volume of procedures as RF ablation, which may provide safe and efficacious treatment to a larger number of patients across centres with variable caseloads. • In a comparison of 860 consecutive patients treated with RF or cryoballoon ablation. Cryoablation outcomes were similar across both low and high AF ablation volume centres. In contrast, outcomes of RF ablation were variable according to centre and had a higher dependency on annual AF ablation case volume (Providencia et al., 2016) • The learning curve associated with cryoablation was reported to be short (~30 cases) in an examination of procedural outcomes of 300 patients in whom	

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				cryoablation was performed by four junior operators and compared with a senior operator. Over a mean follow-up of 11.2 months, the rate of success was not statistically different between the junior operators and experienced operator (Velagic et al., 2017) • Outcomes were evaluated in an examination of 860 patients treated at 30 different centres that were stratified by centre experience. Centre experience did not significantly influence the efficacy outcome in patients treated with cryoablation. These results reinforce the consistency of cryoablation outcomes across centres (Landolina et al., 2018) **References** • Andrade, J., et al. Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring. Circulation. 2019;140(22):1779-1788. • Arujuna, A., Velu, S., Pathiraja, J., Lapper, A., Kidd, G., Forsey, P., Hado, H., Barr, C., Arya, A. and Petkar, S., 2018. 26 Day Case CRYO-Balloon Ablation Procedures: A Single Centre Experience In Trends, Safety And Cost Effective Analysis. • AVATAR AF Late Breaking Clinical Trial (LBCT) at European Heart Rhythm Association (EHRA) 2019 • Bartoletti, S., Mann, M., Gupta, A., Khan, A., Sahni, A., El-Kadri, M., Modi, S., Waktare, J.,	

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				2017. Learning curve using the second-generation cryoballoon ablation. Journal of Cardiovascular Medicine, 18(7), pp.518-527. • Wasserlauf, J., Kaplan, R., Walega, D., Arora, R., Chicos, A., Kim, S., Lin, A., Verma, N., Patil, K., Knight, B. and Passman, R., 2020. Patient-reported outcomes after cryoballoon ablation are equivalent between moderate sedation and general anesthesia. Journal of Cardiovascular Electrophysiology, 31(7), pp.1579-1584. • Wasserlauf J, et al. Moderate Sedation Reduces Lab Time Compared to General Anesthesia during Cryoballoon Abla tion for AF Without Compromising Safety or Long-Term Efficacy. Pacing Clin Electrophysiol. 2016 Dec;39(12):1359-1365.	
Medtronic (contains conf comments)	Evidence Review J3	017	Table 2 – Model Inputs – Serious adverse events first year (decisio n tree)	**Phrenic Nerve Palsy** Within the economic model NICE referenced a persistent phrenic nerve palsy (PNP) rate of 1% for the cryoablation arm. This reference was extracted from the 2016 European Society of Cardiology (ESC) guidelines however the updated 2020 ESC guidelines reference a persistent PNP rate of 0 – 0.04%. Also, Cryo AF registry, providing real world data on cryoablation with Arctic Front Cardiac Cryoablation Catheter Family, assessed a phrenic nerve injury (PNI) rate of [redacted]% at 12 months. In addition, no rate for persistent PNP was attributed to the laser comparator within the model which is not aligned with the current clinical evidence. Tohoku 2020 with a total of 2,433 patients concluded the majority of	Thank you for your comment. We have reviewed the references provided and have edited the risks in the model as follows: Cardiac Tamponade - probability for cryoballoon reduced to 0.4 (this is supported by Du Fay 2020 and Fortuni 2020). Persistent phrenic nerve palsy - we have kept this as 1% for cryoballoon and this same probability was applied to laser ablation. Persistent PNP (ie >48hrs) is at least 1% in both Cryo and Laser. They all eventually recover in Tohoku's paper but can take over a year which is in line with how the cost and disutility of this serious adverse event was modelled in our analysis.

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				PNP in the cryoballoon arm was transient whereas the majority of PNP in the laser balloon arm was persistent. Overall, the rate of persistent PNI did not differ between cryoballoon and laser balloon (1.2% and 1.4%, respectively; p=0.89). We kindly ask the committee to incorporate the cryoballoon PNI rate of [redacted]% from the Cryo AF Registry. **Tamponade/ pericardial effusion:** Within NICEs model a 1% cardiac tamponade rate was used across all ablation types. However, an individual patient data meta-analysis reported for both gender types radiofrequency was associated with a higher rate of pericardial effusions(du Fay de Lavallaz et al., 2020). In addition, a meta-analysis demonstrated that using cryoablation reduced the risk of cardiac tamponade (RR 0.582; p=0.011; NNT 147) and reduced the risk of the combined endpoint of pericardial effusion or cardiac tamponade (RR 0.438; p<0.001; NNT 69) when compared to radiofrequency (RF) (Fortuni et al., 2020). Additionally, the Cryo AF registry, which provides real world data on cryoablation with Arctic Front Cardiac Cryoablation Catheter Family, highlighted the rate of cardiac tamponade or pericardial effusion rate of [redacted]% at 12 months. We respectfully ask the committee to differentiate cardiac tamponade or pericardial effusion rate between cryoballoon and radiofrequency (RF) ablation, and incorporate the cryoballoon ablation rate of [redacted]% from the Cryo AF Registry. **Complications from Real World Data** Leveraging real world data, the Cryo AF registry is the largest global cohort of cryoablated patients	We are unable to use your registry data as this is unpublished. Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.

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				prospectively studied within a single registry. The report on the safety and efficacy of cryoballoon ablation for the treatment of AF demonstrated that the procedure was similarly safe for both paroxysmal and persistent AF patients. Specifically, the rates of PNI at discharge ([redacted]%), cardiac tamponade/pericardial effusion ([redacted]%), and neurological events ([redacted]%) were low (see table below).	

Adverse Events
Total
Supraventricular arrhythmias‡
Atrial fibrillation
Atrial flutter or atrial tachycardia
Groin-site complication*
Phrenic nerve injury
Cardiac tamponade or pericardial effusion
Pulmonary or bronchial complication$
Myocardial infarction or ischemic cardiac event†
Pericarditis
Stroke or TIA**
Postoperative hypotension
Presyncope

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				Cardiac failure		[redacted] ([redacted], [redacted]%)	[redacted] ([redacted], [redacted]%
				Erosive esophagitis		[redacted] ([redacted], [redacted]%)	[redacted] ([redacted], [redacted]%
				Face injury††		[redacted] ([redacted], [redacted]%)	[redacted] ([redacted], [redacted]%
				Fluid overload		[redacted] ([redacted], [redacted]%)	[redacted] ([redacted], [redacted]%
				Headache		[redacted] ([redacted], [redacted]%)	[redacted] ([redacted], [redacted]%
				Sepsis		[redacted] ([redacted], [redacted]%)	[redacted] ([redacted], [redacted]%
				Stress cardiomyopathy		[redacted] ([redacted], [redacted]%)	[redacted] ([redacted], [redacted]%
				Urinary retention		[redacted] ([redacted], [redacted]%)	[redacted] ([redacted], [redacted]%
				#Procedure Analysis Cohort: Total Subjects with an index procedure (N = [redacted] ‡Atrial fibrillation, atrial flutter, atrial tachycardia, nodal arrhythmia, sinus bradycardia, supraventricular tachycardia *Arteriovenous fistula, arteriovenous fistula aneurysm, arteriovenous fistula site hematoma, femoral artery dissection, hematoma, incision site hematoma, puncture site hematoma, vascular access site hemorrhage, vascular pseudoaneurysm, vascular pseudoaneurysm ruptured, vessel puncture site discharge, vessel puncture site hematoma $Hematemesis, hemoptysis, hypercapnia, pneumothorax, pulmonary embolism, pneumonia, pleurisy †Angina pectoris, coronary arteriospasm, myocardial infarction **Cerebral infarction, cerebrovascular accident, ischemic stroke, lacunar stroke ††Due to a post-ablation fall **References:**			

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				course. Journal of Cardiovascular Electrophy siology, 31(8), pp.1932-1941.	
Medtronic (contains conf comments)	Evidence Review J3	036	005	Medtronic would like to thank NICE for the opportunity to comment on the draft clinical guidelines, furthermore Medtronic would like to publicly state we have consistently and will continue to support the approach that NICE in all its forms takes in the evaluation of technologies and its place in ensuring best value for the NHS. However, related to this assessment and the related process, we do feel it necessary to raise some legitimate methodological concerns on what we believe to be a key element to the decision-making. The cost-effectiveness model results are most sensitive to the costs of the different catheter ablation technologies, because the efficacy and safety of the technologies is very similar based on a network meta-analysis of randomized controlled trials carried out. The sourced prices for Medtronic Cryoballoon procedure equipment are incorrect, which impact materially on the model outputs and conclusions. For instance, the Cryoballoon ablation catheter (NPC code FRB14468) has a maximum price available to the NHS via the new NHS Supply Chain of **£3,600**, and not £4,440 that has been currently utilised in the model. The price of £3,600 is available to Trusts for purchase orders with no volume commitment, however, there is an agreed and transparent price/volume grid with the Health Solutions Team (HST) procurement tower so that purchase orders with non-zero volume commitments automatically qualify for lower prices. With the pricing/volume grid, the cryoballoon catheter price would be **£**[redacted] when taking in account a volume price of 50 units. The total	Thank you for your comment. We have verified all NHS supply chain catalogues and these are correct, we were unable to find these costs you quote. Although there may be local negotiations for the equipment, as part of the NICE methods manual, we include nationally and publicly available costs, and in the case of devices (which fall under the category of High Cost tariff excluded devices) these are the costs listed in the NHS supply chain catalogue. For laser ablation the equipment is not listed in the NHS supply chain catalogue, which is why we used a local cost, again this is allowed as part of the NICE methodology. However, given the likelihood of local negotiations, the committee have agreed to increase the local costs by 30% in the basecase analysis rather than only in a sensitivity analysis, to ensure a fair assessment of different ablation techniques. Please note as well as the above edit, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. These were: - Sensitivity analysis on procedural costs for catheter ablation where 'elective' case HRG cost used for RFPP, 'day case' cost used for cryoballoon and 'total HRG' used for all other catheter ablation.

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				equipment cost for a cryoballoon procedure [in Table 28 of the Evidence Review J3 – ablation cost effectiveness analysis report] becomes £[redacted] instead of £6,887, when the nationally agreed price volume grid is used as a source, taking minimum purchase volumes of 50 units. This total equipment cost comprises the following elements: cryoballoon; £[redacted], FlexCath Steerable Sheat £[redacted], Achieve mapping catheter £[redacted],Achieve cable £[redacted] (used in of cases), and the following additional items as costed by NICE: transseptal guidewire £233, Introducer £162 and Needle £132. The British Heart Rhythm Society (BHRS) standards for interventional electrophysiology study and catheter ablation in adults (de Bono, 2020), recommends that all interventional electrophysiologists should perform at least 50 catheter ablation procedures per year. Additionally, centres undertaking complex ablation should perform at least 50 complex ablations per year (which may include ablation of atrial fibrillation using 3D Mapping). As such, the abovementioned prices are significantly in excess of the average price paid by NHS England. The total ablation procedure cost for a cryoballoon procedure [in Table 29 of the Evidence Review J3 - ablation cost effectiveness analysis report] becomes [redacted] instead of £10,951 on this basis. Ablation catheters and associated consumable materials are in the category of High Cost tariff excluded devices (HCTED), for which NHS England is the responsible commissioner. In these circumstances, the new NHS Supply Chain through its management function Supply Chain Coordination limited (SCCL), delegates the procurement of these devices to the Health Solutions Team (HST) procurement tower, which is empowered to procure AF ablation consumables and	-Threshold analysis to see what reduction in procedure cost is needed for Cryoballoon to become most cost effective. This saving was then compared narratively to savings associated with not having general anaesthesia, savings in staff costs from shorter procedure duration and savings from same day discharge. The latter two sensitivity analyses were considered extreme scenarios as the committee noted that laser and RFPP may also be associated with some of these savings and they are not exclusive to cryoballoon ablation. Overall, the results indicate RFPP is the most cost effective option. The sensitivity analyses around costs do not change the conclusions, although the probability of RFPP being most cost effective does reduce. The threshold analysis for cryoballoon indicates a reduction of £2,913 is required. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge, this equated to £1,289 in savings which is not enough for cryoballoon to become more cost effective than RFPP. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP. The committee considered these people to include those for whom a short procedure time or reduced risk of fluid overload from saline

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				equipment on behalf of NHS England for the trusts commissioned to undertake these specialist procedures in NHS England. In this context, NHS England is the direct payer of the technology. Therefore, NHS England directly benefits from the further discounts in the abovementioned price/volume grid for Cryoballoon procedure equipment, which should also be reflected in the economic model under commercial in confidence agreements. These discounts can be shared by the procurement agency responsible or the manufacturer, Medtronic. We believe this provides the required pricing transparency and reflects the fact that the price is consistently available across the NHS. We reaffirm that NHS England in this case would be the sole purchaser. For reference, this approach has also been undertaken in multiple NICE technology appraisals with respect to medical devices. This is in accordance with NICE guidelines process and methods manual (PMG20) *(Chapter 7.6, Page 139) whereby 'Analyses based on price reductions for the NHS will be considered only when the reduced prices are transparent and can be consistently available across the NHS, and when the period for which the specified price is available is guaranteed…..In the absence of a published list price and a price agreed by a national institution (as may be the case for some devices), an alternative price may be considered, provided that it is nationally and publicly available.'* Furthermore, considering the Laser balloon technology, it could be asserted that a single price point for a technology sourced from a single centre should be considered in sensitivity analysis only.	irrigated RF catheters was preferred, for example those with a recent history of decompensated heart failure.

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				We would respectfully ask that NICE consider updating the price in accordance with the volume price of 50 units. In line the BHRS standards for interventional electrophysiology study and catheter ablation in adults (de Bono 2020). The costing of each ablation type depends on prices and on the selection and quantity of equipment typically used for each procedure. It is stated [on page 37 of the Evidence Review 11 ablation cost effectiveness analysis report] that *"The committee, Dr Scott Gall (laser ablation specialist in Blackpool), and Atricure 19 (manufacturer of thoracoscopic equipment) advised on which equipment from the NHS supply chain catalogue was required for each ablation type."* For instance, it was noted [on the same page] that cables for point by point RF ablation can be sterilised and reused and so it was assumed this was done 4 times. For laser ablation the endoscope can be sterilised and reused 50 times. A cryoballoon procedure has several characteristics described further on which can reduce the overall costs of an ablation procedure and enable a more efficient use of hospital facilities for performing AF ablations. We respectfully request the Committee to take into account that evidence is available from multiple studies which demonstrate the characteristics of a cryoballoon procedure, compared to other AF ablation techniques, bring hospital efficiency advantages and cost reductions that have not been taken into account thus far in the cost effectiveness analysis. **References** • de Bono, J., 2020. Standards For Interventional Electrophysiology Study And Catheter	

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				Ablation In Adults. [online] BHRS. Available at: <https://bhrs.com/wp-content/uploads/2020/04/British-Heart-Rhythm-Society-Standards-Ablation-2020-1.pdf> [Accessed 29 October 2020].	
NHS Derby and Derbyshire CCG	Evidence Review G1	General	General	We believe that there is insufficient evidence to rank any particular non-vitamin K oral anticoagulant (NOAC) ahead of the others in terms of clinical effectiveness and, until there are head to head trials, all four NOACs should be considered equal for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). As discussed in the evidence review there are very few head to head trials between NOACs and there is considerable heterogeneity between the 4 landmark studies of each NOAC vs. warfarin. Examples of this include the ages of the patients involved, baseline risk of stroke or systolic embolism, different co-morbidities, mean time in therapeutic range for the warfarin arm, differences in the definitions used for stroke and major bleeding, etc. It seems highly unlikely that any NMA constructed from such different RCTs will be robust as there is clearly an imbalance in the presence of effect modifiers. This is highlighted by the fact that the one head to head trial that does exist (comparing rivaroxaban 15mg daily with dabigtran 150mg BD) concludes that the two had similar effects on stroke and intracranial bleeding, which is clearly at odds with the conclusions of the NMA. This was only a small trial and one could argue that the population isn't particularly relevant to a UK setting but, even so, it raises further doubts about genuine differences between the NOACs.	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals were wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore were no longer confident to recommend a specific DOAC or DOACs (1.6.3 and 1.6.4). The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. The committee discussed the TTR in the included trials (see Evidence Review G1 committee's discussion of the evidence). Trial data stratified by TTR in five studies was discussed. The sub-group analyses in these studies suggested a possible association

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				The other problem with the NMA is that, although it included data from 23 trials, over 75% of the patients included came from the four pivotal NOAC trials and, of the trials including a NOAC arm, 89% of the patients included were from the four pivotal trials. Of the other trials, several were phase two trials which included drug doses that are not currently in use in the UK and INRs outside current guidelines. So this is effectively a NMA of the four main NOAC trials and, as it doesn't appear that any adjustments were made to allow for heterogeneity between the trials, any uncertainties in the original trials will apply equally to the NMA. As well as the differences between the four trials, two of the trials (ARISTOTLE and RE-LY) appear to have flaws in them. In RE-LY the warfarin treatment arm was open label and, perhaps unsurprisingly, this trial reported a higher rate of major bleeding in the warfarin arm than the other trials. It is quite likely that physicians familiar with warfarin would treat bleeds differently in the warfarin patients than they would in the patients randomized to dabigatran, effectively skewing the results in favour of the NOAC. In ARISTOTLE the committee were aware of irregularities in data collection but decided that the effects of this were insignificant. A paper in JAMA from 2015 claims that if patients from the site accused of these irregularities were withdrawn from the study data then the claim of a statistically significant mortality benefit disappears – it is hard to see how such a claim could be dismissed as insignificant.	between lower mean centre TTR and increased relative efficacy of DOACS relative to warfarin in some of the outcomes, which would fit with the premise that lower TTR would impair warfarin performance. The committee noted that although the subgroup analyses may indicate a lower efficacy of DOACs with higher TTRs, they were very concerned that the use of subgroups to fit with a mean UK TTR would inevitably result in underrepresentation of patients with poor INR control typically seen in UK clinical practice. Hence, the committee view was that use of whole trial data by Lopez & Lopez was appropriate to produce an evidence based guideline relevant to the NHS. **Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.**

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				Finally, the evidence discussion in the draft guideline completely contradicts the discussions from the NICE technology appraisals for the NOACs. NICE TA355 for edoxaban was the most recently reviewed (in September 2018) and this review concluded that there was no new evidence to change the original recommendations and that the TA should be moved to the static guidance list. As the Lopez-Lopez NMA was published in the BMJ in November 2017 it would seem that this paper was available at the time of the review. The original TA for edoxaban concluded that there was 'insufficient evidence to distinguish between the clinical and cost effectiveness of edoxaban and the newer oral anticoagulants recommended in previous appraisals (apixaban, dabigatran etexilate and rivaroxaban)'. Given all these concerns it seems inappropriate to rank one NOAC over another and it would be more appropriate to rank all NOACs equally.	
NHS Derby and Derbyshire CCG	Evidence review G2	General	General	We believe that the lack of head to head trials between the NOACs makes it impossible to say with any certainty which one is most clinically effective. Given that the current list prices of the drugs are very similar it is therefore impossible to say which drug is the most cost-effective for stroke prevention in patients with NVAF. There are a number of flaws in the Lopez-Lopez NMA: As discussed in the evidence review there are very few head to head trials between NOACs and there is considerable heterogeneity between the 4 landmark studies of each NOAC vs. warfarin. Examples of this include the ages of the patients involved, baseline risk of stroke or systolic embolism, different co-morbidities, mean time in therapeutic range for the warfarin arm,	Thank you for your comments. On further discussion the committee agreed that the NMA by Lopez Lopez was probably not able to adequately adjust for the differences between treatment comparisons in terms of population characteristics that could affect outcome. Initially we had felt that the meta-regressions used were adequate, but after consideration of the numbers of studies involved it does seem unlikely that the meta-regression would have been able to make realistic adjustments to effect that were sufficient to negate inter-comparison differences in prognostic characteristics. We have therefore amended the guideline to not recommend any of the 4 DOACs over any other(1.6.3 and 1.6.4).

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				differences in the definitions used for stroke and major bleeding, etc. It seems highly unlikely that any NMA constructed from such different RCTs will be robust as there is clearly an imbalance in the presence of effect modifiers. This is highlighted by the fact that the one head to head trial that does exist (comparing rivaroxaban 15mg daily with dabigtran 150mg BD) concludes that the two had similar effects on stroke and intracranial bleeding, which is clearly at odds with the conclusions of the NMA. This was only a small trial and one could argue that the population isn't particularly relevant to a UK setting but, even so, it raises further doubts about genuine differences between the NOACs. The other problem with the NMA is that, although it included data from 23 trials, over 75% of the patients included came from the four pivotal NOAC trials and, of the trials including a NOAC arm, 89% of the patients included were from the four pivotal trials. Of the other trials, several were phase two trials which included drug doses that are not currently in use in the UK and INRs outside current guidelines. So this is effectively a NMA of the four main NOAC trials and, as it doesn't appear that any adjustments were made to allow for heterogeneity between the trials, any uncertainties in the original trials will apply equally to the NMA. As well as the differences between the four trials, two of the trials (ARISTOTLE and RE-LY) appear to have flaws in them. In RE-LY the warfarin treatment arm was open label and, perhaps unsurprisingly, this trial reported a higher rate of major bleeding in the warfarin arm than the other trials. It is quite likely that	

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				physicians familiar with warfarin would treat bleeds differently in the warfarin patients than they would in the patients randomized to dabigatran, effectively skewing the results in favour of the NOAC. In ARISTOTLE the committee were aware of irregularities in data collection but decided that the effects of this were insignificant. A paper in JAMA from 2015 claims that if patients from the site accused of these irregularities were withdrawn from the study data then the claim of a statistically significant mortality benefit disappears – it is hard to see how such a claim could be dismissed as insignificant. Finally, the evidence discussion in the draft guideline completely contradicts the discussions from the NICE technology appraisals for the NOACs. NICE TA355 for edoxaban was the most recently reviewed (in September 2018) and this review concluded that there was no new evidence to change the original recommendations and that the TA should be moved to the static guidance list. As the Lopez-Lopez NMA was published in the BMJ in November 2017 it would seem that this paper was available at the time of the review. The original TA for edoxaban concluded that there was 'insufficient evidence to distinguish between the clinical and cost effectiveness of edoxaban and the newer oral anticoagulants recommended in previous appraisals (apixaban, dabigatran etexilate and rivaroxaban)'. Given the flaws in the NMA and the fact that the pivotal NOAC trials cannot be compared with each other it is inappropriate to use them to undertake a health economics analysis as the clinical effectiveness and safety data are uncertain.	

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				The NICE TA355 review states that there is an ongoing head-to-head NOAC trial (DANNOAC-AF) which is due to complete in September 2021. It would seem prudent to await the results of this trial which will provide direct evidence of the clinical effectiveness and safety of each NOAC compared with the others.	
NHS Derby and Derbyshire CCG	Guideline	005	013	ORBIT is not included in the GP system clinical tools so using it to determine bleeding risk will mean that the clinician has to leave the system and use a web-based version such as MD-Calc. This creates extra work for the clinician and may result in transcription errors as data will need to be manually transferred between the different sites. This may result in clinicians continuing to use HAS-BLED which is available on the GP systems and extracts data from the patient's record automatically. In order to improve uptake of this piece of guidance, NICE should work with the main GP system suppliers to ensure that ORBIT is added to the system clinical tools as soon as possible.	Thank you for your comment and suggestions. Your comments will be considered by NICE where relevant support activity is being planned. We have amended the recommendation to acknowledge that, although ORBIT is the best tool to use to assess the risk of bleeding, other bleeding risk tools may need to be used until ORBIT is embedded in clinical pathways and electronic systems.
NHS Southend CCG	Evidence Review G1	006	008	Whilst we recognise the hierarchy of evidence prioritises RCTs, we are interested to understand whether the guideline committee considered any "real world" evidence on the use of DOACs, accumulated since the last guideline update in 2014. For example, we believe that the committee should consider this observational study which (unexpectedly) identified increased mortality with apixaban and rivaroxaban: Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care BMJ 2018; 362 doi:	Thank you for your comment. It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making.

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				https://doi.org/10.1136/bmj.k2505 (Published 04 July 2018) The 2020 European Society of Cardiology guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) talk about DOACs as a class and do not specify one over another. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation-Management There is an unknown data gap, regarding which is the preferred agent in FRAIL elderly with AF; results due 2022 https://pubmed.ncbi.nlm.nih.gov/31888928/	Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. We will pass your comment on frail elderly with AF to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
NHS Southend CCG	Evidence Review G1	072	013	We consider that the statement in this section, "The committee considered these people could reasonably continue on their current regimen provided they did not wish to change to apixaban/dabigatran, and that they were not experiencing serious problems from their existing prescription" has not been accurately reflected in the Guideline, page 10, line 1. The latter gives a much stronger impression that people should be switched, rather than continue on their existing anticoagulant. In addition, it is difficult to understand what "serious problems" a patient taking e.g. rivaroxaban might be experiencing, that would be resolved by a switch to e.g. dabigatran. We cannot see any marked difference in tolerability in the SPCs that would make edoxaban and rivaroxaban suitable for use if a patient is intolerant of apixaban and dabigatran. An American study evaluating adverse events compiled on an FDA reporting system, showed	Thank you for your comment. As recommendations 1.6.3 and 1.6.4 now recommend any licensed DOACs the recommendation to switch between DOACs has been deleted. We have edited recommendation 1.6.2 to make it clear that a person should continue on their current medication until the opportunity to discuss switching from a vitamin K antagonist to a DOAC can be discussed at the next routine appointment. Time in therapeutic range should be taken into consideration when considering switching.

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				that rivaroxaban had the most adverse effects - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6786266/ We have not been able to find anything which definitively confirms the safety of routine switching between anticoagulants in stable patients. We query why clinicians would risk switching a stable patient with no overt AEs, unless the risk/benefit situation has changed, as we experienced over the last 6 months with the pandemic or there is a risk the patient will become non-compliant with treatment and regular INR tests or other safety monitoring? As per previous comments, the GPs are unlikely to want to change treatment in a stable patient, so any switch discussions would need to be managed by specialist care with associated activity costs. If GPs are persuaded to do advanced anticoagulant care with routine switching depending on patient choice and risk factors, they may expect additional payments.	
NHS Southend CCG	Evidence Review G1	074	032	In discussion of the resource impact, the evidence review states, "However, a recommendation has been made for those who are stable on their current anticoagulant (whether a DOAC or warfarin) to not switch, the impact is likely to be less pronounced". However, Recommendation 1.6.7 states, "For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist **and are stable**, discuss the option of switching treatment at their next routine appointment". (*Our bold and underlining).* We are concerned that this needs clarification. The sentence above also conflicts with line 26 on p74 which says - Finally the committee agreed that patients, who are already taking anticoagulants (DOAC	Thank you for your comment. The committee's discussion of the evidence in evidence G1 has been edited to reflect the change to recommendation 1.6.2. We have edited the recommendation to make it clear that a person should continue on their current medication until the opportunity to discuss switching from a vitamin K antagonist to a DOAC can be discussed at the next routine appointment. Time in therapeutic range should be taken into consideration when considering switching.

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				or warfarin) and are stable, should discuss the decision to switch.	
NHS Southend CCG	General	General	General	The Costing report which accompanied the 2014 guideline estimated that the guideline would result in approximately 10,000 fewer strokes per year in people with AF. https://www.nice.org.uk/guidance/cg180/resources/costing-report-pdf-243730909 (page 7). However, data from the Sentinel Stroke National Audit Program https://www.strokeaudit.org/Home.aspxreports 15,610 AF related strokes in 2013/14 and 16,761 in 2018/19, despite increasing rates of anticoagulation over that time. Even taking into account increased prevalence, there does not appear to have been anything approaching the estimated reduction in AF related strokes. We believe that NICE should investigate the causes of this apparent lack of expected benefit despite increased anticoagulation with DOACs and publish an updated costing report. We consider that the guideline should include practical recommendations for monitoring, appropriate dosing based on renal function, patient information and adherence to help ensure that patients achieve the expected benefits, for example: • There is a table in a Drug Safety Update bulletin published in June 2020 which helpfully sets out the differences between the medicines, including adjustment of therapy for patients with renal impairment and availability of reversal agents.	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned. The results of the evidence review and economic model demonstrated that DOACs were more effective than warfarin across all outcomes prioritised as critical by the committee. Data from RCTs was used to inform the review and model as this is the type of data least prone to bias to address the review question. Please note that a separate resource impact assessment will accompany the guideline based on the new recommendations. Monitoring was outside of the scope of this guideline. Recommendation 1.6.2 directs people at the BNF which contains information on dosing. Information and support were outside of the scope of this update however recommendation 1.6.1 refers to discussing the risks and benefits of anticoagulation. Recommendation 1.6.2 also signposts to the NICE guidelines on adherence and medicines optimisation which contain recommendations on information. Anticoagulant treatment should be discussed in the context of shared decision making (recommendation 1.6.2) as this would include a discussion of whether monitored dosage systems are being used. The pre-hoc decision to use randomised trial data was to reduce selection bias and therefore enable comparisons between treatments to be fairer than otherwise. Whilst it is understood that

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				https://www.gov.uk/drug-safety-update/direct-acting-oral-anticoagulants-doacs-reminder-of-bleeding-risk-including-availability-of-reversal-agents • An article in the June 2020 issue of the Journal of the American Heart Association gives a practical guide to dealing with common challenges around DOAC use and has a comprehensive section on renal impairment - https://www.ahajournals.org/doi/epub/10.1161/JAHA.120.017559 • It should be noted that dabigatran cannot be dispensed in Monitored Dosage Systems whereas the other DOACs can. Discontinuation rates in practice with dabigatran are higher than other DOACs (again potentially increasing costs) possibly due to the tartaric acid, but this is well recognised. • PPI cover to mitigate bleeding risk is also not discussed.	the data from the Sentinel Stroke National Audit program may suggest that the absolute rate of strokes continues to be high despite higher rates of anticoagulation, this does not threaten the conclusions from the trial data that the DOACs are superior to warfarin, and that the DOACS are broadly similar in efficacy to each other. The use of PPIs with anticoagulants was outside of the scope of this guidance.
NHS Southend CCG	Guideline	009	011	We are concerned that this recommendation may conflict with future advice from NHS England if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When	Thank for your comment. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.

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				costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices". If the procurement prices change the cost-effectiveness, then this may change and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices being established with NHSE. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. There does not appear to be any consideration of the cost effectiveness for edoxaban and as the preferred choice locally it would be useful to understand why edoxaban has not been considered. Question 1: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and NHSE. CCGs could be in the impossible position of being asked to implement two sets of guidelines from two	

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				different NHS bodies. It is imperative that they are aligned to be credible and implementable.	
NHS Wakefield CCG	Evidence Review G1	006	008	Whilst we recognise the hierarchy of evidence prioritises RCTs, we are interested to understand whether the guideline committee considered any "real world" evidence on the use of DOACs, accumulated since the last guideline update in 2014. For example, we believe that the committee should consider this observational study which (unexpectedly) identified increased mortality with apixaban and rivaroxaban: Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care BMJ 2018; 362 doi: https://doi.org/10.1136/bmj.k2505 (Published 04 July 2018) The 2020 European Society of Cardiology guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) talk about DOACs as a class and do not specify one over another. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation-Management There is an unknown data gap, regarding which is the preferred agent in FRAIL elderly with AF; results due 2022 https://pubmed.ncbi.nlm.nih.gov/31888928/	Thank you for your comment. It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. We will pass your comment on frail elderly with AF to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
NHS Wakefield CCG	Evidence Review G1	074	032	In discussion of the resource impact, the evidence review states, "However, a recommendation has been made for those who are stable on their current	Thank you for your comment. The committee's discussion of the evidence in evidence G1 has been edited to reflect the change to recommendation 1.6.2. We have edited the

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				anticoagulant (whether a DOAC or warfarin) to not switch, the impact is likely to be less pronounced". However, Recommendation 1.6.7 states, "For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist **and are stable**, discuss the option of switching treatment at their next routine appointment". (*Our bold and underlining).* We are concerned that this needs clarification. The sentence above also conflicts with line 26 on p74 which says - Finally the committee agreed that patients, who are already taking anticoagulants (DOAC or warfarin) and are stable, should discuss the decision to switch.	recommendation to make it clear that a person should continue on their current medication until the opportunity to discuss switching from a vitamin K antagonist to a DOAC can be discussed at the next routine appointment. Time in therapeutic range should be taken into consideration when considering switching.
NHS Wakefield CCG	General	General	General	The Costing report which accompanied the 2014 guideline estimated that the guideline would result in approximately 10,000 fewer strokes per year in people with AF. https://www.nice.org.uk/guidance/cg180/resources/costing-report-pdf-243730909 (page 7). However, data from the Sentinel Stroke National Audit Program https://www.strokeaudit.org/Home.aspxreports 15,610 AF related strokes in 2013/14 and 16,761 in 2018/19, despite increasing rates of anticoagulation over that time. Even taking into account increased prevalence, there does not appear to have been anything approaching the estimated reduction in AF related strokes. We believe that NICE should investigate the causes of this apparent lack of expected benefit despite	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned. Please note that a separate resource impact assessment will accompany the guideline based on the new recommendations. Monitoring was outside of the scope of this guideline. Recommendation 1.6.2 directs people at the BNF which contains information on dosing. Information and support were outside of the scope of this update however recommendation 1.6.1 refers to discussing the risks and benefits of anticoagulation. Recommendation 1.6.2 also signposts to the NICE guidelines on adherence and medicines optimisation which contain recommendations on information. Anticoagulant treatment should be discussed in the context of shared decision making (recommendation 1.6.2)

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				increased anticoagulation with DOACs and publish an updated costing report. We consider that the guideline should include practical recommendations for monitoring, appropriate dosing based on renal function, patient information and adherence to help ensure that patients achieve the expected benefits, for example: • There is a table in a Drug Safety Update bulletin published in June 2020 which helpfully sets out the differences between the medicines including adjustment of therapy for patients with renal impairment and availability of reversal agents. https://www.gov.uk/drug-safety-update/direct-acting-oral-anticoagulants-doacs-reminder-of-bleeding-risk-including-availability-of-reversal-agents • An article in the June 2020 issue of the Journal of the American Heart Association gives a practical guide to dealing with common challenges around DOAC use and has a comprehensive section on renal impairment - https://www.ahajournals.org/doi/epub/10.1161/JAHA.120.017559 • It should be noted that dabigatran cannot be dispensed in Monitored Dosage Systems whereas the other DOACs can. • PPI cover to mitigate bleeding risk is also not discussed.	as this would include a discussion of whether monitored dosage systems are being used. The use of PPIs with anticoagulants was outside of the scope of this guidance.

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NHS Wakefield CCG	Guideline	005	013	"Use the ORBIT bleeding risk score to assess the risk of bleeding when considering anticoagulation in people with atrial fibrillation and when reviewing people already taking anticoagulation." Question 1: The usual scoring system to use in the UK has been HAS-BLED which clinicians are familiar with – what benefits does the ORBIT bleeding risk score tool provide?	Thank you for your comment. The benefits are found mainly in the calibration evidence. Calibration evidence was given priority because of the importance of accurate prediction of absolute risk in the context of using the tools as an aid to the discussion between patient and clinician about the need for risk-modification, rather than as a decision tool about risk modification. In other words, it is envisaged that all patients will be encouraged to risk modify, but that an accurate risk prediction will be helpful in encouraging compliance, particularly in people at higher risk. We have clarified this point in the committee's discussion of the evidence in evidence review E and F. Our committee agreed that ORBIT was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk.
NHS Wakefield CCG	Guideline	009	011	As a CCG we are concerned that this recommendation may conflict with future advice from NHS England if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices".	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.

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				If the procurement prices change the cost-effectiveness, then this may change and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices being established with NHSE. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 2: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and NHSE. We as a CCG could be in the impossible position of being asked to implement two sets of guidelines from two different NHS bodies. It is imperative that they are aligned to be credible and implementable.	
NHS West Essex CCG	Guideline	009	006-019	We are concerned that this recommendation is against national guidelines for anticoagulation which states the most appropriate anticoagulant should be used; this could be a DOAC or VKA.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The evidence review and health economic model showed that DOACs were more

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					clinically and cost effective than warfarin for all outcomes prioritised by the committee as critical for decision making. A vitamin K antagonist is recommended if DOACs are contraindicated, not tolerated or are not suitable (recommendation 1.6.5).
NHS West Leicestershire CCG on behalf of LLR CCGs	Guideline	004	003 - 005	Perform manual pulse palpitation to assess for the presence of an irregular pulse if there is a suspicion of atrial fibrillation. We would welcome further detail around diagnosis in the following situations: • AF is detected by a cardiac pacemaker – my understanding is that 12 lead ECG should be done to reach a diagnosis – the wording in letters to GPs has changed from AF to (I think) atrial arrhythmia. • AF is detected using devices like AliveCor – is an ECG with AF required to reach the diagnosis? Would be very helpful to spell it out so we are all clear on the requirements from NICE.	Thank you for your comments. Cardiac pacemaker devices are all followed up in secondary care, and they can have very high specificity for AF, so rarely is a 12 lead ECG needed. This decision will usually be made by the supervising consultant cardiologist. The committee therefore agreed that it is not necessary for the recommendation to mention pacemakers or loop recorders specifically. In relation to use of devices like the AliveCor, our evidence review showed that there is insufficient evidence that these devices have enough sensitivity and specificity to be able to replace 12 lead ECG as the definitive method of diagnosis. In the example you have given, where the AliveCor (or a similar device) has already provided a positive test, sensitivity is clearly no longer relevant, but the sub-optimal specificity of the AliveCor means that an AF diagnosis could not be assumed from the positive AliveCor result (it would lead to a 4% rate of false AF diagnoses according to our meta-analysed data for AliveCor). Therefore, the findings from a device like the AliveCor should not be used to form a diagnosis if a positive test is obtained.

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NHS West Leicestershire CCG on behalf of LLR CCGs	Guideline	004	011 - 013	"Perform a 12-lead electrocardiogram (ECG) if an irregular pulse is 12 detected in people with suspected atrial fibrillation with or without symptoms. We are concerned that this recommendation lacks detail and should state that the ECG should be carried out at the time of the irregular pulse being found. Sounds obvious but over and over again we hear of people being booked for a routine ECG days later – capture the event then and there.	Thank you for your comment. The committee decided that it would be very difficult to implement ECGs immediately after an irregular pulse has been found.
NHS West Leicestershire CCG on behalf of LLR CCGs	Guideline	006	019 - 020	Perform transthoracic echocardiography (TTE) in people with atrial fibrillation We are concerned that this recommendation lacks detail and needs further definition	Thank you for your comment. This recommendation was not part of the current update. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
North Central London Joint Formulary Committee	Guideline	009	011	We thank NICE for including a treatment hierarchy in the draft guidance.	Thank you for your comment.
North Central London Joint Formulary Committee	Guideline	009	011	Please confirm final publication will be delayed until the NHS England procurement process has concluded, and that these confidential prices will be included in the cost-effectiveness analysis (which will ultimately inform the treatment hierarchy).	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.

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North Central London Joint Formulary Committee	Guideline	009	011	Dabigatran represents a very small proportion of overall DOAC use in England despite being one of the first to market (median CCG = 2.5% of items). Please can NICE re-review whether dabigatran is an appropriate drug to considered as a first-line agent – if it is to be included as a first-line agent, please provide detailed information as to why this significant change in practice is appropriate. This will require NICE to identify the reasons dabigatran is unpopular and address each reason individually. - https://openprescribing.net/analyse/#org=CCG&numIds=0208020X0&denomIds=0208020Z0,0208020X0,0208020AA,0208020Y0&selectedTab=summary	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.
North Central London Joint Formulary Committee	Guideline	009	011	Generic rivaroxaban will be available from ~2023; this will have a major impact on the comparative cost-effectiveness of rivaroxaban compared with apixaban and edoxaban. Please can NICE either, include this important information within their cost-effectiveness model, or provide the price point at which rivaroxaban would become the preferred choice.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. A DOAC cost sensitivity analysis was conducted (section 6.10 of G2) and indicated what price discount would be needed for each DOAC to become the most cost effective option. With regards to patent expiry, NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed. Following completion of the procurement NICE will consider an update of the guideline.

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North Central London Joint Formulary Committee	Guideline	009	011	The decision to recommend DOACs over warfarin is based on results from the updated NIHR cost-utility analysis (CUA). Given the methodological differences between the trials which contribute to the NMA and the challenge in comparing indirect comparisons from an NMA, we feel that NICE should consider and acknowledge information from well-designed observational studies in their decision process. A large UK study of GP data (QResearch and CPRD) found low-dose apixaban (which accounts for ~20% of all DOAC prescribing) and rivaroxaban (~30% of all DOAC prescribing) had an increased risk of all-cause mortality compared to warfarin. - Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care BMJ 2018; 362 doi: https://doi.org/10.1136/bmj.k2505 (Published 04 July 2018) BMJ 2018;362:k2505 In contrast, the NICE NMA did not consider apixaban 2.5mg and rivaroxaban was shown to have a *lower* risk of all-cause mortality (Evidence Review 5; Table 21). A series of European projects have also published which the Committee may like to consider. The meta-analysis of studies from Europe and Canada found rivaroxaban had a modestly increased risk of major bleed compared to warfarin. - Project: http://www.encepp.eu/encepp/viewResource.htm?id=28664 - Meta-analysis http://www.encepp.eu/encepp/openAttachment/studyResultLatest/37104	Thank you for your comments. On further discussion the committee agreed that the NMA by Lopez Lopez was probably not able to adequately adjust for the differences between treatment comparisons in terms of population characteristics that could affect outcome. Initially we had felt that the meta-regressions used were adequate, but after consideration of the numbers of studies involved it does seem unlikely that the meta-regression would have been able to make realistic adjustments to effect that were sufficient to negate inter-comparison differences in prognostic characteristics. We have therefore amended the guideline to not recommend any of the 4 DOACs over any other (1.6.3 and 1.6.4). RCTs were prioritised in the evidence review protocol by the committee as they are least prone to methodological bias.

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				In contrast, the NICE NMA found rivaroxaban did not increase the risk of major bleeding compared to warfarin (Evidence Review 5; Table 22)	
Powys Teaching Health Board	Evidence review G1	006	008	Whilst we recognise the hierarchy of evidence prioritises RCTs, we are interested to understand whether the guideline committee considered any "real world" evidence on the use of DOACs, accumulated since the last guideline update in 2014. For example, we believe that the committee should consider this observational study which (unexpectedly) identified increased mortality with apixaban and rivaroxaban: Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care BMJ 2018; 362 doi: https://doi.org/10.1136/bmj.k2505 (Published 04 July 2018) The 2020 European Society of Cardiology guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) talk about DOACs as a class and do not specify one over another. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation-Management There is an unknown data gap, regarding which is the preferred agent in FRAIL elderly with AF; results due 2022 https://pubmed.ncbi.nlm.nih.gov/31888928/	Thank you for your comment. It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. We will pass your comment on frail elderly with AF to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Powys Teaching Health Board	Evidence review G1	072	013	We consider that the statement in this section, "The committee considered these people could reasonably continue on their current regimen provided they did not wish to change to apixaban/dabigatran, and that they	Thank you for your comment. As recommendations 1.6.3 and 1.6.4 now recommend any licensed DOACs the recommendation to switch between DOACs has

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				were not experiencing serious problems from their existing prescription" has not been accurately reflected in the Guideline, page 10, line 1. The latter gives a much stronger impression that people should be switched, rather than continue on their existing anticoagulant. In addition, it is difficult to understand what "serious problems" a patient taking e.g. rivaroxaban might be experiencing, that would be resolved by a switch to e.g. dabigatran. We cannot see any marked difference in tolerability in the SPCs that would make edoxaban and rivaroxaban suitable for use if a patient is intolerant of apixaban and dabigatran. An American study evaluating adverse events compiled on an FDA reporting system, showed that rivaroxaban had the most adverse effects - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6786266/ We have not been able to find anything which definitively confirms the safety of routine switching between anticoagulants in stable patients. We query why clinicians would risk switching a stable patient with no overt adverse effects, unless the risk/benefit situation has changed, as we experienced over the last 6 months with the pandemic, or there is a risk the patient will become non-compliant with treatment and regular INR tests or other safety monitoring? As per previous comments, the GPs are unlikely to want to change treatment in a stable patient, so any switch discussions would need to be managed by specialist care with associated activity costs. If GPs are persuaded to do advanced anticoagulant care with routine switching depending on patient choice and risk factors, they may expect additional payments.	been deleted. We have edited recommendation 1.6.6 to make it clear that a person should continue on their current medication until the opportunity to discuss switching from a vitamin K antagonist to a DOAC can be discussed at the next routine appointment. Time in therapeutic range should be taken into consideration when considering switching.

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Powys Teaching Health Board	Evidence review G1	074	032	In discussion of the resource impact, the evidence review states, "However, a recommendation has been made for those who are stable on their current anticoagulant (whether a DOAC or warfarin) to not switch, the impact is likely to be less pronounced". However, Recommendation 1.6.7 states, "For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist **and are stable**, discuss the option of switching treatment at their next routine appointment". (*Our bold and underlining).* We are concerned that this needs clarification. The sentence above also conflicts with line 26 on p74 which says - Finally the committee agreed that patients, who are already taking anticoagulants (DOAC or warfarin) and are stable, should discuss the decision to switch.	Thank you for your comment. The committee's discussion of the evidence in evidence G1 has been edited to reflect the change to recommendation 1.6.2. We have edited the recommendation to make it clear that a person should continue on their current medication until the opportunity to discuss switching from a vitamin K antagonist to a DOAC can be discussed at the next routine appointment. Time in therapeutic range should be taken into consideration when considering switching.
Powys Teaching Health Board	Guideline	009	011	We are concerned that this recommendation may conflict with future national advice if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices".	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.

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				If the procurement prices change this may then change the cost-effectiveness and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 1: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and national . Health Boards could be in the impossible position of being asked to implement guidance where the cost-effectiveness estimates have been arrived at based on prices negotiated for English prescribers. It is imperative that they are aligned to be credible and implementable.	NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.
PrescQIPP	Evidence review G1	006	008	Whilst we recognise the hierarchy of evidence prioritises RCTs, we are interested to understand whether the guideline committee considered any "real	Thank you for your comment. It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and

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				world" evidence on the use of DOACs, accumulated since the last guideline update in 2014. For example, we believe that the committee should consider this observational study which (unexpectedly) identified increased mortality with apixaban and rivaroxaban: Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care BMJ 2018; 362 doi: https://doi.org/10.1136/bmj.k2505 (Published 04 July 2018) The 2020 European Society of Cardiology guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) talk about DOACs as a class and do not specify one over another. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation-Management	therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.
PrescQIPP	Evidence review G1	072	013	We consider that the statement in this section, "The committee considered these people could reasonably continue on their current regimen provided they did not wish to change to apixaban/dabigatran, and that they were not experiencing serious problems from their existing prescription" has not been accurately reflected in the Guideline, page 10, line 1. The latter gives a much stronger impression that people should be switched, rather than continue on their existing anticoagulant. In addition, it is difficult to understand what "serious problems" a patient taking e.g. rivaroxaban might be experiencing, that would be resolved by a switch to e.g. dabigatran.	Thank you for your comment. As recommendations 1.6.3 and 1.6.4 now recommend any licensed DOACs the recommendation to switch between DOACs has been deleted. We have edited recommendation 1.6.6 to make it clear that a person should continue on their current medication until the opportunity to discuss switching from a vitamin K antagonist to a DOAC can be discussed at the next routine appointment. Time in therapeutic range should be taken into consideration when considering switching.

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				We cannot see any marked difference in tolerability in the SPCs that would make edoxaban and rivaroxaban suitable for use if a patient is intolerant of apixaban and dabigatran. An American study evaluating adverse events compiled on an FDA reporting system, showed that rivaroxaban had the most adverse effects - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6786266/ The significant risks to patients of routine switching far outweigh any minor benefits that the erroneous calculation of cost-effectiveness suggests.	
PrescQIPP	Evidence review G1	074	032	In discussion of the resource impact, the evidence review states, "However, a recommendation has been made for those who are stable on their current anticoagulant (whether a DOAC or warfarin) to not switch, the impact is likely to be less pronounced". However, Recommendation 1.6.7 states, "For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist **and are stable**, discuss the option of switching treatment at their next routine appointment". (*Our bold and underlining).* We are concerned that this needs clarification. The sentence above also conflicts with line 26 on p74 which says - Finally the committee agreed that patients, who are already taking anticoagulants (DOAC or warfarin) and are stable, should discuss the decision to switch.	Thank you for your comment. The committee's discussion of the evidence in evidence G1 has been edited to reflect the change to recommendation 1.6.2. We have edited the recommendation to make it clear that a person should continue on their current medication until the opportunity to discuss switching from a vitamin K antagonist to a DOAC can be discussed at the next routine appointment. Time in therapeutic range should be taken into consideration when considering switching.
PrescQIPP	General	General	General	The Costing report which accompanied the 2014 guideline estimated that the guideline would result in approximately 10,000 fewer strokes per year in people with AF.	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned. Please note that a separate resource impact

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				https://www.nice.org.uk/guidance/cg180/resources/costing-report-pdf-243730909 (page 7). However, data from the Sentinel Stroke National Audit Program https://www.strokeaudit.org/Home.aspxreports 15,610 AF related strokes in 2013/14 and 16,761 in 2018/19, despite increasing rates of anticoagulation over that time. Even taking into account increased prevalence, there does not appear to have been anything approaching the estimated reduction in AF related strokes. We believe that NICE should investigate the causes of this apparent lack of expected benefit despite increased anticoagulation with DOACs and publish an updated costing report. We consider that the guideline should include practical recommendations for monitoring, appropriate dosing based on renal function, patient information and adherence to help ensure that patients achieve the expected benefits, for example: • There is a table in a Drug Safety Update bulletin published in June 2020 which helpfully sets out the differences between the medicines https://www.gov.uk/drug-safety-update/direct-acting-oral-anticoagulants-doacs-reminder-of-bleeding-risk-including-availability-of-reversal-agents • An article in the June 2020 issue of the Journal of the American Heart Association gives a practical guide to dealing with	assessment will accompany the guideline based on the new recommendations. Monitoring was outside of the scope of this guideline. The results of the evidence review and economic model demonstrated that DOACs were more effective than warfarin across all outcomes prioritised as critical by the committee. Data from RCTs was used to inform the review and model as this is the type of data least prone to bias to address the review question. Recommendation 1.6.2 directs people to the BNF which contains information on dosing. Information and support were outside of the scope of this update however recommendation 1.6.1 refers to discussing the risks and benefits of anticoagulation. Recommendation 1.6.2 signposts to the NICE guidelines on adherence and medicines optimisation which contain recommendations on information. Anticoagulant treatment should be discussed in the context of shared decision making (recommendation 1.6.2) and this would include a discussion of whether monitored dosage systems are being used. The pre-hoc decision to use randomised trial data was to reduce selection bias and therefore enable comparisons between treatments to be fairer than otherwise. Whilst it is understood that the data from the Sentinel Stroke National Audit program may suggest that the absolute rate of strokes continues to be high despite higher rates of anticoagulation, this does not threaten the conclusions from the trial data that the DOACs

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				common challenges around DOAC use and has a comprehensive section on renal impairment - https://www.ahajournals.org/doi/epub/10.1161/JAHA.120.017559 • It should be noted that dabigatran cannot be dispensed in Monitored Dosage Systems whereas the other DOACs can. • PPI cover to mitigate bleeding risk is also not discussed.	are superior to warfarin, and that the DOACS are broadly similar in efficacy to each other. The use of PPIs with anticoagulants was outside of the scope of this guidance.
PrescQIPP	Guideline	009	011	We are concerned that this recommendation may conflict with future advice from NHS England if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices". If the procurement prices change the cost-effectiveness, then this may change and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.

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				and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices being established with NHSE. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 1: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and NHSE. CCGs could be in the impossible position of being asked to implement two sets of guidelines from two different NHS bodies. It is imperative that they are aligned to be credible and implementable. NHS bodies have access to rebate arrangements for two DOACs and hospital trusts receive one at a discounted price, using list prices loses relevance therefore and you risk the guidance being ignored widely and some media embarrassment that will damage the reputation of NICE.	
Primary Care Cardiovascular Society	Evidence Review G1	070	011	The committee note the small proportion of patients in the ARISTOTLE trial who were treated with the 2.5mg twice daily dose (4.7% of the study population). The PCCS would like to highlight that there is no outcomes data to support use of this dose and yet one third of all apixaban prescribing in England is for the 2.5mg dose.	Thank you for your comment. The NMA separated out the different doses of the DOACs as separate comparators. In the health economic model, although apixaban and dabigatran may be given in lower doses to the elderly, it was assumed that all patients would receive the higher dose, and remain on it, even as they age. However, results were robust to a

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					sensitivity analysis assuming only the lower doses of apixaban (2.5mg bd) and dabigatran (110mg bd) were administered.
Primary Care Cardiovascular Society	Evidence Review G1	071	042	With respect to once versus twice daily dosing. The committee dismissed this issue, but this does not reflect the experience of frontline clinicians or their patients. By not offering a once daily option first line the committee are reducing patient choice. Once daily dosing has been shown to improve adherence to cardiovascular disease medication and specifically to DOACs. Coleman CI, et al. Curr Med Res Opin. 2012;28:669–680; McHorney CA, et al. Curr Med Res Opin. 2015;31:2167–73; Alberts MJ, et al. Int J Cardiol. 2016;215:11-3. Poor adherence to anticoagulant therapy leads to increased risk of death, stroke and non-fatal bleeding; Shore S, et al. Am Heart J. 2014;167:810-17	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence to the NICE guidelines on medicine adherence, medicines optimisation and patient experience in adult NHS services which would include taking into account personal preferences such as dose frequency.
Primary Care Cardiovascular Society	Guideline	005	013	The new recommendation to use the ORBIT score to replace HASBLED is of concern given that various studies that have compared the two scores have concluded that the ORBIT score does not perform better in predicting major bleeding events in anticoagulated AF patients. Wang C et al Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: a systematic review and meta-analysis. Oncotarget. 2017;8:109703-109711; Lip GY et al Bleeding scores in AF patients using Non-Vitamin K Antagonist Oral Anticoagulants. The American Journal of Medicine. 2018;131:185-191	Thank you for your comment. The committee did consider the head to head discrimination evidence that you cited during committee discussion, but the committee agreed that the head to head calibration data was the most important to consider, because it gave the best indication of which tool had the best absolute risk accuracy. These calibration data suggested that ORBIT was a better tool in terms of predicting absolute risk. Importantly, this held at all risk levels, including the higher risk levels where it is particularly important to be aware of the risks.
Primary Care Cardiovascular Society	Guideline	009	006	We strongly support the statement that apixaban, dabigatran, edoxaban and rivaroxaban are all recommended as options, within their marketing authorisation, for the prevention of stroke and systemic embolism in people	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC.

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				with non-valvular atrial fibrillation, in line with the criteria specified in the relevant NICE technology appraisal guidance on direct-acting oral anticoagulants (DOACS) and strongly recommend that all the DOACs are positioned equally within the guidance based on the NICE Technology Appraisals.	
Primary Care Cardiovascular Society	Guidelines	009	011	The committee do not appear to have considered the increased complexity of prescribing apixaban and dabigatran compared to rivaroxaban and edoxaban specifically the need to take into account a number of variables such as renal function, bodyweight and age to ensure safe and effective dosing. Several studies have shown that there is an increased risk of inappropriate dosing, particularly under-dosing, with apixaban and dabigatran compared to edoxaban and rivaroxaban; Mostaza JM, Jimenez MJR, Laiglesia FJR ´ et al. Clinical characteristics and type of antithrombotic treatment in a Spanish cohort of elderly patients with atrial fibrillation according to dependency, frailty and cognitive impairment. J. Geriatr. Cardiol. 15(4), 268–274 (2018); Cerda M, Cerezo-Manchado JJ, Johansson E ´ et al. Facing real-life with direct oral anticoagulants in patients with nonvalvular atrial fibrillation: outcomes from the first observational and prospective study in a Spanish population. J. Comp. Eff. Res. 8(3), 165–178 (2019); Steinberg BA, Shrader P, Pieper K et al. Frequency and outcomes of reduced dose non-vitamin K antagonist anticoagulants: results from ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). J. Am. Heart Assoc. 7(4), pii: e007633 (2018), Ruiz Ortiz M, Muniz J, Ra ˜ na M ˜ ´ıguez P et al. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: prevalence and associated factors. A sub-analysis of the FANTASIIA registry. Europace 20(10),	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. We refer to the guidance in the BNF on prescribing (see recommendation 1.6.2). The risks and benefits of anticoagulants for the individual person would need to be considered when deciding on anticoagulation (see recommendation 1.6.1). We do now cross refer (recommendation 1.6.2) to the guidance on shared decision making in the NICE guidelines on medicines adherence, medicines optimisation and patient experience in adult NHS services.

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				1577–1583 (2018); Sato T, Aizawa Y, Fuse K et al. The comparison of inappropriate-low-doses use among 4 direct oral anticoagulants in patients with atrial fibrillation: from the database of a single-center registry. J. Stroke. Cerebrovasc. Dis. 27(11), 3280–3288 (2018). In contrast to other DOACs, under-dosing with apixaban is associated with an increased risk of stroke; Yao X et al. JACC 2017;69(23): 2779-2790.	
Primary Care Cardiovascular Society	Guidelines	009	011	Dabigatran cannot be used in the whole patient population as it is contraindicated in patients with a creatinine clearance <30ml/min, and it also needs automatic dose adjustment at 80 years – this increases the complexity of prescribing and limits the patient population in which it can be used, especially as a lot of patients managed in UK practice are over 80. It is also not suitable for use in a standard medicines compliance aid which again limits its utility. Finally in the RE-LY study, 25% of patients recruited to the dabigatran arm dropped out due to side effects. We cannot see any indication that these issues have been considered in the NICE analysis	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The DOACs should prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2). See the committee's discussion of the evidence in evidence review G1 for how the committee reached their decision.
Primary Care Cardiovascular Society	Guideline	009	011	The recommendation to use apixaban and dabigatran first line is in direct contradiction to statement 1.6.2 that all Direct oral anticoagulants (DOACs) are recommended within their licensed indications. The premise of comparing the safety and efficacy of the individual DOACs is fatally flawed as there have been no head to head comparisons of these drugs. The conclusion drawn, largely based on a network meta-analysis published by Lopez-Lopez fails to take into account: • The different underlying stroke risk profiles in the DOAC studies • The different underlying bleeding risk profiles in the DOAC studies	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. The credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The

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				Both the RELY study (dabigatran) and the ARISTOTLE study (apixaban) recruited low risk populations (mean CHADS-2 score of 2.1 in both studies) whilst ENGAGE -AF (edoxaban) and ROCKET-AF (rivaroxaban) recruited higher risk populations, more reflective of the patients we treat in real life UK practice (mean CHADS2 scores of 2.8 and 3.5 respectively). Similarly, bleeding risk differed widely between these studies with only 10% of the RELY population having a HASBLED score of 3 or more, rising to 62% in the ROCKET-AF study. These differences mean direct comparison of results should not be made and the conclusions of such comparison will not be clinically valid. Furthermore, the Lopez-Lopez meta-analyses assumed full dose DOAC use which is not the case in the clinical trials and most certainly not in real world studies and clinical practice, further making direct and health economic comparisons inaccurate. Further challenges in direct comparison of the DOAC studies due to methodological differences are summarised by Camm et al (Europace. 2018 Jan 1;20(1):1-11. doi: 10.1093/europace/eux086)	committee therefore are no longer confident to recommend a specific DOAC or DOACs. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC.
Public Health England	Guideline	005	013 - 015	While ORBIT does seem to fit better within the population, it uses haemoglobin and haematocrit. We acknowledge that the authors suggest these would be sampled before anticoagulation. However, blood is not usually drawn as part of the assessment process in deciding anticoagulation. It is drawn once the decision has been made. This would be a change to current practice and would have patient/clinician/service/financial implications and these have not been considered.	Thank you for this comment. The decision to use anticoagulation should not normally depend on the ORBIT score (as ORBIT would be used instead to facilitate discussions about risk factor modification). Instead the decision to use anticoagulation would depend on the results from the stroke risk score (CHADSVASC). Therefore, ORBIT could be used *after* the decision to anticoagulate, which means that the haemoglobin and haematocrit measurements could also be done after a decision to use anticoagulation. This concurs with current practice.

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Public Health England	Guideline	008 022	022 - 024012 - 013	We welcome these points, because they reinforce the importance of ensuring that more eligible people benefit from anticoagulation.	Thank you for your comment.
Public Health England	Guideline	009	006 - 028	Prescribing DOACS: rationalising prescribing will have an impact on current practice; patient profiles are diverse and often define which product is used. We therefore recommend this needs further review.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. We do now cross refer (recommendation 1.6.2) to the guidance on shared decision making in the NICE guidelines on medicines adherence, medicines optimisation and patient experience in adult NHS services.
Roche Diagnostics	Evidence Review E&F	010	013	Esteve-Pastor, 2017a does not use the same biomarkers (GDF-15 is not measured) for the ABC score as is validated in the study by Hijazi et al (2016). Therefore we believe it should be excluded from the review.	Thank you for your comment and for pointing out this error. Esteve-Pastor 2017a has not been excluded, but instead the data relating to the ABC from Esteve Pastor 2017a has been reported under the heading 'ABC Bleeding CrC'. The analyses for the Hijazi-validated ABC (with GDF-15) have been redone without the data from Esteve-Pastor 2017a.
Roche Diagnostics	Evidence Review E&F	010	013	We believe this newly published study is within scope and should be included within this review: Hijazi Z. et al., JAMA Network Open. 2020;3(9):e2015943	Thank you – we were unable to add this paper to the review because it was published outside our search date limits. The committee did look at the paper's results, however, and had they agreed it would change recommendations the paper would have been included. However, the committee did not change their recommendation after seeing the results from this paper. This was because the quantity of evidence overall for ABC, even including the data from this study, was insufficient to convince the committee that ABC would be superior to ORBIT. The study

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					may be included in the next update of this guideline.
Roche Diagnostics	Evidence Review E&F	081	004	Given the findings of Hijazi 2016, we were unsure why the ABC bleeding score had no mention within the committee discussion, please could NICE clarify why the ABC bleeding score was not considered/discussed or document the committee's discussion of the evidence if it takes place at the post consultation committee meeting?	Thank you for your comment. The committee focussed on the tools that had been subject to the most study: ABC had relatively little evidence to support it, and the committee did agree that there would be insufficient data to make a recommendation. However, in the light of your comments, ABC was discussed at the post consultation meeting. Although the C statistic data were good, particularly for people on NOACs, there was limited calibration data, no NRI data and no data on sensitivity/specificity at specific thresholds. The committee therefore felt that there were insufficient data on which to recommend ABC.
Roche Diagnostics	Evidence Review G1	008	018-038	As shown in a multi-centre UK based study by Abohelaika et al (2018) , average TTRs are dependent on many factors including the type of anticoagulation service (hospital vs GP vs individual) and also the age and gender of patients (https://onlinelibrary.wiley.com/doi/full/10.1111/ejh.131300). We also know that patient self-monitoring, which is recommended in NICE DG14, may improve % TTR compared to standard care (https://www.nice.org.uk/guidance/dg14/chapter/5-Outcomes). NICE DG14 concluded that "in 15 of the 18 trials, TTR was higher in self-monitoring participants compared with those in standard care". Evidence review G1 concludes that sub optimal trial TTRs are likely representative of UK general practice. However, due to the factors outlined above this may be an oversimplification and we feel that information on patient age, service type and self-monitoring should be considered when making recommendations on	Thank you for your comment. The committee were aware that the TTRs within UK practice were dependent on many such potential factors, but had the opinion, based on their clinical experience, that the TTRs in clinical practice would nevertheless be relatively low and similar to those observed in many of the included RCTs. In particular, the committee argued that there would always be a significant proportion of people on warfarin who would have poor TTR, at a level below even the lowest TTR in some of the RCTs, and that these were the most vulnerable and thus important group to consider when making decisions about whether TTR level in the RCTs were appropriately characteristic. We acknowledge that warfarin may still be relatively effective in a sub-group of the UK population there was no evidence to support a recommendation for this. We agree that information on patient age and self-monitoring

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				initiation, and switching between, treatments. Similarly, we feel that the evidence the committee has looked at on comparisons of warfarin vs DOACs may not be generalisable to those who are taking warfarin and effectively self-monitoring. This could have been included as an indirect comparator in the evidence synthesis.	should be considered in the context of shared decision making when discussing anticoagulant treatment (1.6.2). Recommendation on switching from a vitamin K antagonist to DOACs now refer to considering time in therapeutic range.
Roche Diagnostics	Evidence Review G1	008	031-034	In line with the committee's discussion of the evidence, we would like to highlight that they have seen no strong evidence that it would be cost-effective to switch patients who are taking warfarin and have high TTR to a DOAC. It may therefore be inappropriate to encourage clinicians to actively switch these patients onto a DOAC.	Thank you for your comment. We have edited recommendation 1.6.6 and now refer to time in therapeutic range when discussing whether to switch from a vitamin K antagonist to a DOAC.
Roche Diagnostics	Evidence Review G2	499	014-015	NICE state further analyses are to be undertaken to assess the link between TTR for those on warfarin and how that could affect comparisons with direct-acting oral anticoagulants, as many studies reported sub optimal TTRs. We could not find any further mention of what these analyses would comprise of, could NICE clarify these, possibly in the "Research needs" section?	Thank you for your comment. The research needs section is part of the NIHR HTA report and not the NICE guidelines. Only the sections in the blue boxes were updated and form part of the NICE guideline.
Roche Diagnostics	Evidence Review G2	499	014-015	Given NICE plan further analyses on the relationship between time in therapeutic range (TTR) and the effectiveness of warfarin vs direct-acting oral anticoagulants (DOAC) we would like to suggest a research recommendation for an 'enrichment trial' along the following lines:- Start new atrial fibrillation patients on warfarin, after X months those with sub-optimal TTR are removed from the study. The remaining patients (those with high TTR) are then randomized into two arms: Arm 1: Remain on warfarin Arm 2: Move from warfarin to DOAC	Thank you for your comment. The research needs section is part of the NIHR HTA report and not the NICE guidelines. Only the sections in the blue boxes were updated and form part of the NICE guideline.

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				Outcomes would be those included within the evidence review Alternatively recruitment to the trail could be those already on warfarin and stable instead of new atrial fibrillation patients. The trial would help to clarify the effectiveness of DOACs vs. warfarin in patients with high TTR.	
Roche Diagnostics	General	General	General	A large amount of work has been done by NICE's Public Involvement team and stakeholder groups in patient choice in this area. There are a number of tools and resources available on the section of NICE's website devoted to shared decision-making. This work has highlighted that remaining on warfarin is the preferred option for many patients, particularly those who are stable. We are concerned that this guidance does not emphasise clearly enough that patients who are doing well on warfarin should not be encouraged to switch treatment if they are stable and feel it is the right option for them.	Thank you for your comment, we have edited recommendation 1.6.6 to make it clearer that risks and benefits of switching should be discussed at the next routine appointment but the person should remain on their current medication meanwhile. We now refer to the time in therapeutic range when discussing the risks and benefits of switching. The rationale and impact section describes how the option of switching should be discussed with the person.
Roche Diagnostics (contains conf comments)	Evidence Review B	006	007	While NT-proBNP is not currently approved as a point of care screening tool for atrial fibrillation but is due to gain CE mark approval in this indication in April 2021 for this reason we are highlighting studies that are possibly within scope: Engdahl J. et al., Europace 2017; 19(2):297-302 Gudmundsdottir K.K. et al., Europace 2020; 22(1):24-32 It may be cost-effective to use NT-proBNP to triage patients to assessment with ECG in a two-stage process of the sort discussed by the NICE committee.	Thank you for this comment. As this test is not currently approved it would not be eligible for this guideline. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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Royal College of General Practitioners	Evidence review A	006	010 - 012	Conventional detection methods may be from symptoms which are then followed by pulse palpation. Or, with 10% of strokes being from undetected AF, detection can be from investigation (e.g. 24 hour tape) on someone who has had a stroke.	Thank you for this comment. We agree, and have amended that section (added words in italics) to : **"**Conventional approaches for detecting AF involve identifying patients with an irregular pulse and then performing a 12-lead ECG in those with suspected AF, *or using longer-term investigations such as 24 hour tape in those who have had an unexplained stroke*."
Royal College of General Practitioners	Evidence review A	006 - 007	Table 1	Did the committee consider rates of heart failure or cardiac events (including MI) as important outcomes? These are also associated with AF and have significant economic and health burdens.	Thank you for your comment. Although those outcomes are associated with AF, they were not outcomes identified as important or critical by the committee for this review question at the protocol stage. In the systematic review process, it is important to limit the number of outcomes considered to those most critical for decision-making, and all possible outcomes cannot be covered. The outcomes covered in this review that were deemed most crucial for decision-making are described in table 1.
Royal College of General Practitioners	Evidence review A	010 - 011	Table 2	For the SAFE trial, it isn't clear why the systematic screening arm (which, if current trials are successful, may become a national programme) is not of interest to this review.	Thank you for your comment. Systematic screening is outside the remit of NICE.
Royal College of General Practitioners	Evidence review A	027	Table 12	It appears that Welton et al's 2017 paper "Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis", which has a cost effectiveness analysis of AF detection, was not identified/included. We suggest that this paper should be considered for inclusion and/or its primary studies should be reviewed and included as appropriate.	Thank you – this review was included in the exclusion list of review B. All primary papers were checked for eligibility in both reviews, and any relevant papers were included (or were already included). With regards to the HE review, his paper was excluded at second sift (incorrect population:

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					study included all people over 65 rather than people with symptoms suggestive of atrial fibrillation as stated in the review protocol) and so would not be listed in the HE exclusion list as only papers included at third sift (those assessed for applicability and quality) are included in the exclusion list.
Royal College of General Practitioners	Evidence review A	General	General	In view of the STROKESTOP study and other similar studies, it may be worth noting that using AF detection methods may increase anticoagulation of those with known AF – an outcome of interest to this review and certainly in view of a major issue that we are not anticoagulating the optimum number of patients with AF, which inhibits health and economic gains.	Thank you for this comment. This issue was not identified in the evidence review and was therefore not discussed by the committee.
Royal College of General Practitioners	Evidence review A	General	General	Did the committee consider including implementation studies? This would support the aim stated in the introduction to help with the implementation of AF detection. Using a narrow study type inclusion reduces the chance of meaningful implementation information and prioritises information on the accuracy from RCTs of detection methods – diagnostic accuracy. The search terms also reflect this with few terms related to implementation or delivery. We suggest that implementation studies should be searched for and considered for inclusion in order to gain useful lessons for implementation. For example, studies by Orchard et al from Australia would be useful to consider but are not included under current PICO.	Thank you for your comment. At the protocol stage it was decided that this review should be restricted to RCTs. When comparing the efficacy of different diagnostic strategies in terms of patient-centred health-related outcomes (not diagnostic accuracy), a rigorous design is essential because the danger of the treatment strategies subsequent to diagnostics being too different between arms is high in non-randomised studies. Such confounding may be difficult to adjust for where there is little between-group overlap in treatment approaches. Hence implementation studies that are not randomised have not been included.
Royal College of General Practitioners	Guideline	006	010	1.2.3. ''Offer monitoring and support to modify risk factors for bleeding, including: … Reversible causes of anaemia.'' Can the committee consider adding a recommendation or link to relevant guidance to ensure that underlying	Thank you for your comment. We are unable to provide cross references to all of the relevant guidelines in this recommendation. We refer to managing the causes of anaemia in the committee's discussion of the evidence in evidence review E and F.

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				anaemia will be investigated fully to determine the cause where possible.	
Royal College of Nursing	General	General	General	Thank you for the opportunity to contribute to this consultation, however we do not have any comments on this occasion.	Thank you for your comment.
Royal College of Physicians	General	General	General	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the BCS.	Thank you for your comment.
Royal College of Physicians of Edinburgh	General	General	General	REFERENCES 1. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP and Peterson ED. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. European heart journal. 2015;36:3258-64. 2. Lip GY and Lane DA. Assessing bleeding risk in atrial fibrillation with the HAS-BLED and ORBIT scores: clinical application requires focus on the reversible bleeding risk factors. European heart journal. 2015;36:3265-7. 3. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ and Chen SA. Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: A Comparison of Baseline, Follow-up and Delta HAS-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. Thrombosis and haemostasis. 2018;118:768-777. 4. Lip GY and Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the	Thank you.

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				use and misuse of bleeding risk scores. Journal of thrombosis and haemostasis : JTH. 2016;14:1711-4. 5. Friberg L, Rosenqvist M and Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. European heart journal. 2012;33:1500-10. 6. Apostolakis S, Lane DA, Guo Y, Buller H and Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. Journal of the American College of Cardiology. 2012;60:861-7. 7. Brown JD, Goodin AJ, Lip GYH and Adams VR. Risk Stratification for Bleeding Complications in Patients With Venous Thromboembolism: Application of the HAS-BLED Bleeding Score During the First 6 Months of Anticoagulant Treatment. Journal of the American Heart Association. 2018;7. 8. Kooiman J, van Hagen N, Iglesias Del Sol A, Planken EV, Lip GY, van der Meer FJ, Cannegieter SC, Klok FA and Huisman MV. The HAS-BLED Score Identifies Patients with Acute Venous Thromboembolism at High Risk of Major Bleeding Complications during the First Six Months of Anticoagulant Treatment. PloS one. 2015;10:e0122520. 9. Guo Y, Lane DA, Chen Y, Lip GYH and m AFAIITi. Regular Bleeding Risk Assessment Associated with Reduction in Bleeding Outcomes: The mAFA-II Randomized Trial. The American journal of medicine. 2020;133:1195-1202 e2. 10. Lip GYH, Skjoth F, Nielsen PB, Kjaeldgaard JN and Larsen TB. The HAS-BLED, ATRIA, and ORBIT Bleeding Scores in Atrial Fibrillation Patients	

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				Using Non-Vitamin K Antagonist Oral Anticoagulants. The American journal of medicine. 2018;131:574 e13-574 e27. 11. Guo Y, Zhu H, Chen Y and Lip GYH. Comparing Bleeding Risk Assessment Focused on Modifiable Risk Factors Only Versus Validated Bleeding Risk Scores in Atrial Fibrillation. The American journal of medicine. 2018;131:185-192. 12. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ and Chen SA. Major bleeding and intracranial hemorrhage risk prediction in patients with atrial fibrillation: Attention to modifiable bleeding risk factors or use of a bleeding risk stratification score? A nationwide cohort study. International journal of cardiology. 2018;254:157-161. 13. Wang C, Yu Y, Zhu W, Yu J, Lip GYH and Hong K. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: a systematic review and meta-analysis. Oncotarget. 2017;8:109703-109711. 14. Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, Sharan L, Allen LaPointe NM, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski A, Al-Khatib SM and Sanders GD. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. Thrombosis and haemostasis. 2018;118:2171-2187. 15. Sanders GD, Lowenstern A, Borre E, Chatterjee R, Goode A, Sharan L, LaPointe NMA, Raitz G, Shah B, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski A and Al-Khatib S. Stroke Prevention in Patients With Atrial Fibrillation: A Systematic Review Update Rockville (MD); 2018. 16. Larsen TB, Potpara T, Dagres N, Pison L, Estner H, Blomstrom-Lundqvist C and Scientific	

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				Initiative Committee EHRA. Stroke and bleeding risk evaluation in atrial fibrillation: results of the European heart rhythm association survey. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2014;16:698-702. 17. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, Patel S and Moores L. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018;154:1121-1201. 18. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL and Group ESCSD. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European heart journal. 2020. 19. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM and Investigators RA. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine. 2011;365:883-91. 20. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T and Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955-62.	

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				21. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D and Investigators C-A. Catheter Ablation for Atrial Fibrillation with Heart Failure. The New England journal of medicine. 2018;378:417-427. 22. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, Hamann F, Heidbuchel H, Hindricks G, Kautzner J, Kuck KH, Mont L, Ng GA, Rekosz J, Schoen N, Schotten U, Suling A, Taggeselle J, Themistoclakis S, Vettorazzi E, Vardas P, Wegscheider K, Willems S, Crijns H, Breithardt G and Investigators E-AT. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. The New England journal of medicine. 2020;383:1305-1316. 23. Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P and Hendriks JML. Integrated care in atrial fibrillation: a systematic review and meta-analysis. Heart (British Cardiac Society). 2017;103:1947-1953. 24. Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W, Wen J, Xing Y, Wu F, Xia Y, Liu T, Wu F, Liang Z, Liu F, Zhao Y, Li R, Li X, Zhang L, Guo J, Burnside G, Chen Y, Lip GYH and m AFAIITI. Mobile Health Technology to Improve Care for Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 2020;75:1523-1534. 25. Guo Y, Guo J, Shi X, Yao Y, Sun Y, Xia Y, Yu B, Liu T, Chen Y, Lip GYH and m AFAIITi. Mobile health technology-supported atrial fibrillation screening and integrated care: A report from the mAFA-II trial Long-term Extension Cohort. European journal of internal medicine. 2020. 26. Pastori D, Pignatelli P, Menichelli D, Violi F and Lip GYH. Integrated Care Management of Patients With Atrial Fibrillation and Risk of Cardiovascular	

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				Events: The ABC (Atrial fibrillation Better Care) Pathway in the ATHERO-AF Study Cohort. Mayo Clinic proceedings. 2019;94:1261-1267. 27. Proietti M, Lip GYH, Laroche C, Fauchier L, Marin F, Nabauer M, Potpara T, Dan GA, Kalarus Z, Tavazzi L, Maggioni AP, Boriani G and Group E-EAFGL-TRI. Relation of outcomes to ABC (Atrial Fibrillation Better Care) pathway adherent care in European patients with atrial fibrillation: an analysis from the ESC-EHRA EORP Atrial Fibrillation General Long-Term (AFGen LT) Registry. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2020. 28. Proietti M, Romiti GF, Olshansky B, Lane DA and Lip GYH. Improved Outcomes by Integrated Care of Anticoagulated Patients with Atrial Fibrillation Using the Simple ABC (Atrial Fibrillation Better Care) Pathway. The American journal of medicine. 2018;131:1359-1366 e6. 29. Proietti M, Romiti GF, Olshansky B, Lane DA and Lip GYH. Comprehensive Management With the ABC (Atrial Fibrillation Better Care) Pathway in Clinically Complex Patients With Atrial Fibrillation: A Post Hoc Ancillary Analysis From the AFFIRM Trial. Journal of the American Heart Association. 2020;9:e014932. 30. Guo Y, Lane DA, Chen Y and Lip GYH. Mobile health technology facilitates population screening and integrated care management in patients with atrial fibrillation. European heart journal. 2020;41:1617-1619. *ORBIT score good for predicting mortality post MI*	

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				Correlation of the ORBIT Score With 30-Day Mortality in Patients With ST-Segment Elevation Myocardial Infarction. Shen JH, Wang HM, Zheng KL, Lu HH, Zhang Q.Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620940047. doi: 10.1177/1076029620940047	
Royal College of Physicians of Edinburgh	Guideline	005	003 - 011	College Fellows have stated that the final point on "a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm" is not well made, as the risk of arrhythmia recurrence is not significant overall. The addition of catheter ablation would however be appropriate in this section.	Thank you for your comment. The committee confirmed that the third part of 1.2.1 is necessary. This is because there is indirect evidence from rhythm control trials that stopping anticoagulation after cardioversion causes an excess of strokes. There is also evidence from the 'resolved AF' study [Uhm JS, Won H, Joung B, Nam GB, Choi KJ, Lee MH et al. Safety and efficacy of switching anticoagulation to aspirin three months after successful radiofrequency catheter ablation of atrial fibrillation. Yonsei Medical Journal. 2014; 55(5):1238-1245] included in the discontinuing anticoagulation review. We therefore think that the recommendation should remain in its current format. We have added catheter ablation as another reason for using the CHADSVASC score in the recommendation.
Royal College of Physicians of Edinburgh	Guideline	005	012 - 015	The College considers that there is insufficient evidence to recommend the ORBIT score to assess bleeding risk and certainly insufficient evidence to recommend a change from the HAS-BLED score to the ORBIT. The ORBIT score contains some of the same variables as HAS-BLED with some notable omissions such as	Thank you for your comment. All of the evidence on the tools that met the review protocol criteria were included (see appendix A in evidence review E and F). The guidelines did not intend to indicate that bleeding risk may be used as a deterrent to

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				labile INR, uncontrolled blood pressure, harmful alcohol excess and liver disease. There is some confusion as the guidelines appear to indicate that bleeding risk may be used as a deterrent to anticoagulation in 1.2.2 The College suggests that Table 2 requires some amendment: ▪ In Table 2, HEMORR$_2$HAGES requires genetic testing to calculate so the 'None' in the 'Additional tests required to complete risk tool' is incorrect. ▪ In Table 2, the 'H' in HAS-BLED is uncontrolled hypertension NOT hypertension per se ▪ In Table 2, definitions of the 'D' criteria need to be corrected as 'alcohol use' is incorrect and 'medication usage predisposing to bleeding' is incorrect. It should just state 'alcohol excess/abuse' and 'concomitant antiplatelets or NSAIDs, respectively. Page 82 of Evidence Review E&F states, "*Meanwhile, the NRI evidence was fairly equivocal, suggesting similarities between ORBIT and HAS-BLED, and the committee felt that it did not negate the calibration evidence that ORBIT was the most appropriate tool*" The purpose of a bleeding risk tool is to try to reduce the person's risk of bleeding by focussing on modifiable bleeding risks due to treatment with OAC for stroke prevention in AF (hence any bleeding risk assessment needs to be applicable, in all parts of the patient pathway, ie. on no antithrombotic treatment, aspirin or whilst on OAC, both warfarin and DOAC). HAS-BLED however does include modifiable bleeding risks that if used to do the assessment, consideration would be given to the risk factors that can be changed (controlling	anticoagulation – this source of confusion has been rectified in the committee's discussion of the evidence in evidence review E and F. Recommendation 1.6.1 states that bleeding risk should not be used as a reason not to be anticoagulated. Thank you for the corrections to Table 2 – these amendments have been made. The committee noted that ORBIT does not involve measurement of some of the important modifiable risk factors, but such modifiable risk factors can be measured in other ways, and may already be available on the patient's data. Furthermore, whether ORBIT or HAS-BLED are used does not actually change the amount of modifiable risk factor investigations that need to be carried out by the investigating clinician. For example, measurement of haemoglobin, labile INR, blood pressure, liver function tests and renal function tests will need to be carried out in both cases to evaluate whether current bleeding, increased blood pressure or treatable liver or renal disorders are present, each of which can be treated if needed to reduce bleeding risk. The only difference is that the results of labile INR, blood pressure, liver function tests and renal function tests will feed into informing the HAS-BLED score whereas haemoglobin and renal function results (GFR) will feed into the ORBIT score. This does not make ORBIT any more costly in terms of clinician time and resources, as other variables in ORBIT do not require invasive investigations. In addition, the notion that if the modifiable risk factors are not part of

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				BP, reducing alcohol intake, controlling INR if on VKA, removing non-essential antiplatelets and NSAIDs), thereby potentially reducing the person's bleeding risk. ORBIT mainly includes risk factors that cannot be changed, with the exception of antiplatelets.If there is no clinical evidence of a benefit of one bleeding risk tool over another then the score which is more practical /helpful to the healthcare professional to think about and assess bleeding risk factors and includes those that can be modified should be recommended.	the tool then clinicians will not be prompted to discuss their modification is not a real disadvantage. This is because enquiring about modifiable risk factors of bleeding forms part of routine clinical assessment. We would therefore argue that the real benefits of the greater absolute risk prediction accuracy from ORBIT outweigh the disadvantages of ORBIT not incorporating some of the modifiable risk factors, because the advantages are very real but the disadvantages are surmountable. The decisions were made on a combination of calibration and discrimination. However, calibration was given priority because of the importance of accurate prediction of absolute risk in the context of using the tools as an aid to the discussion between patient and clinician about the need for risk-modification, rather than as a decision tool about risk modification. In other words, it is envisaged that all patients will be encouraged to risk modify, but that an accurate risk prediction will be helpful in encouraging compliance, particularly in people at higher risk. We have clarified this point in the committee's discussion of the evidence in evidence review E and F.
Royal College of Physicians of Edinburgh	Guideline	006	001 – 010	The College would welcome clarification of "poor INR control".	Thank you for your comment. This is covered by the recommendations in section 6 on assessing

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					anticoagulation control with vitamin K antagonists.
Royal College of Physicians of Edinburgh	Guideline	009	001 - 031	Anticoagulation The background behind these proposals is theNetwork meta-analysis (NMA) from Lopez-Lopez 2017 and Sterne 2017:all reasoning is built upon these two NMA and with no direct inference from the original trials or observational studies. Whilst the NMA method is good for making comparisons across interventions which never been directly compared, it relies upon (strong) assumptions, most importantly *transitivity* in indirect comparisons. The analytic strategy to estimate the difference in the trials between warfarin and comparator (apixaban or dabigatran) were different for the assessment of the bleeding outcomes (ITT or modified PP). Additionally, there were major differences in inclusion criteria and therefore, in patient characteristics, which will without doubt affect the absolute risk of outcomes in the included populations. This was clearly outlined in the metaanalysis by Ruff et al.[20] showing that proportions with a $CHADS_2$ score of 3-6 was 87% in the ROCKET-AF trial and 53-54% in the ENGAGE AF-TIMI 48 trial; in both the RE-LY trial and ARISTOTLE trial these proportions were 33% and 30%, respectively. This is bound to impact the NMA outputs. NMA comparisons across trials and between different countries also pose additional issues. NMA are no substitute for a head to head RCT comparison. The NMA includes both Phase 2 and 3 RCTs. Phase 2 are dose finding studies. Phase 3 are definitive pivotal RCTs to inform efficacy and safety outcomes.	Thank you for your comment**.** On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.

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				Ultimately there is very little to choose between the different NOAC agents in terms of effectiveness/efficacy outcomes. Some differences are apparent for safety outcomes (major bleeding) which could inform the *initial choice* when initiating the drug for the first time (i.e., OAC naïve or in those patients at high risk of bleeding)[17] – but the ORBIT score has not been tested in such patients (while the HAS-BLED score has been extensively tested).	
Royal Free Hospital NHS Foundation Trust	Guideline	004	011	It would be helpful to allow 6 lead technologies like Alivecor Kardia 6L to be approved – we used these during COVID with patients sending us ideal information to be able to detect AF and due to lockdown had to accept these as adequate to continue management. Considerable data on accuracy of 6L version is now available.	Thank you for your comment. The evidence showed that 6 lead devices would miss significant numbers of people with AF detected on 12 lead. The committee agreed that, although the evidence showed that accuracy varied, there was some evidence that new devices were accurate and showed promise. The committee made a research recommendation on tests to diagnose persistent atrial fibrillation to encourage further high-quality research in this area to guide future practice.
Royal Free Hospital NHS Foundation Trust	Guideline	004	018	By not clarifying better – a lot of NHS resources may be spent on implanting loop recorders as this seems very open and there are much more economic alternatives such as the Alivecor or Bardy 14 day strips and others. It would help to be more specific then leave these in research	Thank you for your comment. The evidence did not support changing the recommended diagnostic tests to either replace 12-lead ECG as the test to confirm persistent atrial fibrillation or replace pulse palpation as the initial test for persistent atrial fibrillation in a 2-test strategy. The committee clarified that 12-lead ECG should be used as the test to confirm atrial fibrillation, to prevent the use of less accurate ECG devices, such as mobile and lead-I ECG devices. The committee agreed that, although the evidence showed that accuracy varied, there was some evidence that new devices were accurate and

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					showed promise. The committee made a research recommendation on tests to diagnose persistent atrial fibrillation to encourage further high-quality research in this area to guide future practice.
Royal Free Hospital NHS Foundation Trust	Guideline	005	007	Should this also state paroxysmal, persistent or permanent atrial flutter rather than just atrial flutter	Thank you for your comment. The committee agreed that there was no evidence to change the 2014 recommendation.
Royal Free Hospital NHS Foundation Trust	Guideline	005	012	Bleeding risk – this is very helpful – thank you	Thank you for your comment.
Royal Free Hospital NHS Foundation Trust	Guideline	006	010	Can you be a little more specific about anemia (chronic, recent, unstable or non-dietary) etc…?	Thank you for your comment. The presence of anaemia should not contribute to bleeding risk unless caused by iron deficiency. Please see the committee's discussion of the evidence in evidence review E and F. The original study on the design of the ORBIT tool specifies 'a history of anaemia' with no more specific details on the type.
Royal Free Hospital NHS Foundation Trust	Guideline	006	015	Thank you for this section – this should also then relate to a choice for a once a day or twice a day anticoagulant frequency downstream	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. We refer to shared decision making in recommendation 1.6.2 which should include consideration of dosing frequency.
Royal Free Hospital NHS Foundation Trust	Guideline	007	005	Thank you – very useful especially where CHADSVASc scores are raised only due to age or gender.	Thank you for your comment.
Royal Free Hospital NHS	Guideline	007	014	During COVID when TOEs were not easy CTCAs were being used to assess for left atrial appendage	Thank you for your comment. This recommendation was not part of the current

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Foundation Trust				thrombus – could this be an option mentioned in research or a note here?	update. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Royal Free Hospital NHS Foundation Trust	Guideline	009	011	This is a very difficult area and the economic model has had far too much weight placed on it to allow the selection of only 2 agents. There Lopez Lopez model is a NMA simulation. It is inherently limited by assumptions of data available during the trials. The trials were performed at the different times (several years apart across various guideline changes, RELY and ROCKET earlier than ARISTOTLE and ENGAGE) on the different types of patients (differing CHADS score means and proportions and data not available on the same set of patients at PID level) under different designs (RELY was open label) with the different event adjudication committees and rules (MI) and differing time horizons (ENGAGE has 2.8 median follow up). All these are key issues that cannot be re-based as the same and adjusting these lose power considerably. ENGAGE as the last trial included more lower CHADSVASc score patients (then RELY and ROCKET) and would not be able to show the mortality benefit as easily, because the trial was event driven and lower risk patients would have lower seriousness of events (more heart attacks and strokes then deaths) so a competing bias due to lower CHADSVASc risk to not be able to show a better survival benefit. Composite endpoints makes it difficult therefore to compare the trials equally as RCTs are first event driven and not economic driven for timing of how to stop trials. If ENGAGE was death driven, then the NMA would be considerably biased in another direction. We are over stretching the interpretation of this model to the extreme of providing needless monopoly to one DOAC – Apixaban, as Dabigatran has many practical	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. Dosing frequency should be considered in the context of shared decision making when deciding on anticoagulant treatment (1.6.2).

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				delivery and compliance issues. At present Apixaban has excellent data from ARISTOTLE which has been accepted by us as clinicians to make it the most prescribed OAC already. However many patients prefer and need a once daily DOAC and both Edoxaban and Rivaroxaban provide this option. Rivaroxaban has the widest licence and experience in many overlapping disease states of ACS, peripheral artery disease and VTE without needing bridging LMWH. Edoxaban has excellent post authorisation safety data from ETNA-AF over 13,000 patients in a robust international registry showing safety data in elderly patients, patients considered frail and patients with renal impairment. This safety data and some cost considerations has allowed Edoxaban from Daiichi Sankyo (a smaller company with few molecules being prescribed in the UK) to be used by a small but growing and important group of patients preferring once a day anticoagulation. The stroke costs in the model need some revision as more recently published data and National reference costs 2018/2019 differ from those chosen in the model. When all of these factors are taken into account, all DOACs are cost effective compared to warfarin with poor INR control. This section of the NICE guidance should be softer to allow use of all DOACs for their differential prescribing benefits – prescribing, need for an available antidote, gastric tolerance, need to eat with food or not, ability to store in dosette boxes etc. These considerations have already made a natural place for all 4 DOACs in the UK market and this does not need further disruption from NICE guidance. I feel the guidance may not be adhered to and may become irrelevant and will harm the value of NICE guidance. At Royal Free London, we prescribe all DOACs and our GPs and pharmacists and patients benefit from access to all 4 DOACs and we would prefer to	The DOACs should be prescribed in accordance with the guidance in the BNF including on older adults (1.6.2).

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				continue the status quo rather than this excessive directing from this section to only two twice a day DOACs. There is also consider publication bias due to the number of years these agents have been in use and this limits NICE's ability to include this evidence to the committee and this bias is critical to also consider. Rivaroxaban and Edoxaban have not been used in so many economic exercises as Apixaban and Dabigatran.	
Royal Surrey County Hospital	Guideline	007	014	"1.3.3 Perform transoesophageal echocardiography (TOE) in people with atrial fibrillation: • in whom TTE is technically difficult and/or of questionable quality and when there is a need to exclude cardiac abnormalities" There does not seem to be any evidence presented for this statement in any of the NICE documentation, and it would be at odds with typical clinical practice, which would very rarely move to a TOE in such instances. A TOE is an unpleasant experience for the patient. Patients must fast beforehand, sign a consent form warning of them risks such as aspiration pneumonia, a painful throat afterwards and perforation of their oesophagus. Most patients will require sedation and will need to stay in hospital for a period of observation afterwards. Many will be unable to take themselves home and will need assistance. It seems odd to suggest a TOE when a cardiac MRI scan can comfortably resolve the situation in a far safer and more pleasant way for the patient. The 2020 European Society of Cardiology (ESC) AF guidance details the advantages of MRI over echo (Figure 9) and demonstrates that an MRI scan is able to provide	Thank you for your comment. This recommendation was not part of the current update. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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				additional information over & above that available from a TOE. There is no needs for consent form, no risk of complication and the patient can walk out of the scan room afterwards and immediately leave the hospital. The 2017 ESC heart failure guidance gives a level 1 evidence for cardiac MRI in assessment of myocardial structure & function whereas TOE is not even mentioned as an option. "CMR is acknowledged as the gold standard for the measurements of volumes, mass and EF of both the left and right ventricles. It is the best alternative cardiac imaging modality for patients with nondiagnostic echocardiographic studies (particularly for imaging of the right heart) and is the method of choice in patients with complex congenital heart diseases. CMR is the preferred imaging method to assess myocardial fibrosis using late gadolinium enhancement (LGE) along with T1 mapping and can be useful for establishing HF aetiology. For example, CMR with LGE allows differentiation between ischaemic and non-ischaemic origins of HF and myocardial fibrosis/scars can be visualized. In addition, CMR allows the characterization of myocardial tissue of myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease non-compaction cardiomyopathy and haemochromatosis. CMR may also be used for the assessment of myocardial ischaemia and viability in patients with HF and CAD (considered suitable for coronary revascularization)."	

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				A TOE would appear to be the investigation of choice for mitral valve disease or left atrial appendage thrombus exclusion. Beyond that it is not the correct investigation for exclusion of "cardiac abnormalities" (undefined and non-specific) when a TTE is technically difficult or image quality is suboptimal. MRI is superior, risk free, and far more pleasant for a patient. From a Coivd point of view, a TOE is considered an aerosol generating procedure whereas MRI is not. This area of the guidance needs revision as following it in its present form involves unnecessary patient discomfort and risk.	
Royal Surrey County Hospital	Guideline	007	021	"1.4 Personalised package of care and information" The scope of the personalised care package defined by the draft guidance is inadequate. While there is much talk of medications and invasive techniques in the draft guidance, there is none of assessment and treatment of underlying risk factors, that may promote & worsen AF. This is at odds to the 2020 ESC AF guidance, which recommends at least the following: • Identification & management of risk factors & concomitant disease (level 1) • Modification of unhealthy lifestyle & targeted therapy of intercurrent conditions, to reduce AF burden & symptom severity (level 1) • Attention to good BP control in AF patients with hypertension to reduce AF recurrences, risk of stroke & bleeding (level 1) • In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms (level 2a)	Thank you for your comment. This recommendation was not part of the current update. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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				• Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for OAC therapy (level 2a) • Physical activity should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote A (level 2a) The AF guidance should be revised and must also acknowledge the importance of underlying risk factors for development of AF and should recommend that these (e.g. high BMI, alcohol excess etc) be addressed with the patient & MDT members where appropriate. It is inappropriate and substandard care to proceed with medication +/- ablation without addressing underlying cause of the condition.	
Royal Surrey County Hospital	Guideline	007	034	"One member of the committee commented that Lopez-Lopez was an extremely high quality piece of work, and probably the best work published in the area. On this basis, the committee agreed that it was highly unlikely that the resources allocated to performing a new NMA based on our own data would be justified by any gains over Lopez-Lopez, and therefore that using Lopez-Lopez might be preferable to carrying out our own NMA." This is factually incorrectly and it is concerning that, the committee appears to have accepted the view of one individual, and proceeded with it without further exploration of the topic. It is wrong for NICE to describe this study as "extremely high quality", when it is apparent that it has a number of basic errors and	Thank you for your comment. This recommendation was not part of the current update. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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				conflicting statements. It should most certainly not be used to dictate the entirety of the anticoagulation strategy for the NICE guidance. The network meta-analyses in Lopez-Lopez is likely to be misleading evidence since comparable studies were not included. For example, in the comparison of clinically relevant bleeding, three large phase III trials for apixaban (ARISTOTLE), rivaroxaban (ROCKET AF) and edoxaban (ENGAGE AF-TIMI 48) were brought together with two very small phase II trials for dabigatran (AFDABIG-VKA-JAPAN and PETRO). The RELY trial (for dabigatran) did not report clinically relevant bleeding as an outcome measure and was therefore not included for this endpoint. This issue of comparing different studies is worsened by the use of a fixed effects model rather than a more easily justified random effects model where there is heterogeneity between studies. This results in dabigatran appearing to have considerably higher bleeding than the other NOACs and warfarin, despite major and minor bleeding for dabigatran 150mg being similar to warfarin in the RELY study. The trials included for the comparison of clinically relevant bleeding for dabigatran (AF-DABIG-VKA-JAPAN and PETRO, 14 and 36 events, respectively), included unlicensed dabigatran doses. In PETRO, patients were randomised to receive dabigatran 50mg (not licenced or used in clinical practice), 150mg, or 300mg (not licenced or used in clinical practice) twice daily either alone or combined with 81mg or 325mg aspirin once daily. Over half of the clinically relevant bleeding events for dabigatran from this study occurred in patients receiving 300mg twice daily (with or without aspirin) (17 of 32 events). How is it therefore	

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				fair, or correct, to conclude that the bleeding rate of dabigatran is higher than apixaban when the comparison of an unlicensed dose against a licenced one? The abstract and body of the Lopez-Lopez text do not accurately reflect the results of the authors' analysis. The authors state that 'apixaban 5mg was ranked the highest for most outcomes evaluated including stroke or systemic embolism'. However, dabigatran 150mg is ranked highest for both stroke or systemic embolism and ischaemic stroke, and has a lower rate of these outcomes in the comparisons versus apixaban 5mg (stroke and systemic embolism: odds ratio 0.82, 95% confidence interval [CI] 0.62-1.08; ischaemic stroke: odds ratio 0.83, 95% CI 0.59-1.16). It is unclear how the 'rankograms' in Lopez-Lopez are derived, and these do not appear consistent with other elements of the authors' analysis. For example, in Table 3, which presents the bleeding outcomes, dabigatran is shown to have the lowest rate of intracranial haemorrhage (ICH) compared to warfarin. However, in the rankograms dabigatran 150mg is ranked at 5 out of 6 for ICH, while apixaban 5mg is ranked between 1 and 2 out of 6 despite having a higher ICH rate in their comparison versus warfarin, and a similar ICH rate in their comparison versus dabigatran 150mg. Dabigatran 150mg is ranked lowest of the NOACs for all-cause mortality, despite having a similar rate of all-cause mortality in the comparison versus apixaban 5mg (ranked first) (odds ratio 1.00, 95% CI 0.84-1.19); and edoxaban 60mg (ranked second) having a similar rate in their comparison versus warfarin, and a	

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				numerically higher rate in the comparison versus dabigatran 150mg (odds ratio 1.03, 95% CI 0.87-1.22)	
Royal Surrey County Hospital	Guideline	009	011	1.6.3 Offer anticoagulation with either apixaban or dabigatran to people with 12 atrial fibrillation and a CHA2DS2-VASc score of 2 or above This recommendation is at odd with previous NICE guidance, and all major international guidance in this area, where each of the NOAC agents are given equal preference. The methodology of how NICE arrived at this conclusion appears to be deficient and unsatisfactory. Following this guidance is likely to result in significantly higher drug costs, with the benefit of one NOAC over another not sufficiently demonstrated.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and we now recommend any licensed DOAC. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs.
South London Cardiovascular Medicines Working Group	Guideline	004	004	When considering CVD preventative strategies, should a manual pulse palpation occur at each face to face blood pressure check also when checking heart rate, to detect underlying asymptomatic AF?	Thank you for your comment. Opportunistic screening is outside of the remit for NICE.
South London Cardiovascular Medicines Working Group	Guideline	004	018	Does the committee recommend the use of devices such as AliveCor or KardiaMobile in general practice? Could refer to previous guidance (https://www.nice.org.uk/advice/mib232)	Thank you for your comment. The committee does not recommend the use of such devices in general practice. The evidence showed that such devices do not have sufficient sensitivity and specificity to be used as an adequate proxy for 12 lead ECG (as the definitive test). Furthermore, they do not have adequate sensitivity to be able to replace pulse palpation as a first line screening test.

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South London Cardiovascular Medicines Working Group	Guideline	005	013	Bleeding risk assessment with ORBIT is a change to current practice of HASBLED which is embedded in many hospital and primary care prescribing templates. We agree that the emphasis should be on identifying and addressing bleeding risks rather focussed solely on the results of a score.	Thank you for your comment. We have amended the recommendation to acknowledge that, although ORBIT is the best tool to use to assess the risk of bleeding, other bleeding risk tools may need to be used until ORBIT is embedded in clinical pathways and electronic systems.
South London Cardiovascular Medicines Working Group	Guideline	009	011	We are concerned with the recommendation for apixaban or dabigatran as preferred anticoagulation options. What is important to emphasize is that patients should be safely and effectively anticoagulated to reduce their stroke risk. The risk of over- and under- coagulation should also be considered: Some anticoagulants eg edoxaban and rivaroxaban have a more favourable patient adherence profile as they are taken once daily, and some prescribers prefer the simpler dosing regimes for the once daily preparations- as less factors to consider in dosing decisions and less risk of error. Dabigatran, in particular, has tolerability issues, cannot be used in medicine compliance aids and in patients with renal functions less than CrCl 30ml/min, so would not be suitable for many UK patients.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and we now recommend any licensed DOAC. We now refer to the guidance in the BNF on prescribing (see recommendation 1.6.2). Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence to the NICE guidelines on medicine adherence, medicines optimisation and patient experience in adult NHS services which would include taking into account personal preferences such as dose frequency.
The Stroke Association	Comment Form Question 1	N/A	N/A	***Question 1: Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why:*** Given existing challenges to the compliance with the existing guideline, we are concerned that the new guideline may pose similar challenges to both clinicians and patients. Research has highlighted that a large proportion of people with known AF in England, and the rest of the UK, are not properly anticoagulated. For example,	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned.

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				27.8% of patients with known AF admitted to hospital because of a stroke were not on anticoagulants in 2018/19. There is also regional variation in the proportion of high-risk patients with AF treated with anticoagulants. In 2019/20, the Midlands and East of England treated the highest proportion of patients and London the lowest.[1] There is a need for both national and local drivers to be in place to enable and ensure better compliance to the updated guidelines. We have highlighted some of these drivers in our response to question 3.	
The Stroke Association	Comment Form Question 2	N/A	N/A	***Question 2: Would implementation of any of the draft recommendations have significant cost implications?*** While the guideline recommendations may have cost implications for specific interventions, there are clear and demonstrable financial and societal benefits to the detection and management of AF in England. If the management of AF was properly controlled in the UK, as well as preventing strokes, it would contribute to significant cost savings. Stroke Association research suggests that, as of 2016, the cost of stroke to the NHS was around £3.4bn annually, which was estimated to rise by 2035 to over £10bn. Current societal costs UK-wide are around £26bn and could reach over £90bn by 2035.[2] Without action, in under	Thank you for your comment. The committee agree that NICE guidelines are an important part of improving patient care within the NHS and in ensuring that people receive the most clinically and cost effective treatment. Thank you for signposting to the 'Atrial Fibrillation High Impact Tool'. NICE routinely produce baseline assessment and resource impact tools. A resource impact assessment report is being developed for this guideline To encourage the development of other practical support tools, NICE run an endorsement scheme aimed at encouraging our partners to develop these in alignment with NICE recommendations. Eligible tools are assessed and if successful, will be endorsed by NICE and

1 NHS Digital, Quality and Outcomes Framework, (2019-20) Available: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2019-20

[2] Patel A, berdunov V, King D, Quayyum Z, Wittenberg R, Knapp M, (2017). *Executive summary Part 2: Burden of Stroke in the next 20 years and potential returns from increased spending on research*. Stroke Association.

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				two decades the number of strokes will increase by almost half, and the number of stroke survivors by a third. Moreover, evidence suggests that 'for every 25 people diagnosed with AF and appropriately treated with anticoagulation, one stroke is prevented, saving an average of £46,039 per stroke in health and social care costs over 5 years.'[3] NHS RightCare, in collaboration with Imperial College Health Partners, have developed an 'Atrial Fibrillation High Impact Intervention Tool' that uses data published by NHS Digital. The tool can help commissioners measure the value of identifying, treating and managing AF patients. For example, in West Yorkshire the tool demonstrates that 21% of the local population have undiagnosed AF and by optimally treating AF in that area over the next 3 years, 790 strokes could be prevented and £11,674,282 saved.[4] This research clearly highlights the importance of working together across the stroke community to ensure that AF is diagnosed and effectively managed. These NICE guidelines are a vital element of this.	featured on the NICE website alongside the relevant guideline.
The Stroke Association	Comment Form Question 3	N/A	N/A	***Question 3: What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)***	Thank you for your comment. Evidence reviews A and B report on the diagnostic accuracy of new technologies with manual pulse taking combined with 12 Lead ECG when indicated.

[3] Health Innovation Network, UK, Using mobile ECG devices to increase detection of atrial fibrillation across a range of settings in south London. (February 2020). Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7032580/

[4] Imperial College Health Partners, Atrial Fibrillation High Impact Intervention Tool. Available: http://afhiit.imperialcollegehealthpartners.com/dashboards/index/afhiit/tabs:dashboard-object-164210:0,dashboard-object-164218:0,dashboard-object-164193:0,dashboard-object-164168:0,dashboard-object-164249:0,dashboard-object-164225:0/stp_code:E54000005/org_code:E54000005_ENG/

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				As the leading UK-wide charity on stroke, we are uniquely placed to share best practice and learnings from across the nations to drive service improvement and development. The key areas highlighted below should be considered to contextualise the guideline and to provide further evidence to help users overcome any challenges. ***National initiatives*** In England, the NHS Long Term Plan places prevention at its heart and reflects on the progress other countries have made on working towards people knowing their 'ABC' (AF, Blood pressure and Cholesterol). The plan suggests that 'replicating this approach will be increasingly possible with digital technology, and major progress could be achieved working with the voluntary sector, employers, the public sector and NHS staff themselves'.[5] As we highlighted in our response to the UK National Screening Committee Screening for Atrial Fibrillation in June 2019, there is a growing range of new technologies which can detect possible AF and research has shown technologies are more accurate at detecting AF than manually pulse taking alone.[6] The plan also recognises the valuable role of pharmacists and nurses within Primary Care Networks (PCNs) in detecting AF, highlighting 'where 100 people with AF are identified and receive anticoagulation medication, an average of four strokes are averted,	This showed that the diagnostic accuracy of the new devices were not significantly better than pulse taking and performing a 12 lead ECG. In the asymptomatic, detection of AF on a 12 lead ECG in those with risk factors for anticoagulation warrants anticoagulation. By contrast, the significance of a short duration of AF detected by a single lead ambulatory monitoring device is uncertain. The committee acknowledged the importance of new technologies in the detection of AF and made a research recommendation 'What is the diagnostic accuracy of key index tests (such as Alive Cor, MyDiagnostik, Microlife BP monitors, iPhone plethysmography and pulse palpation) compared with the gold standard of 12-lead ECG in people with risk factors for or symptoms of atrial fibrillation?' We now acknowledge the importance of primary care networks and Integrated Stroke Delivery Network in the detection of AF in the committee's discussion of the evidence in evidence review B. We will pass this information to our local practice collection team. More information on local practice can be found here https://www.nice.org.uk/about/what-we-do/into-practice/shared-learning-case-studies

[5] NHS England and Improvement, NHS Long Term Plan, (January, 2019) Available: https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf
[6] Taggar JS, Coleman T, Lewis S, Heneghan C, Jones M, (2016), Accuracy of methods for detecting an irregular pulse and suspected atrial fibrillation: A systematic review and meta-analysis, European Journal of Preventive Cardiology Available: https://www.ncbi.nlm.nih.gov/pubmed/26464292

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				preventing serious disability or even death.' The guideline should emphasise the role PCNs can, and should, play in AF management – as well as the importance of the full multidisciplinary team in AF detection and management. The emphasis of social prescribing and Universal Personalised Care in Long Term Plan also presents key opportunities to help people live well and manage their own conditions, like AF, effectively. Stroke prevention is one of the five programme work streams in the National Stroke Programme, which underpins the Long Term Plan with actions specifically around better diagnosis and management of AF. ISDNs have been set up across England to deliver on these commitments locally, and to implement improvements across the pathway at a regional level and should support efforts to improve AF detection and management. The new national stroke delivery model, currently in draft, points to the role of ISDN as the key drivers of stroke prevention activity.[7] The delivery model highlights 'patient understanding of and adherence to prevention should be everyone's responsibility' and in particular 'it is…the responsibility of the ISDN and all health care practitioners involved in stroke care to ensure that secondary prevention is considered, screened for and patients offered intervention at every opportunity and at least at regular intervals'.[8] It is also noted that 'the use of innovative strategies and technologies to detect and address adherence of both	

[7] NHS England and Improvement, National Stroke Service Model, Draft, (October, 2020) Available: https://future.nhs.uk/gf2.ti/f/1022498/82334053.1/PDF/-/ISDN_National_Stroke_Service_Model__DRAFT_October_2020.pdf
[8] Ibid.

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				modifiable physical and social economic risk factors for stroke should be encouraged'. The new stroke delivery model and the current context around emerging systems like ISDNs should be referenced within the guideline in order to coordinate efforts to improving prevention activities. Neglecting to mention the current changes to the health and care landscape means the guidelines are less relevant and useful to those implementing them locally and fails to put the guidelines into the context of the emerging landscape and national policy commitments. Bodies such as ICSs, ISDNs and PCNs, have huge potential to coordinate action and lead on population health initiatives, such as the management of AF, to prevent ill-health. It is vital that other local authority and NHS bodies are ready to work with ISDNs, as many of their objectives will require a cross-systems approach. As part of this cross-system approach, the voluntary sector are also a key partner in delivering national prevention ambitions. The Long Term Plan emphasises the role of joint-working between ICSs and the third sector and there is a big potential for charities and local systems to work together on quality improvement partnerships around AF. The Stroke Association is currently working in partnership with NHS England and Improvement and other key arm's length bodies to deliver the National Stroke Programme, which sets out in greater detail the activities that will support the successful implementation of the Long Term Plan's commitments around stroke.	

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				CVDPREVENT, a national CVD prevention audit for primary care, commissioned by NHS England and Improvement, will offer reporting locally and nationally to help PCNs and practices identify ways to improve patient outcomes. The audit will help support adherence to the guidelines by helping to 'provide data to highlight gaps, identify inequalities and monitor improvement and impact on inequalities, as well as enabling and guiding opportunities for improvement' and will 'generate quarterly, anonymised data at national, regional, PCN and CCG practice level, across a broad range of metrics'.[9] PHE have also suggested further action for CVD prevention, which are necessary to comment on, including: • 'Strengthening the NHS Health Check to support early diagnosis and management; • Integrated Care Systems developing and delivering new CVD prevention models of care; • Implementing NHS England and Improvement's RightCare CVD prevention pathway; • Using existing data to make the case for action; • Making positive behavioural changes for preventing CVD; and • Raising public awareness of CVD risk factors and opportunistic detection'.[10] ***Current examples of good practice***	

[9] NHS England and Improvement, CVDPREVENT. Available: https://www.england.nhs.uk/ourwork/clinical-policy/cvd/cvdprevent/
[10] NHS Health Check e-Bulletin, World Heart Day (2020) Available: https://www.nhshealthcheck.nhs.uk/nhs-health-check-e-bulletin-world-heart-day/front-page/nhs-heath-check-e-bulletin-world-heart-day

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				In England, AF virtual clinic models were announced as part of the Long Term Plan across 23 CCGs in England. The two pilot CCGs saw a 25% reduction in the rate of AF-related stroke. More information on the project here and more information on the initial sites can be found here. In 2017, NHS England and Improvement commissioned AHSNs to procure and distribute 6,000 mobile ECG devices to community settings across the country, with groups at an increased risk of AF being targeted. More information on this national pilot can be found here. In Northern Ireland, the charity Northern Ireland Chest Heart & Stroke have recently published a paper following an independent inquiry into the detection and management of AF that ran from March 2019 to January 2020.[11] In the paper, they highlight good practice case studies. These include: 1. South Eastern Health & Social Care Trust - Pilot Community Pharmacy Offer; 2. NICHS Well Check; and 3. A Cardiac Nurse Led AF Clinic. Furthermore, in Wales, the 'Stop a Stroke' project aims to support health boards in Wales to review the treatment of patients with AF and reduce their risk of having a stroke. Implementation of the project has been part of the GP Quality Assurance and Improvement Framework and forms part of the	

[11] Northern Ireland Chest Heart & Stroke, An independent inquiry into the identification and management of AF to reduce stroke risk. Link available: https://nichs.org.uk/about-us/news/10-000-more-reasons-why-its-time-we-need-to-focus-on-patient-need

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				guidance for the General Medical Services contract.[12] Requirements include: • 'Each practice will have access to an online AF dashboard providing computerised feedback on patients identified to be at risk from inappropriate prescribing of antiplatelet therapy or suboptimal use (including no use) of anticoagulant therapy.' • 'Individual practices will identify a lead who will be a doctor, pharmacist or nurse working at the practice, to develop and progress actions in the plan'. • 'Following the initial meeting, the practice will be expected to identify AF patients at risk of stroke and undertake structured and documented reviews with a view to improving prescribing and reducing risk.' • 'Each GP practice will lead the implementing a stroke reduction action plan'.[13] In Cardiff, the Stop a Stroke project has reduced the number of AF patients treated with aspirin from 26% to 6% since 2014.[14] ***Existing practical resources*** NHS RightCare has produced a CVD Prevention Pathway which aims to provide local health economies 'best practice case studies for elements of the pathway demonstrating what to change, how to change and a scale of improvement'.[15] Included within the pathway is	

[12] NHS Wales, Quality Assurance and Improvement Framework Guidance for the GMS Contract Wales (2019/20) Available: http://www.wales.nhs.uk/sites3/Documents/480/Guidance%20for%20GMS%20Contract%20Wales%20-%20Quality%20and%20Improvement%20Framework%202019-20.pdf, p.20 & p.25
[13] Ibid.
[14] Cross Party Group on Stroke, *The future of stroke care in Wales on the inquiry into the implementation of the Welsh Government's Stroke Delivery Plan*, P.7
[15] NHS England and Improvement, High value intervention in atrial fibrillation. Available: https://www.england.nhs.uk/rightcare/products/pathways/cvd-pathway/af/

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				a sectionon high value intervention in AF with recommendations such as 'work with practices and local authorities to maximise NHS Health Check uptake and follow up' and 'add pulse checking to existing GP and pharmacy enhanced services for people over 65'.[16] The third sector, often in collaboration with industry, also has a good record of producing tools and resources for primary care in particular around AF identification and management.	
The Stroke Association	Comment Form Question 4	N/A	N/A	***Question 4: The recommendations in this guideline were developed before the coronavirus pandemic. Please tell us if there are any particular issues relating to COVID-19 that we should take into account when finalising the guideline for publication.*** There are some considerations to take into account, in light of the COVID-19 pandemic, that will affect the recommendations in this guideline. COVID-19 will have a major and adverse effect for the lifetime of this guideline and it will not become insignificant in this period of time. COVID-19 has already decreased the efficiency of the NHS, which has contributed to even longer waiting lists. Difficulties in accessing the NHS, alongside a growing number of people who are afraid to seek help has resulted in an increasingly number of patients with delayed treatment and under diagnosis of serious conditions. These NICE guidelines need to recognise the consequences of COVID-19 and adapt.	Thank you for your comment. We agree that COVID-19 has markedly reduced the opportunities for detection of AF by pulse palpation. Our evidence review found that some Lead 1 and BP monitoring devices had equal sensitivity to manual pulse palpation and could be used, as you suggest, as part of a 2 part test with 12 lead ECGs. Given that they were not clearly more sensitive than manual pulse we did not change our recommendation. However, the devices would need to be used outside GP premises to overcome the issues related to the COVID-19 pandemic. There remain practical issues related to their provision, such as instruction of persons using the device and remote safe transfer of the data when used outside of GP premises. We now refer to the challenges faced in the NHS due to COVID-19 in the committee's discussion of the evidence in evidence review B.

[16] Ibid. RK: please check responses for typos, punctuation and missing words please (i.e.ID11, 12, 13 and others), probably needs a good proof read once responses finalised – will add to table on p.1.

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				The disruption to health and care services caused by COVID-19 has resulted in national stroke initiatives across the UK being paused or slowed - including those focused on prevention, such as the delay to the rollout of CVDPREVENT. This is putting the progress made in stroke care over recent years at significant risk and we welcome the update to the guidance in spite of current external challenges faced. Moreover, although the pandemic has also indirectly resulted in the disbanding of PHE, public health and prevention initiatives are still of paramount importance. In the midst of this pandemic, decision-makers cannot overlook the huge potential to save lives, and lessen pressures on the health system in coming years, with the right investment in stroke prevention programmes now. AF management must remain a priority to help meet the prevention ambitions in the Long Term Plan, which remain as important as ever. The COVID-19 pandemic has affected almost all aspects of stroke care and treatment. And, there is a clear tension between the guidelines' recommendations regarding face-to-face testing and management of AF and the reduced access to in-person appointments and chances for opportunistic testing that we've seen in recent months as a result of COVID-19. For example, there has been a reduced number of face-to face and opportunistic interactions where AF might usually be detected due to lockdown measures. Encouraging pulse checking as part of the NHS Health Check, for example, will not have been possible.	

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				Methods of usual care have been impacted and the public have been less readily accessing usual healthcare services. NHS England and Improvement's 'Help Us Help You' campaign aims to encourage the public to use health and care services during the pandemic to mitigate against findings showing that 'four in ten people are too concerned about being a burden on the NHS to seek help from their GP'.[17] A recent population-based study from The Lancet on the impact of the pandemic on GP usage and subsequent diagnoses, including of AF, found that 'patients seem to be avoiding all clinical settings rather than using alternatives'.[18] Subsequently, '456 fewer diagnoses of circulatory system diseases were recorded', representing a 43.3% reduction in the population studied.[19] Moreover, the number of first prescriptions of medicines commonly used to treat cardiovascular disease were lower than expected during the period between March and May. The study concludes that 'the COVID-19 pandemic has resulted in a large number of potentially missed or delayed diagnoses of health conditions, which carry high risk if not promptly diagnosed and effectively treated'.[20] Opportunities for secondary prevention of stroke may have also been missed. We have heard that due to	

[17] NHS England and Improvement, *Help us help you: NHS urges public to get care when they need it* (April, 2020) Available: https://www.england.nhs.uk/2020/04/help-us-help-you-nhs-urges-public-to-get-care-when-they-need-it/
[18] Williams, R, et al. (2020) Diagnosis of physical and mental health conditions in primary care during the COVID-19 pandemic: a retrospective cohort study. Available: http://www.thelancet-press.com/embargo/ECCVIDtlph.pdf
[19] Ibid.
[20] Ibid.

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				COVID-19 most of the 6 month reviews for stroke survivors have been completed over the phone, meaning that screenings for AF will not have taken place as they usually would have. We have also recently published a report on the impact of the pandemic on stroke survivors and their carers, which assessed the impact of COVID-19 on different parts of the pathway. The report is based on a survey of almost 2,000 stroke survivors and their carers, which found that 55% had appointments related to stroke cancelled or postponed during the pandemic.[21] 56% of stroke survivors told us that they have not felt safe to go to scheduled appointments, meaning that some people may not feel comfortable attending appointments as the pandemic continues and for the foreseeable future.[22] There was also an option for respondents to the survey to provide additional information, in the form of free-text responses. The below quotes from stroke survivors highlight concerns around access to ECG appointments during the pandemic: • 'No follow up consultations with either hospital or GP (…) [the] consultant said I need an ECG and yet my appointment isn't until sept which is a major concern'. (Stroke survivor in England who had a stroke during the pandemic and made this comment in June 2020) • 'Cardiology Appointment - by telephone - with the consultant - Aphasia made it strange & very nerve racking for me - and he stated he would still have to see me for Echo & ECG - it was nice to know that I wasn't	

[21] Stroke Association, Stroke recoveries at risk (2020) Available: https://www.stroke.org.uk/sites/default/files/campaigning/jn_2021-121.1_-_covid_report_final.pdf
[22] Ibid.

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				forgotten about'. (Stroke survivor in Northern Ireland who had a stroke in 2018 or before) • 'The stroke has caused problems with my heart which are getting worse. Having a phone call with a cardiologist isn't really helping to speed up my treatment. He can't do even simple tests, ECG, BP etc. over the phone'. (Stroke survivor in England who had a stroke in 2018 or before) To mitigate against the current obstacles to in-person AF detection and management, alternatives to face-to-face should be considered when delivering healthcare and helping people to manage their own health and health conditions. The pandemic presents a huge opportunity for technology to change the way people are supported to manage their own health and health conditions. NHS England and Improvement's NHS at Home initiative, for example, aims to support people to remote monitor their health conditions and to use technology to allow clinicians to monitor their conditions remotely. Despite this, there are clear limitations of virtual methods of care, and equality considerations should be taken into account in order to not increase health inequalities and there is a need for enhanced patient choice around AF management. For example, our 'Stroke Recoveries at Risk' report found that 'for most stroke survivors who used it, telehealth was positive, or even preferable to face-to-face appointments, with 52% satisfied and only 17% dissatisfied with the appointments'.[23] However, virtual methods of care were not suitable for everyone, especially those with	

[23] Ibid.

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				communication difficulties or cognitive impairments, and those less digitally literate and many people told us that virtual appointments were not a suitable alternative for them. There is, however, a need to include within the guidelines processes of diagnosing and managing AF that are not reliant on physical contact. The COVID-19 pandemic has also highlighted the strain and shortage of clinicians in the NHS, and the guidelines should recognise the role non-clinicians can play in diagnosing and managing AF. The guidelines as they are do not solve the challenges COVID-19 has placed upon the health and care system. We suggest the guidelines encourage the use of technology to identify AF on the basis that it will rely on less physical contact and can be carried out by non-clinicians. Sensitivity and specificity are not as important if the patient is then referred for a 12 lead ECG. Thus, we welcome more research into this area but do not think it is a legitimate reason for delay. The guidance needs to reflect that the pandemic may have further impacted the management of AF in England. Stroke prevention and the management of AF needs to remain a focus of targeted efforts across the stroke community and more widely, given the burden stroke places on society, individuals, families, carers and others. Unless the diagnosis and management of AF is prioritised by systems like ICSs then it will be unsuccessful. Concerted efforts should be made to capitalise on opportunities for innovative delivery of AF detection and management, and the implementation of AF initiatives should continue to be prioritised – particularly given the challenges that the pandemic has presented and the ever increasing	

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				importance of public health and prevention. We would point to the potential for alternatives to face-to-face models of delivery, at least in the interim, though would acknowledge the impact this may have on equalities.	
The Stroke Association	Equality Impact Assessment	General	General	There are a number of equality considerations the guidance should take into account. Geographic location should be considered within the equalities impact assessment. There are, on average, 40 AF-related strokes every day in England.[24] The PHE AF prevalence indicator shows the variation across England, broken down by CCG level and GP level. It demonstrates that there is huge geographic variation in prevalence across the country depending on the demographic profile. At a GP level, this can mean prevalence ranges anywhere from 0.009% to 27.5%.[25]Those who are from low socioeconomic groups are 'more likely to be among those who go undiagnosed and untreated' for AF and stroke incidence is higher in lower socioeconomic groups.[26]We would urge again, as we have recommended in the past, that public health and prevention activity, such as AF management, is targeted in areas of deprivation. This, in conjunction with the increased use of technology and data, such as the Quality Outcomes Framework, Sentinel Stroke	Thank you for your comment. Geographic location is included in the equalities impact assessment (section 3). The guideline committee discussed the impact of geographic location on the recommendations but did not consider that any edits or additional recommendations needed to be made. All of the recommendations could be implemented irrespective of geographic location. However, your comments will be considered by NICE where relevant support activity is being planned. The committee acknowledged that further research is needed on gender, ethnicity and age. However, research recommendations can only be made on review questions that were asked in the guideline. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

[24] Public Health England, Health Matters: preventing cardiovascular disease (2019) Available: https://www.gov.uk/government/publications/health-matters-preventing-cardiovascular-disease/health-matters-preventing-cardiovascular-disease
[25] Ibid.
[26] NHS England and Improvement, NHS Stroke action will save hundreds of lives (2019) Available: https://www.england.nhs.uk/2019/05/nhs-stroke-action-will-save-hundreds-of-lives/

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				National Audit Programme and CVDPREVENT, will help to identify and address health inequalities. Katherine Thompson, Head of the Cardiovascular Disease Prevention Programme, PHE, reflects that 'CVD doesn't affect everyone equally' as 'people living in England's most deprived areas are disproportionately affected' and it is 'more common among men, older people, people with a severe mental illness and among South Asian or African Caribbean communities. This not only bears a great cost to those affected, but health care costs are estimated at £7.4 billion and those to wider society at £15.8 billion per annum'.[27] We are pleased that the relationship between gender, ethnicity and age were considered as part of the equalities assessment. However, as the equality impact assessment noted 'the current evidence is unclear regarding the relationship between ethnic group and atrial fibrillation'.[28] We therefore suggest further research is needed into the impact and prevalence of AF in different populations and demographics, especially in relation to ethnicity. Without this clear understanding, targeted recommendations will not be possible to improve equality. Our Stroke Recoveries at Risk report highlights that 'the pandemic has also bought existing health	

[27] NHS Health Check e-Bulletin, World Heart Day (2020) Available: https://www.nhshealthcheck.nhs.uk/nhs-health-check-e-bulletin-world-heart-day/front-page/nhs-heath-check-e-bulletin-world-heart-day
[28] NICE, Atrial Fibrillation: management consultation, equality impact assessment (2020) Available: https://www.nice.org.uk/guidance/GID-NG10100/documents/equality-impact-assessment-2

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				inequalities into sharp focus. Like Covid-19, the impact of stroke is disproportionate in some communities. Strokes are more likely to happen to those from socially deprived areas, and these are often more severe'.[29]People from Black and South Asian backgrounds in the UK may be more likely to have a stroke than those who are white. In the UK, black people are more likely to have a stroke than white people. And, both Black and South Asian people are more likely to have a stroke at an earlier age than white people.Our report outlined that 'risk factors such as high blood pressure also disproportionately affect these communities, contributing to their risk of stroke. In light of the pandemic, and the structural disadvantages it has brought to the fore, understanding health inequalities must be a priority for all aspects of stroke prevention, treatment and post-hospital care. The Stroke Association has already embarked on developing its own strategy to highlight, challenge and address or tackle health inequalities that exist in stroke health'.[30] There are clear demographic inequalities that the guidance needs to take into account and we would urge NICE to include recommendations for those undertaking AF management activity to consider how to reduce health inequalities as a key focus of their activity. More widely, further research needs to be undertaken to understand how AF impacts different populations.	

[29] Stroke Association, Stroke recoveries at risk (2020) Available: https://www.stroke.org.uk/sites/default/files/campaigning/jn_2021-121.1_-_covid_report_final.pdf
[30] Ibid.

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The Stroke Association	Guideline	004	002	***Detection and diagnosis*** Currently, the guideline only suggests pulse checking for those where there is a suspicion of AF and those presenting with certain symptoms. We would suggest that this is a missed opportunity to improve the detection and diagnosis of AF in England, given the scale of the problem and the number of people currently undiagnosed. There should be an increased emphasis in the guideline of opportunistic pulse checking at every given opportunities to make 'every contact count' to help increase AF diagnosis, especially given that there are currently low rates of AF detection. PHE have similarly recommended 'raising public awareness of CVD risk factors and opportunistic detection' to improve AF detection.[31] Pharmacists and other health professionals should be supported to check for AF. As we pointed to in our submission to the UK National Screening Committee Screening for Atrial Fibrillation, 'opportunistic checking for AF should be carried out at any point a patient is checked for hypertension in their routine health appointments and inpatient care. The inclusion of regular AF checking as part of standard practice will ensure every health professional contact counts. These low-cost interventions could see significant improvements in the early identification of AF. We believe improved rates of opportunistic testing would increase the numbers of people who are diagnosed with AF, and with medication would reduce the number of strokes'. In relation to section 1.11 around stopping anticoagulation, there's a need for better	Thank you for your comment. Opportunistic screening is outside of the remit of NICE.

[31] NHS Health Check e-Bulletin, World Heart Day (2020) Available: https://www.nhshealthcheck.nhs.uk/nhs-health-check-e-bulletin-world-heart-day/front-page/nhs-heath-check-e-bulletin-world-heart-day

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				communication between primary and secondary services. We hear anecdotal reports of people on anticoagulation having haemorrhagic strokes and their anticoagulation is stopped in hospital to prevent any further bleeds. However, as soon as they return to the community, their prescriptions start again, with potentially catastrophic affects. Good AF management is determined in large part by bits of the system working and speaking together.	
Thrombosis UK	Guideline	008- 011	General	NICE advocate '***Patient Choice'***. They also advocate consideration for '***simplest medicine possible'*** for the user and recognise the need for '***medicine management'***. The recommendations proposed across this draft guideline are in complete conflict with these ideas. We are shocked and dismayed and strongly urge NICE to review and change the draft guidance.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. This enables the health professional and person to choose the most appropriate DOAC in the context of shared decision making (1.6.2).
Thrombosis UK	Guideline	008- 011	General	Under these proposed guidelines, primary care would be expected to restrict their prescribing of DOAC therapy for stroke prevention in AF patients to apixaban or dabigatran. Our understanding is, dabigatran, due to efficacy and some tolerance issues, is currently only used in a very small number of suitable AF patients. This means that in reality, general practice would have only one main DOAC option – apixaban. Restricting patient choice even further.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. This enables the health professional and person to choose the most appropriate DOAC in the context of shared decision making (1.6.2).
Thrombosis UK	Guideline	008- 011	General	Anticoagulation is an identified high-risk therapy and one that is most commonly managed in primary care. AF accounts for the majority of anticoagulation prescribing reasons. However, smaller but significant numbers of patients who have suffered a venous thromboembolism (VTE), also require anticoagulation management, some long-term. For these patients, all DOACs have been	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. This enables the health professional and person to choose the most appropriate DOAC in the context of shared decision making (1.6.2). This would include taking into consideration a person's medical history.

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				approved and are considered in line with evidence, medical suitability and patient choice – as per guidelines: TA341, TA327, TA354, TA287, TA261. If general practitioners are restricted in managing only one DOAC for AF patients, this may considerable reduce their experience and expertise in managing other DOACs available for other disease areas but whose patient numbers are considerably smaller. We are extremely worried that this may inadvertently place VTE patients at risk of harm or force greater workload on hospital services to manage these patients. Repeated hospital appointments for management of a DOAC would be costly, time consuming and not in the patient or NHS best interest.	
Thrombosis UK	Guideline	008- 011	General	Thrombosis UK is very concerned that the draft update AF Guideline will impact on future access to therapies for VTE patients, either because of reduced confidence in prescribing alternative DOAC therapies in primary care, or in an unofficial meta-analysis being rolled out across future VTE guidelines.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. This guidance is for patients diagnosed with atrial fibrillation and does not change any of the recommendations in the NICE guideline on VTE.
Thrombosis UK	Guideline	008- 011	General	We strongly urge NICE to reconsider these recommendations. We believe patient safety will be compromised – not just for AF patients but also potentially for other disease areas where patients require anticoagulation. Crucially, patient choice is unjustifiably being restricted and as a result, patient outcomes are being placed at risk.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. This enables the health professional and person to choose the most appropriate DOAC in the context of shared decision making (1.6.2).
Thrombosis UK	Guideline	009	011	We are concerned that in draft guidance 1.6.3 there seems to be a contradiction with existing NICE Guidance, which is quoted in the line above (1.6.2) where is it clearly set out that NICE has approved: "*Apixaban, dabigatran, edoxaban and rivaroxaban are*	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and we now recommend any licensed DOAC.

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				all recommended as options, within their marketing authorisation".	
UK Clinical Pharmacy Association	Algorithm	001 - 005	General	Consider reformat of algorithm so text can be easily ready and visually inviting, particularly Algorithm 2	Thank you for your comment. We have edited to the algorithms to make them more readable.
UK Clinical Pharmacy Association	Algorithm 1	002	General	Include all contraindications and intolerance criteria	Thank you for your comment. As this information is contained in the BNF we do not repeat it in the recommendations or algorithms.
UK Clinical Pharmacy Association	Guideline	004	003 - 020	No mention of opportunistic screening or role for technology devices to aid in identification of AF – please consider inclusion to assist with detection and diagnosis	Thank you for your comment. Opportunistic screening is outside of the remit of NICE. The role of technology devices was considered in evidence review A. The evidence did not support changing the recommended diagnostic tests to either replace 12-lead ECG as the test to confirm persistent atrial fibrillation, or replace pulse palpation as the initial test for persistent atrial fibrillation in a 2-test strategy. The committee agreed that, although the evidence showed that new devices showed promise, further research was required before they could replace existing strategies. The committee therefore made a research recommendation on tests to diagnose persistent atrial fibrillation to encourage further high-quality research in this area to guide future practice.
UK Clinical Pharmacy Association	Guideline	005	012 - 015	ORBIT score places more patients in low-risk category than HAS-BLED – consider recommending HAS-BLED or ORBIT to assess bleeding risk, particularly as HAS-BLED is embedded in clinical practice/electronic prescribing systems	Thank you for your comment. The decisions were made on a combination of calibration and discrimination. However, calibration was given priority because of the importance of accurate prediction of absolute risk in the context of using the tools as an aid to the discussion between patient and clinician about the need for risk-modification, rather than as a decision tool about

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					risk modification. In other words, it is envisaged that all patients will be encouraged to risk modify, but that an accurate risk prediction will be helpful in encouraging compliance, particularly in people at higher risk. We have clarified this point in the discussion, which we feel we had not made sufficiently clearly before. Although some of the discrimination data suggested that ORBIT may underestimate risk, the calibration evidence did not show this, and instead showed that ORBIT was consistently accurate at predicting absolute risk across risk levels.
University College Hospitals NHS Foundation Trust	Algorithm	N/A	N/A	The algorithm seems to imply that that you cannot use a once daily preparation even though the sentence above states offers pt a choice based on their preferences. Patients may prefer a once daily option.	Thank you for your comment. We have edited the algorithm to reflect the changes in the recommendations. Recommendations 1.6.3 and 1.6.4 have been amended to recommend any licensed DOAC.
University College Hospitals NHS Foundation Trust	Evidence Review G1	057	032	They should also mention that these are all meta analyses and none based on head to head trials and despite analysing for heterogeneity there were different demographics	Thank you – this paragraph (Lopez-Lopez et al.'s summary of their results) has now been deleted because the summary contained an error in relation to the efficacy of apixaban.
University Hospitals Birmingham	Evidence review A	General	General	The evidence review needs to define atrial fibrillation with regard to those interventions shown to provide benefit. The gold standard used in the almost all the trials studied is a cardiologist review of the traces, not a true endpoint such as 12 lead ecg confirmation of atrial fibrillation or a hard clinical endpoint such as stroke. In the absence of such a hard endpoint all these studies do is redefine the definition of atrial fibrillation. Yet all the original trials of intervention which showed a prognostic benefit used the hard definitions of atrial fibrillation	Thank you for your comment. Evidence review A was not a review of diagnostic accuracy, but instead a review of the effects of different diagnostic strategies on outcomes. We used 'confirmed diagnosis of AF' as one of the outcomes, but this was a pragmatic outcome, designed to utilise whatever method had been used to confirm diagnosis in the studies.

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University Hospitals Birmingham	Evidence review B	006	008	In this evidence review you use 2 gold standards 1) 12 lead ECG - this is valid and 2) Ambulatory monitoring for >24 hours. This is incorrect all the evidence for prognostic data is based on a 12 lead ECG. By using this second standard you are redefining atrial fibrillation. What duration of an irregular rhythm on a prolonged monitoring should be defined as atrial fibrillation (>30S, >6 minutes, >6 hours, >24 hours) We have very clear evidence that short bursts of atrial arrhythmia detected on prolonged monitoring do not have the same prognosis or complications as atrial fibrillation detected on a 12 lead ECG. By redefining the gold standard you are potentially exposing a large number of patients to treatment with anticoagulation where there is a risk, significant cost and no benefit, increasingly these patients may also be exposed to other treatments with significant complications on the basis of the guidelines without actually having atrial fibrillation. There is no evidence for anticoagulation of patients with short episodes of device detected "atrial fibrillation" yet there is a significant risk and cost. Unless you more clearly define what is atrial fibrillation for the purposes of treatment the rest of the guidelines are dangerous.	Thank you for your comment. The use of two gold standards was to account for the fact that the first gold standard of a 10-second strip of 12-lead ECG is only appropriate for detection of persistent AF. The second gold standard (ambulatory monitoring > 24 hrs) was used solely to help us evaluate diagnostic tests for paroxysmal AF, where a standard 10-second 12-lead ECG may not be appropriate, because paroxysmal periods may not coincide with the short period of testing. For paroxysmal AF, longer durations of measurement are required, which would ideally be in the form of 12-lead ECG continued for 24 hours or more. However, because we were unsure when designing the review protocol that any study would have such an exacting gold standard when looking for paroxysmal AF, we took the pragmatic approach of evaluating all studies where any longer-term ambulatory gold standards had been used, such as from a Holter >24 hours (see page 93, lines 1-10). This was to increase the probability of being able to evaluate a study that had used an adequate (if not perfect) longer-term gold standard appropriate for paroxysmal AF. Defining the second gold standard (as the bare minimum that we were prepared to accept for the review) as 'ambulatory monitoring > 24 hours' does not mean that we are proposing that AF picked up on ambulatory monitoring >24 hours should form a new definition of AF. As explained above, we are setting the boundaries for a broad and inclusive gold standard that would allow us to consider all the literature, and then make a decision based on a reasoned interpretation based on the limitations of some of

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					the gold standards that would be likely included in that remit. In the end, none of the actual long-term gold standards used in the studies turned out to be adequate gold standards (in terms of their measurements being 'true'), and the conclusion of the committee was that because of this there could be no valid evidence for the accuracy of any form of longer-term index test. If a person suffers short bursts of atrial arrythmia that are clinically insignificant then we agree they should not necessarily always be treated, and that in some cases treating such patients can be dangerous because of the potential harms of anticoagulation. However, this review question was concerned with the detection of AF – whether or not an index test can pick up who has and who hasn't got AF – and is not about directly detecting clinically significant AF. The decision on whether AF events are clinically significant goes beyond initial testing, and relies on further examination and clinical judgement.
University Hospitals Birmingham	Evidence Review B	009 – 023 023 - 026	Table 2 and 3	The evidence review does not look closely at the false positive rate. Patients with some evidence of device detected AF who did not have a 12 lead ECG or atrial fibrillation	Thank you for your comment. The false positive rate of the various tools – as defined by the specificity – was evaluated in detail within this review.
University Hospitals Birmingham	General	General	General	My organisation, University Hospitals Birmingham as a pathway/guideline for prescribing oral anticoagulants that has been authenticated and approved by clinicians in Haematology, Stroke and Cardiology within the trust Birmingham and Solihull CCG and the Area prescribing Committee. We have multiple numbers of patients who struggle with twice daily medication and therefore concordance will be difficult to achieve in a real world clinical setting. If the guidelines are only recommending twice daily	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence in the NICE guidelines on medicine adherence, medicines optimisation and patient experience in adult NHS services which would include taking into account personal preferences such as dose frequency.

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				medication then this is not a true reflection of patient's choice.	
University Hospitals Birmingham	General	General	General	I am happy to provide a copy of our local guideline, karen Beale, Lead Nurse for Anticoagulation Services UHB, karen.beale2@uhb.nhs.uk	Thank you for your comment.
University Hospitals Birmingham	General	General	General	Only recommending twice daily medication is detrimental for patients who prefer once daily which provides increased concordance. By offering choice we are allowing the patient to have some ownership of their healthcare …	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence in the NICE guidelines on medicine adherence, medicines optimisation and patient experience in adult NHS services which would include taking into account personal preferences such as dose frequency.
University Hospitals Birmingham	General	General	General	All patients are offered a choice based on clinical indication, clinicians recommendation, co-morbidities, contra indication and clinical presentation…	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence in the NICE guidelines on medicine adherence, medicines optimisation and patient experience in adult NHS services which would include taking into account personal preferences such as dose frequency as well as clinical indications.
University Hospitals Birmingham	General	General	General	all patients should have twice daily medication	Thank you for your comment. We now recommend any licensed DOAC enabling dosing regimen to be taken into consideration.
University Hospitals Birmingham	Guideline	004	016	The guideline should define what constitutes atrial fibrillation on a 24 hour tape or event recorder. Strictly the evidence for anticoagulation in atrial fibrillation (the only prognostic ally relevant intervention) relies on a 12 lead ECG diagnosis. Many centres will diagnose	Thank you for your comment. We have now referred to the fact that the benefit of anticoagulation for asymptomatic AF (which would support a diagnosis of AF) that has not been documented on 12 lead ECG is uncertain

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				short bursts of atrial high rate episodes as atrial fibrillation requiring intervention but there is no evidence for this. In trials of ablation 30s is used as a marker but this is purely a technical assessment and not based on any prognostic data for intervention. THIS IS CRITICALLY important to prevent large numbers of patients being inappropriately anticoagulated	and that further research is being conducted on this. In the absence of evidence the committee were unable to make a recommendation on this area.
University Hospitals Birmingham	Guideline	004	018	The guideline suggests the use of ambulatory ECG monitor, event recorder or other ECG technology to detect less frequent episodes of atrial fibrillation. This guideline makes the assumption that atrial fibrillation detected by these techniques is the same as atrial fibrillation detected with a 12 lead ECG or 24 hour tape. This is known not to be true. Indeed we do not have any evidence that patients with device detected atrial high rate episodes (often called erroneously atrial fibrillation) should be anticoagulated the only significant intervention in atrial fibrillation with a prognostic benefit. Indeed there is currently a randomised trial ongoing to assess whether atrial fibrillation (atrial high rate episodes) detected by an implantable loop recorder or pacemaker should be treated with anticoagulation. Until we have this data the term atrial fibrillation should be reserved for patients with atrial fibrillation on a 12 lead ECG or 24 hour tape.	Thank you for your comment. We have now referred to the fact that the benefit of anticoagulation for asymptomatic AF that has not been documented on 12 lead ECG is uncertain and that further research is being conducted on this. In the absence of evidence the committee were unable to make a recommendation on this area.
University Hospitals Birmingham	Guideline	005	002	The guidelines does not make any recommendation of how long an episode of atrial fibrillation needs to be for the clinician to recommend anticoagulation – The evidence base is for patients with 12 lead ECG documentation, but if a patient has 12s of "AF" on a 24 hour tape should they be assessed for anticoagulation, or should it be 30s or should it be 5 minutes. This is critical NICE should state what the threshold is for defining AF and performing a stroke risk assessment	Thank you for your comment. We have now referred to the fact that the benefit of anticoagulation for asymptomatic AF that has not been documented on 12 lead ECG is uncertain and that further research is being conducted on this. In the absence of evidence the committee were unable to make a recommendation on this area.

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University Hospitals Birmingham	Guideline	005	002	The guideline recommends using ChadsVasc to assess stroke risk after cardioversion – please clarify do you mean electrical/chemical cardioversion or cardioversion by ablation. Most electrophysiologists would consider stopping anticoagulation after cardioversion of flutter using cavotricuspid isthmus ablation.	Thank you for your comment. The recommendation refers to any cardioversion. The committee agreed that apparently successful ablation was not a reason to stop anticoagulation.
University Hospitals Birmingham	Guideline	005	General	The guideline needs to be more specific about what constitutes a true diagnosis of atrial fibrillation. Again this is critically important in terms of exposing large numbers of patients to inappropriate treatment. Is it 1) a 12 lead ECG showing atrial fibrillation (the true definition in terms of the original anticoagulation trials) 2) Episodes of an atrial high rate detected by a 24 hour tape lasting at least ?30s ? 5 minutes? Longer. 3) Episodes of atrial high rate detected using an implantable loop recorder lasting longer the 30s,? 5 mins, ? Longer 4) Episodes of pacemaker detected atrial high rate lasting longer than 6minutes (the definition in one study), 6 hours or 24 hours. Until AF is properly defined the rest of the guideline is meaningless 7) Irregular heart rhythm detected by a phone or watch app. For much of the guideline atrial fibrillation lasting longer than 30s was used as a definition of atrial fibrillation. NICE should assess whether this is appropriate. We have no evidence that anticoagulation of patients with 30s of atrial fibrillation reduces stroke risk; indeed from pacemaker studies such short bursts of atrial fibrillation were not associated with increased stroke risk. This may appear a trivial point but with the increasing use of longer term patches, implantable devices and wearable heart rate monitors there is a tsunami of asymptomatic irregular heart rhythms being detected. We know from studies that these episodes do not have the same risk as 12	Thank you for your comment. In the protocol we did not define AF recurrence in terms of the length of minimum detection or how it should be detected, so all biologically plausible definitions used in the literature were included in our analyses. In general, however, the vast majority of included studies used definitions of AF that the committee deemed appropriate.

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				lead ECG detected atrial fibrillation yet the implication of the guidance is that they should be treated the same. There are at least two ongoing trails assessing whether there is any role for anticoagulation in these patients. In the absence of evidence the guidelines should stick to the classical definitions of atrial fibrillation used in the original atrial fibrillation trials.	
SH	AliveCor Ltd.	Guideline	025	022-024	All mobile and lead I- ECG devices have been given a blanket statement of less accurate. This reflects KardiaMobile single lead device accuracy as misleading according to the recently published MIB232 – "Specificity and sensitivity data Diagnostic accuracy studies show that KardiaMobile's sensitivity ranged between 77.0% and 96.6% and specificity ranged between 76.0% and 99.1% in AF". *Please see table below for reference pg 5-6 NICE guideline 22 "The committee clarified that 12-lead ECG should be used as the test to confirm atrial 23 fibrillation, to prevent the use of less accurate ECG devices, such as mobile and 24 lead-I ECG devices. " Would the NICE guideline consider including accuracy data specific to KardiaMobile and/or refer to the existing MIB232 regarding accuracy and the NIHR publication comparing single lead devices? https://www.journalslibrary.nihr.ac.uk/hta/hta24030#/abstract	Our data supported the fact that lead I devices miss detection compared to 12 lead.
SH	Aneurin Bevan University Health Board	Guideline	009	017	We are concerned with the recommendation to offer apixaban and dabigatran as first line. We would like to highlight that the cost effectiveness analysis does not take into account any potential local or national rebates. If the procurement price changes then the cost effectiveness as calculated in the guideline will be inaccurate and will require updating. We are aware of the forthcoming advice from NHSE however from a Welsh perspective we are not subject to the same procurement arrangements that NHSE are negotiating and therefore NHS Wales could be disadvantaged via any subsequent decisions regarding a	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for

					review of the recommendations on cost effectiveness and choice of agent. As such we would support a less prescriptive approach to recommending specific agents, with acknowledgement that the cost effectiveness may be variable across different areas depending on local rebates and over time, especially with patent expiries for dabigatran and rivaroxaban in 2023. The choice of DOAC agent in Wales is also influenced by the All Wales Advice on Oral Anticoagulation for Non-valvular Atrial Fibrillation Guidance. The guidance recommends that any DOAC can be considered as an option and if no specific patient characteristics or preferences, the agent with the lowest acquisition cost should be considered.	technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.
SH	Aneurin Bevan University Health Board	Guideline	009	023	We are concerned with the recommendation to offer apixaban and dabigatran as first line. We would like to highlight that the cost effectiveness analysis does not take into account any potential local or national rebates. If the procurement price changes then the cost effectiveness as calculated in the guideline will be inaccurate and will require updating. We are aware of the forthcoming advice from NHSE however from a Welsh perspective we are not subject to the same procurement arrangements that NHSE are negotiating and therefore NHS Wales could be disadvantaged via any subsequent decisions regarding a review of the recommendations on cost effectiveness and choice of agent. As such we would support a less prescriptive approach to recommending specific agents, with acknowledgement that the cost effectiveness may be variable across different areas depending on local rebates and over time, especially with patent expiries for dabigatran and rivaroxaban in 2023. The choice of DOAC agent in Wales is also influenced by the All Wales Advice on Oral Anticoagulation for Non-valvular Atrial Fibrillation Guidance. The guidance recommends that any DOAC can be considered as an option and if no specific patient characteristics or preferences, the agent with the lowest acquisition cost should be considered.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.
SH	Aneurin Bevan University Health Board	Guideline	009	029	We are concerned with the recommendation that only if direct-acting oral anticoagulants are contraindicated, not tolerated or not suitable in people with atrial fibrillation, should a vitamin K antagonist be offered. We would like to highlight that these draft recommendations may have significant cost implications to the NHS across the UK. Although there has been a general trend away from warfarin and towards DOACs, this recommendation will encourage an acceleration in the pace of change. Whilst it is recognised that the cost of warfarin includes the cost of INR monitoring provision, it will be unlikely that	Thank you for your comment. The results of the evidence review demonstrated that DOACs are more clinically and cost effective than warfarin across all outcomes critical to decision making. A separate resource impact assessment will accompany the guideline and it is expected that there will be a financial impact as a result of increased DOAC prescribing. Although there will not be any cash savings it is expected there will be a non-cash releasing saving for providers, such as

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					Health Boards and other NHS bodies can disinvest in the fixed assets, such as staff who undertake INR monitoring. Money is unlikely to flow from acute sites who undertake the INR monitoring back to CCG/HBs who bear the increased prescribing costs. This has the potential to increase drug costs (due to increased DOAC costs) without reducing warfarin monitoring costs, as adequate arrangements for warfarin monitoring will still need to be maintained within the Health Board.	community, primary and secondary care which is driven by a reduction in anticoagulation clinics for the management of INR levels in people receiving treatment with warfarin.
SH	Aneurin Bevan University Health Board	Guideline	010	001	We are concerned with the recommendation for adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist and are stable, discuss the option of switching treatment at their next routine appointment. We should highlight that this the recommendation to switch existing patients would present a potential cost pressure for Health Boards where a rebate for alternative agents is available. In addition to this, any active switching programme would be likely to be resource intensive for GPs, especially given the current context of the pandemic.	Thank you for your comment. We now recommend all licensed DOACs and the recommendation to switching between DOACs has therefore been deleted. Recommendation 1.6.6 recommends that a person who is on a vitamin K antagonist and are stable may continue on their current medication and discuss the option of switching at their next routine appointment taking into consideration time in therapeutic range.
SH	Anticoagulation UK	Guideline	009	011 - 016	There are four DOACs recommended for prevention of stroke and systemic embolism for AF. Dabigatran and Apixaban are both twice daily (BD) treatments where Rivaroxaban and Edoxaban are once daily dosages. Has this been given any consideration by the Committee in terms of meds optimisation and adherence? These are long term treatments and may sit along side other drug regimes with individuals with co -morbidities. Our understanding is that dabigatran cannot not be decanted into a dosette box Within the shared decision process, will the patient be advised that there are other doacs which are once daily options? Idarucizumab (praxbind) is a specific reversal agent for dabigatran and is indicated in adult patients where rapid reversal of anticoagulation is required (life threatening bleeding/emergency surgery, etc).We are aware of the current consultation for Adexanet Alpha and have commented as stakeholders. Within the rationale and impact section on stroke prevention, we cannot see any reference to reversal agents and would ask whether this was given consideration by the committee during the consultation process and whether in the AF landscape, this will now have a significant impact on clinicians directing patients to dabigatran to reassure patients that this is an added benefit when presenting all the treatments currently licensed for this indication?	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and we now refer to any licensed DOAC. We cross refer to the NICE guideline on adherence and shared decision making in recommendation 1.6.2. Drug formulation and co-morbidities should be considered in the context of shared decision making when deciding on anticoagulation treatment. The committee were aware of the reversal agents when making their decision and this would be considered when discussing the choice of DOAC in the context of shared decision making (recommendation 1.6.2). The use of reversal agents was not central to the committee's decision and is discussed in the evidence report G1.

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SH	Anticoagulation UK	Guideline	009	023 - 028	'If apixaban or dabigatran are not tolerated in people with AF - offer edoxaban or rivaroxaban' Whilst options to switch may be available if patients experience side effects, patients should be informed from initiation of doac treatment ***of all the options*** and be made aware that there are other treatments available and advised **specifically why** they are being prescribed a preferred treatment. This needs to be transparent at all time especially as this appears to be cost specific.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and we now recommend any licensed DOAC. The recommendation on switching to edoxaban or rivaroxaban has been deleted as it is no longer applicable. When deciding on what DOACs to offer the health professional and person should decide in the context of shared decision making (recommendation 1.6.2).
SH	Anticoagulation UK	Guideline	009	029 - 031	This should directly link to the paragraph on self – monitoring an self – management of VKA (page 12 line 1- 4) for completeness and transparency for clinicians and patients who may have a preference for VKA due to the monitoring regime, reversal agent and once a day dosage.	Thank you for your comment. We have made the edit suggested.
SH	Anticoagulation UK	Guideline	010	001 - 004	***We are very concerned*** on the impact of this recommendation on patients who are 'stable'. If a shared decision making process was in place when the patient was initiated on either warfarin or doac, how will the managing clinician make a case for introducing the switching option? ' Stability' is key here, if an individual feels that their current anticoagulation is effective, safe and causing no harm or issues, ***why would and should they then have to be switched for cost effective purposes – this is inequitable.*** Warfarin patients who have good TTR levels and are used to the monitoring regime may welcome a doac with limited monitoring, dietary and drug interactions. They may also question why they were initiated on warfarin in the first instance if the doacs have been available for several years to treat their AF? For the warfarin patients who have not enjoyed 65% TTR, we hope will have already been switched due to the current COVID 19 restrictions and the anticoagulation guidelines produced during this period… https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0077-Specialty-guide_Anticoagulant-services-and-coronavirus-v1-31-March.pdf The onus on getting patients to switch will fall in the main to GPs to undertake these discussions. We can envisage many problems ahead if switching becomes a directive. Some patients may challenge and be curious as to why they need to switch; our concerns lie with the more vulnerable patients who may comply without the fullness of understanding the rationale based around the decision being imposed by NHS.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation (1.6.6) and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.
SH	Anticoagulation UK	Guideline	012	001	This is a reference only – please expand to say that this is an option for individuals on long term warfarin therapy and to discuss with their managing clinician.NICE Guideline DG 14 is	Thank you for your comment. The recommendations on self-monitoring were not part of this update and therefore cannot be edited.

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					current and during COVID 19, many warfarin patients have benefitted from access to self – monitoring as directed by their managing clinician in certain circumstances. Reference guidelines https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0077-Specialty-guide_Anticoagulant-services-and-coronavirus-v1-31-March.pdf ACUK is a stakeholder for the current NICE Guideline in development around Covid19/ thromboembolism guideline which is due for publication shortly.	However, recommendation 1.6.5 hyperlinks to the recommendations on self-monitoring and self-management.
SH	Anticoagulation UK	Guideline	028	022 - 029	We note 'Clinically most effective option Apixaban followed by rivaroxaban and dabigatran' Costs knocked out rivaroxaban – this should not be the only factor in the decision process. .	Thank you for your comment. The rationale and impact has been edited to reflect the changes in the recommendations. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.
SH	Anticoagulation UK	Guideline	029	001 - 006	Description as to the effectiveness of apixaban and dabigatran presented without any reference to the benefits of rivaroxaban and edoxaban as comparators. For a lay person reading this document who may be on rivaroaban or edoxaban, this could be a cause for concern and anxiety as it potentially throws up that rivaroxaban and edoxaban are inferior treatments… If you are describing the evidence based outcomes for use here, these should also be referenced in section 1.6 for completeness and transparency.	Thank you for your comment. The recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC and the rationale and impact has been edited.
SH	Anticoagulation UK	Guideline	029	012 - 015	Agree – information and education key however, the delivery and consultation process between clinician and patient needs to be recorded to ensure patients/carers are fully engaged in the decision around their AC therapy. This should just be a tick box exercise **Standardised NHS information is needed to ensure that all patients receive accurate and current information which is reviewed annually or if further guidance is recommended.**	Thank you for your comment. We now refer to shared decision making when choosing anticoagulant treatment (see recommendation 1.6.2).
SH	Arrhythmia Alliance	Guideline	009	011 - 017	We do not accept that only apixaban or dabigatran should be offered to people with AF and a CHA2DS2-VASc score of 2 or above. All approved anticoagulants should be reviewed and assessed as to which is most suited for the individual. An informed decision should be made between the healthcare professional and the patient. The two DOACs being recommended are both twice daily dosed drugs – for many patients this will reduce adherence as they may be on a multitude of medication for other co-morbidities and remembering to take a second tablet is likely to reduce adherence. It is particularly difficult for many patient to take drugs on a 12 hourly cycle because if they take the medicine on getting up they must take the second tablet and about 7.00 in the evening. If they take the drug on going to bed they must take the	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. We now cross refer (recommendation 1.6.2) to the guidance on shared decision making in the NICE guideline on patient experience in adult NHS services. In the context of shared decision making factors such as dose frequency should be taken into account. The rationale and impact and

					second tablet at about 10.00 in the morning. This is very difficult for ambulant patients to deal with this because they do not always have the drugs with them and older patients may not have sufficient health care support to ensure that they take the twice daily medication reliably. Dabigatran does not fit into the dosset boxes and for some this will also create a barrier to adherence and many patient with AF are elderly and struggle to remember to administer their mediation or open the pill boxes hence the need for dosset boxes and therefore this DOAC may be forgotten or overlooked. Dabigatran produces nasty gastrointestinal side effects in many patients and they quickly stop taking the drug. NICE has previously recommended all four DOACs against clinical evidence and it does not make sense to now only recommend two specific DOACs. During the pandemic many AF patients were switched to DOACs from warfarin as anticoagulation clinics closed and it was more difficult for patients to undertake regular INR testing. This caused anxiety and stress and the charity saw a three-fold increase to its helpline from worried, anxious, confused patients. If they are once again told to change anticoagulation as this guidance recommends it will cause even more mental illness and anxiety and many patients will lose faith and confidence in their healthcare professional. A survey undertaken by Arrhythmia Alliance and AF Association, for which 357 people with AF responded, showed that less than 7.6% are prescribed dabigatran so a huge number of patients, if this guidance is approved, will be changed to a drug that is not commonly use. 41% of those responding stated that twice daily medication would affect their ability to take the medicines as prescribed and that for some the 12 hour time between one dose and the next would be impossible to adhere to. They pointed out that elderly people sleep late and go to bed early therefore if they administered the drug at midday they would miss the next dose due at midnight as they would be sleeping. This could lead to under-dosing if medication is missed or patient mis-understands. Ultimately this recommendation of switching anticoagulation therapy will lead to more (not fewer) AF-related strokes, killing or severely disabling people with AF and increasing costs to the over-burden NHS unnecessarily. Newly diagnosed people with AF could be considered for the two DOACs proposed in this guidance ONLY if they have been offered the full choice of drugs available and clearly understand the difference between the drugs and the frequency of dosage. This recommendation places huge restriction on patient choice and adherence and must be reviewed.	committee's discussion of the evidence in evidence review G1 have been edited and now refer to adherence and dosing frequency.
SH	Arrhythmia Alliance	Guideline	009	029	Some patients are unable to tolerate any oral anticoagulant and therefore LAAO should also be included as a last resort if they are unable to take DOACs or vitamin K antagonist.	Thank you for your comment. Recommendation 1.6.19 recommends LAAO if anticoagulation is contraindicated or not tolerated.
SH	Arrhythmia Alliance	Guideline	010	001	People with AF who are currently anticoagulated and stable and have been for more than five year will, if this guidance is approved, have to switch to a different anticoagulant which will cause unnecessary worry and anxiety when society is already suffering with massive mental	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching

					health issues during the Covid-19 crisis. This will also increase the workload of healthcare professionals and increased appointments and visits by patients to discuss and review with their healthcare professional. All this during a pandemic and when the NHS is at crisis dealing with a backlog of appointments, cancelled clinics and cancelled/postponed operations. These recommendations seem unnecessary, costly and above all detrimental to the person with AF.	between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.
SH	Arrhythmia Alliance	Guideline	016	023	With less than 8% of ablation procedures being undertaken using laser ablation we do not understand why NICE would recommend laser above cryoablation. Over 92% of centres regularly use cryoablation according to a survey Arrhythmia Alliance & AF Association undertook with healthcare professionals providing ablation for AF. ESC guidelines recently published recommend cryoablation. Cryoablation is often quicker and undertaken as a day case therefore reducing costs for the NHS and time spent in hospital for patients. Ablation was one of the first procedures to be cancelled during the first lockdown of the Covid-19 pandemic. Centres are only now beginning to reopen and catch up with the back-log of cases. Evidence demonstrates that the earlier ablation is performed on an AF patient the greater the success and outcomes; therefore it is important that procedures are not delayed further. If laser ablation is recommended in this guidance centres will be further delayed due to lack of equipment and the cost to Trusts in purchasing new equipment plus delay in treatment for patients will lead to detrimental outcomes for patients and their quality of life. Cryoablation could contribute towards the covid recovery treatment as patients can be seen, treated and discharged far quicker and with greater success. We urge NICE to review and amend this recommendation as it will be more costly, delay access to treatment and most importantly patient choice and quality of life for patients will be denied due to this decision. Arrhythmia Alliance recommends laser ablation being changed to cryoablation or ablation in general to provide choice. Patient choice & Patient access should be paramount throughout the guidance.	Thank you for your comment. The evidence based on all relevant studies showed that radiofrequency point by point ablation was more cost effective over a lifetime than antiarrhythmic drug treatment and other ablation strategies in people for whom 1 or more antiarrhythmic drug has failed. Our de novo model demonstrated that the greater costs of cryoballoon made it less cost-effective in our model. A threshold analysis was conducted where we explored the costs of cryoballoon. The threshold analysis for cryoballoon indicated a reduction of £2,913 in the procedure costs is required for it to become cost effective. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge, this equated to £1,289 in savings which is not enough for cryoballoon to become more cost effective than RFPP. Nevertheless, recommendations 1.7.19 and 1.7.20 have been amended to reflect the fact that RF point by point may not always be possible. 1.7.20 now recommends cryoballoon or laser ablation in

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						people who are assessed as unsuitable for radio frequency point-by-point ablation.
SH	Arrhythmia Alliance	Guideline	017	021	Inclusion of lifestyle changes to prevent and/or improve outcomes for people with AF should be emphasised in this guidance – especially addressing obesity – however this should not lead to patients not being allowed access to treatment for AF.	Thank you for your comment. Lifestyle changes were outside of the scope of this update.
SH	Arrhythmia Alliance	Guideline	General	General	Arrhythmia Alliance would be unable to support NICE guidance for AF Management in its current form and with certain recommendations. In summary the current suggestions deny patient access and patient choice of anticoagulation drugs to reduce their risk of AF-related stroke which are known to be more debilitating, more disabling and often prove more fatal than any other type of stroke. This current guidance also denies a person with AF to access treatments previously approved and recommended by NICE with proven positive outcomes. The patient engagement and joint decision-making is being removed; patient outcomes will be affected and adherence to medication will be reduced; successful treatment will be denied and therefore the patient will ultimately suffer and pay the price for incorrect recommendations.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.
SH	Arrhythmia Alliance	Guideline	General	General	Arrhythmia Alliance welcomes this new updated AF guidance however have noted many recommendations which will reduce or remove patient choice, patient access and patient-informed decision making as well as access to all available therapies and treatments. Recommendations previously recommended by NICE have been removed and with it denies access to approved medications which will restrict patient choice.	Thank you for your comment. The recommendations were developed in accordance with NICE methods https://www.nice.org.uk/process/pmg20/resources. The most clinically and cost effective test and interventions have been recommended. We have promoted patient choice and shared decision making throughout the guidelines (for example see recommendations 1.4.2, 1.6.1 and 1.6.2).
SH	Atrial Fibrillation Association	Guideline	009	011 - 017	This recommendation is against previous NICE recommendations for the use of the four DOACs and removes patient choice and informed patient decision making. AF Assoc is unable to accept that only apixaban and dabigatran should be made available for AF patients with a CHAD2DS2-VASc score of 2 or above. A decision based on what is best for the individual and in discussion with their healthcare professional should include all approved anticoagulants. Apixaban and Dabigatran are both twice daily dosed drugs and should be taken at 12-hour intervals. For many patients (as supported by a survey AF Assoc & Arrhythmia Alliance undertook with AF patients) this will lead to adherence issues. 41% of the 357 respondents said that twice daily medication would impact on their ability to adhere as prescribed. Less than 7.6% were currently prescribed dabigatran Many are already on a cocktail of drugs due to other co-morbidities and many use dosset boxes for their pills for ease and to ensure they adhere to instructions of dosage. Dabigatran does not fit into a dosset box so immediately	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. We now cross refer (recommendation 1.6.2) to the guidance on shared decision making in the NICE guideline on patient experience in adult NHS services. In the context of shared decision making factors such as dose frequency should be taken into account. The rationale and impact and committee's discussion of the evidence in evidence review G1 have been edited and now refer to adherence and dosing frequency. Recommendation 1.6.5 refers to when a vitamin K antagonist should be offered. We have edited recommendation 1.6.6 and recommend that

					there is an issue. Many elderly AF patients are unable to open pill bottles with safety caps (hence use of dosset box) – another restriction for the twice daily dose. The twice daily interval must be 12 hours apart. If someone take their medication at 11am they have to wait until 11pm to take the second dose. Many elderly rise late and go to bed early – yet another barrier to adherence. This is also very difficult for those who may travel or move around as they may not always have the second dose with them. Elderly patient may be lacking carers to support and remind them to take an extra tablet. Most home carers put elderly to bed and leave – it would be costly and for many not possible to have a carer stay late to ensure they take the second dose. Many elderly simply forget to take their medication and the dosset box acts as a reminder as to whether they have or have not taken prescribed dose. There are many unpleasant side-effects with Dabigatran therefore many who are prescribed this often quickly stop taking the drug. In essence recommending Dabigatran and Apixaban is cutting the choice to only Apixaban since patients (and doctors) dislike Dabigatran. Previously NICE recommended all four DOACs so we are unsure as to why, in this guidance, it would not only recommend two specific drugs. Surely it is a share-decision between the healthcare professional and the patient themselves. The Covid-19 pandemic has seen many AF patients have the anticoagulation therapy changed from warfarin to a DOAC as anticoagulation clinics we cancelled/closed or postponed and unable to offer INR testing for those prescribed warfarin. In fact it was recommended for patients to be switched from warfarin to a DOAC to relieve some pressure on the over-burden NHS. This led to anxiety, stress and an overwhelming demand for our services as worried patients and carers made contact seeking clarification. Many who tolerate warfarin well and for many years were concerned as they would not know if the 'new' drug was working due to lack of blood tests. We provided support, information and education to allay their concerns. If these same patients are told their medication must be changed again due to new NICE guidance it will do untold damage to their mental well-being and anxiety levels will once again be heightened. The person will lose faith in their doctor (some already questioned this when told to stop taking warfarin). For many this may lead to lack of adherence, mental health issues and loss of trust and confidence in the healthcare professional. The current recommendation must be amended, changing the prescribed anticoagulant therapy will lead to more AF-related strokes and AF-related stroke are more disabling, more devastating and in many case prove fatal, far more than any other type of stroke. Recommending only two DOACs will not be cost-saving as increase in more AF-related strokes will actually cost the NHS more in treatment and long-term care for those that survive	a person should stay on their current medication until the option of switching can be discussed at the next routine appointment taking into account time in therapeutic range.

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					an AF-related stroke. It is completely unnecessary to cause this increase cost on the NHS especially during a time when the NHS is already overwhelmed with Covid-19 cases and demand on services. AF Assoc recommends that patients are offered the range of anticoagulation therapies available and in discussion with their healthcare professional an individualised, informed decision is made that best suits the person with AF. Informed decision making and package of care is should be paramount. Patient choice and adherence is vital to ensure the patient safety and understanding of why they are being asked to take a medication.	
SH	Atrial Fibrillation Association	Guideline	009	029	For people unable to tolerate any oral anticoagulant left atrial appendix occlusion (LAAO) should be considered and added to this point.	Thank you for your comment. Recommendation 1.6.19 recommends LAAO if anticoagulation is contraindicated or not tolerated.
SH	Atrial Fibrillation Association	Guideline	010	001	The recommendation in this section that anyone who has been stable on an anticoagulant for more than five years should still have to switch to one of the two DOACs being recommended in this guidance. This concerns the AF Assoc. Why switch someone who is stable and adhering to a twice daily drug that may not be adhered to, may introduce new side effects and will cause unnecessary anxiety, stress and worry. Society is already experiencing the highest levels of mental health issues due to lockdown and the Covid-19 pandemic, this will cause an added worry and once again removes patient choice and patient informed decision making. Added work, more appointments and additional costs to the NHS as healthcare professional will need to see their patients to review their current medication and therefore expose patients to a greater risk of contracting Covid-19 when it is unnecessary for both the patient and the healthcare professional. AF Assoc believes this recommendation is not required and will be detrimental to the health and well-being of the AF patient. It could even lead to unnecessary AF-related strokes if the patient is not suited or does not adhere to the new anticoagulant.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. We therefore no longer recommend switching people on edoxaban or rivaroxaban. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend (1.6.6) that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.
SH	Atrial Fibrillation Association	Guideline	016	023	AF Assoc (in conjunction with Arrhythmia Alliance) carried out a survey of healthcare professionals who routinely perform ablation procedures for AF. Cryoablation is used in over 92% of centres so the recommendation that laser ablation be the first choice for AF ablation treatment would again remove patient choice, patient informed decision making and be detrimental to the patient accessing ablation treatment. It would also mean that many centres would not have the equipment to perform laser ablation so patients would be denied treatment and this would be detrimental to the outcomes for patients. Centres would also need to invest in new equipment at a huge cost to the NHS and delay in treatment to patients – all very unnecessary.	Thank you for your comment. Recommendations 1.7.19 and 1.7.20 have been amended. 1.7.20 recommends cryoballoon or laser ablation in people who are assessed as unsuitable for radio frequency point-by-point ablation. The evidence showed that radiofrequency point by point ablation was more cost effective over a lifetime than antiarrhythmic drug treatment and other ablation

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					Recently published European Society of Cardiology (ESC) recently published their updated AF Guidelines. These guidelines are recognised international and across Europe – they recommend cryoablation which is quicker, often as a day case, reducing time and costs to the NHS plus reduce exposure to viruses in hospital and anxiety for the patient. The sooner a patient can be ablated post diagnosis of AF the greater their chance of success for treating the AF. Therefore with cancellations and delays of ablation procedures due to the Covid-19 pandemic it is vitally important there are no further delays for patients accessing ablation treatments. Cryoablation will contribute towards the recovery of the NHS post-Covid-19 as patients can be seen, treated and discharged far quicker, less or at equal cost to laser and with greater success. Therefore improved outcomes for people with AF. AF Association strongly recommends that this guidance be amended to cryoablation or not to be so specific and just recommend ablation for AF and let healthcare professionals and patients have the choice and make informed decisions to improve outcomes for people with AF. Quality of life is essential for AF patients, many of whom feel lethargic, thumping in their chest, breathless and high anxiety. They are often unable to work or walk, some become housebound. There a previously recommended treatment with excellent results should not be denied to those that need them most – the AF patient.	strategies in people for whom 1 or more antiarrhythmic drug has failed.
SH	Atrial Fibrillation Association	Guideline	017	021	NICE should ensure that people with AF are aware of potential lifestyle changes that could lead to improved outcomes. AF Assoc feels this has not been emphasised enough in this guidance. However patients should not be penalised if they are overweight or struggle with lifestyle changes – they should still be considered where appropriate for treatments and an informed discussion between the healthcare professional and the patient, leading to a joint decision, ensuring the patient is included and informed at every stage.	Thank you for your comment. Lifestyle changes were outside of the scope of this update.
SH	Atrial Fibrillation Association	Guideline	General	General	The new updated AF guidance is very much welcomed by the **Atrial Fibrillation Association** (AF Assoc) however we have listed below our concerns and recommendations to ensure the patient is at the forefront of any proposed change to their access to anticoagulation therapy or treatment options. In its current format patient choice has been removed on many occasion and patient access to previously approved therapies and treatments. It is of great concern to AF Assoc that this will have a detrimental impact on people with AF. The patient will not be able to make an informed decision as to how best live with and manage AF as many options are being denied them according to the proposed guidance.	Thank you for your comment. The recommendations were developed in accordance with NICE methods https://www.nice.org.uk/process/pmg20/resources. The most clinically and cost effective management options have been recommended by the committee. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. We refer to shared decision making when discussing anticoagulant treatment (recommendation 1.6.2).

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SH	Atrial Fibrillation Association	Guideline	General	General	AF Association is unable to support NICE guidance for AF Management with the current recommendations. Patient Choice, Patient Access, Patient decision making and Personalised Package of Care are al being denied to the patient with some of these recommendations. Reducing patient choice of anticoagulation therapy; increasing the risk of an AF-related stroke by denying them access or changing successful therapy; denying access to successful and previously recommended by NICE treatments such as cryoablation. Patient Choice, Patient Access, Patient Engagement and joint decision-making is being removed; therefore the patient will ultimately suffer due to incorrect recommendations.	Thank you for your comment. A personalised package of care is recommended in recommendation 1.4.1. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. We refer to shared decision making when discussing anticoagulant treatment (recommendation 1.6.2. Patient preference is also referred to in recommendation 1.6.1). Radiofrequency point-by-point ablation was the most cost-effective ablation technique in the economic model. Cryoablation is now recommended if radiofrequency point-by-point ablation is not suitable (1.7.20).
R (TBC)	Bayer PLC	Guideline	009	029-031	Bayer welcome the displacement of vitamin K antagonists (VKAs) for appropriate patients needing an anticoagulant for stroke prevention in atrial fibrillation. The well-known limitations of VKA prescribing, monitoring and management have been further highlighted during the ongoing COVD-19 pandemic, with national guidance issued earlier in 2020, to review the management of patients taking warfarin (1-3). (1) Clinical guide for the management of anticoagulant services during the coronavirus pandemic. NHS England and NHS Improvement. March 2020. Publications approval reference: 001559 (2) NHS. Specialist Pharmacy Service. Management of patients currently on warfarin during Covid-19. April 2020, updated September 2020. https://www.sps.nhs.uk/articles/management-of-patients-currently-on-warfarin-during-covid-19/ (3) RPSGB. Guidance for the safe switching of warfarin to direct oral anticoagulants (DOACs) for patients with non-valvular AF and venous thromboembolism (DVT / PE) during the coronavirus pandemic. March 2020. https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Coronavirus/FINAL%20Guidance%20on%20safe%20switching%20of%20warfarin%20to%20DOAC%20COVID-19%20Mar%202020.pdf?ver=2020-03-26-180945-627	Thank you for your comment.
R (TBC)	Bayer PLC	Guideline	010	001-004	Bayer are concerned by the recommendation in 'clause' 1.6.7 and the potential for inadvertent harm.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that

					Encouraging switching when the patient is already stable on a medication that is recognised as being a clinically and cost-effective treatment option is inappropriate and has the potential for negative consequences. It is of interest that the guideline committee in developing NG158 (1) noted that *"there are risks involved in switching anticoagulant treatment, particularly if there have been no adverse events with the current treatment"……"the first option for most people should be to continue the current treatment if it is well tolerated".* As such, this would indicate there is inconsistency in approach between different NICE guideline committees. A recent systematic review (2) found that non-medical switching (NMS) was commonly associated with negative or neutral endpoints and was seldom associated with positive ones. Non-medical switching was associated with a negative impact on clinical, economic, health-care utilisation and medication-taking behaviour outcomes in 26.9%, 41.7%, 30.3% and 75.0% of cases, respectively. Switching of treatment is a resource-intensive intervention as patients need to be identified, evaluated for their suitability for the proposed treatment, considering co-morbidities and concurrent medications. This will then require a consultation with the patient to discuss the proposed change and any subsequent monitoring. Importantly, dose reduction considerations between the DOACs vary with the potential for dosing errors. Careful consideration should be given to patient preference and any impact on adherence and therefore outcomes. Poor adherence to DOACs is linked with high stroke rates, particularly in those with a CHA2DS2-VASc score ≥2 (3). Switching may also undermine the confidence in the doctor-patient relationship relating to their prescribed medication, and for those who may be taking the 'switched' medication for other indications. Considering the 2020 NHS advice to review patients treated with warfarin during the ongoing COVID-19 pandemic (4,5,6), many patients will have been switched from warfarin to a DOAC. Switching to another DOAC within such a short period of time could also undermine the doctor-patient relationship and would be a waste of valuable NHS resource and has the potential for causing confusion. Indeed, the MHRA has recently issued advice after it became aware of a small number of patients in whom warfarin treatment was continued after starting treatment with DOACs (7). The recently published document by the NHS Confederation sets out the resource challenges and pressures ahead for the NHS in an era peri- and post-COVID 19 (8). The pandemic's	DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend (1.6.6) that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.

					impact on the capacity in the NHS is being felt and is likely to be felt for several years leading to a back-log of patients needing care as well as new demands on services. Switching 'programmes' would unnecessarily add to this pressure. Considering the increased use of virtual consultations and the importance of patient self-management during the COVID-19 pandemic, patient choice alongside physician preference has never been more important in supporting adherence and persistence. Further to this, there are still many patients currently on the AF register who either haven't been risk assessed, or have been risk assessed as high risk, but are currently not being anticoagulated. Using data from the Quality and Outcomes Framework (NHS digital) and the National Cardiovascular Intelligence Network, Bayer estimate there could be approximately 280,000 patients with undiagnosed AF in England, 143,000 patients who have been risk assessed as having a CHA2DS2-VASc score ≥2 not treated with an oral anticoagulant, and a further 27,000 AF patients who have not been risk assessed. Bayer contend that any efforts to review anticoagulant treatment for patients with AF should focus on these patients who are not optimally treated, rather than switching patients who are stable. Switching based on this guideline, considering that the committee have not evaluated the full body of evidence and could have come to different conclusions if they had, and that **the guideline recommendations are based on NHS list prices instead of the actual cost to the NHS**, could have significant cost implications leading to a waste of valuable NHS resources. Bayer contends that the committee have not evaluated the full body of evidence and, if they had, as well as considering the true drug acquisition costs to the NHS, could have come to different conclusions. Bayer advocates the removal of sections 1.6.3, 1.6.4, 1.6.5 and 1.6.7 from the draft guideline. (1) NICE. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. NG158. March 2020. https://www.nice.org.uk/guidance/ng158/chapter/rationale-and-impact#long-term-anticoagulation-for-secondary-prevention-2 (2) Weeda et al. The impact of non-medical switching among ambulatory patients: an updated systematic literature review. Journal of Market Access & Health Policy 2019, VOL. 7, 1678563	

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					(3) Yao X, et al. Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation. J Am Heart Assoc 2016 Feb 23;5(2):e003074 (4) Clinical guide for the management of anticoagulant services during the coronavirus pandemic. NHS England and NHS Improvement. March 2020. Publications approval reference: 001559 (5) NHS. Specialist Pharmacy Service. Management of patients currently on warfarin during Covid-19. April 2020, updated September 2020. https://www.sps.nhs.uk/articles/management-of-patients-currently-on-warfarin-during-covid-19/ (6) RPSGB. Guidance for the safe switching of warfarin to direct oral anticoagulants (DOACs) for patients with non-valvular AF and venous thromboembolism (DVT / PE) during the coronavirus pandemic. March 2020. https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Coronavirus/FINAL%20Guidance%20on%20safe%20switching%20of%20warfarin%20to%20DOAC%20COVID-19%20Mar%202020.pdf?ver=2020-03-26-180945-627 (7) MHRA. October 2020. Warfarin and other anticoagulants – monitoring of patients during the COVID-19 pandemic. https://www.gov.uk/government/publications/warfarin-and-other-anticoagulants-monitoring-of-patients-during-the-covid-19-pandemic (8) NHS Confederation. NHS Reset: A New Direction for Health and Care. September 2020. https://www.nhsconfed.org/-/media/Confederation/Files/Publications/Documents/NHS-Reset-a-new-direction-for-health-and-care.pdf	
R (TBC)	Bayer PLC	Guideline	General	General	Bayer contest in the strongest possible terms the use of the DOAC NHS list prices to inform decision making. This is not only inappropriate given the existing commercial arrangements in place, but also reduces the credibility of the draft NICE guidelines and is misleading. It is insufficient simply to add a box stating "***The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct-acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance***", whilst making recommendations based on list prices that are not applicable to the target audience for the guideline. Making such recommendations will cause confusion, potentially inappropriate decision making and waste valuable NHS resource. Use of NHS list prices to inform decision making also undermines any arrangements that NHS England may come to with individual pharmaceutical companies.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.

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					At the current time, there are hospitals and we estimate about of CCGs paying the NHS list price for rivaroxaban (Xarelto). Bayer are aware that there are additional commercial arrangements with other DOACs. Had the guideline committee considered the actual pricing offered to the NHS, the committee may have come to different conclusions. Indeed, the recommendations on cost-effectiveness and DOAC ranking may not apply at local levels in the NHS leading to confusion, potentially flawed decision-making and waste of valuable NHS resources. Evidence review 6, page 190 states that *"there is a high degree of uncertainty around the costs for all treatments*". This, taken together with the use of NHS list prices (which even when considering only one DOAC, rivaroxaban, is incorrect for ~ of CCGs), confirms that the guideline committee is making recommendations on not only an incomplete review of the evidence base, but also on a cost base that is flawed. As commercial arrangements vary now and over time, Bayer consider that all DOACs should be recommended as per recommendation 1.6.2 with no preference.	
SH	Boehringer Ingelheim	Guideline	009	011-022	Boehringer Ingelheim support NICE's recommendations to offer anticoagulation with either apixaban or dabigatran to people with atrial fibrillation and a CHA_2DS_2-VASc score of 2 or above, taking into account the risk of bleeding; and to consider anticoagulation with either apixaban or dabigatran for men with atrial fibrillation and a CHA_2DS_2-VASc score of 1, taking into account the risk of bleeding. When using warfarin as the common comparator, dabigatran 150mg bd had the lowest odds for stroke/systemic embolism of all the DOACs, was the only DOAC to demonstrate a statistically significant benefit for ischaemic stroke, and had the lowest odds for intracranial bleeding, which are the events with the highest acute costs to the NHS. The safety and efficacy profile of dabigatran has been confirmed by multiple independent studies utilising real world evidence. Comparative real world studies have also shown dabigatran to have a superior risk-benefit ratio to rivaroxaban, particularly in terms of risk of major bleeding (Graham DJ, et al. JAMA Int Med 2016;176:1662-71. Graham DJ, et al. Am J Med 2019;132:596-604. Bai Y, et al. Stroke 2017;48:970-6). Dabigatran is the only DOAC with two well-characterised doses compared to warfarin. The safety profile of the dabigatran 110mg bd dosing regimen in non-valvular atrial fibrillation is also consistent between the randomised controlled trial and real world evidence.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. The availability of a reversal agent should be discussed with the patient

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					The availability of immediate and sustained reversal should be considered when discussing choice of anticoagulation in patients with non-valvular atrial fibrillation. Dabigatran has a specific reversal agent (idarucizumab) licensed for use in both emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding. Idarucizumab is widely available and is included on the UK National Antidote List of antidotes to be available within one hour to all Emergency Departments (i.e within the hospital) (Royal College of Emergency Medicine and National Poisons Information Service. Guideline on Antidote Availability for Emergency Departments. January 2017). The specific reversal agent for apixaban and rivaroxaban (andexanet alfa) is not currently reimbursed on the NHS, and is only licensed for life-threatening or uncontrolled bleeding. Additionally, the cost of reversal with the dabigatran-specific reversal agent (idarucizumab) is significantly lower than the specific reversal agent for apixaban and rivaroxaban (andexanet alfa) (£2,400 per patient versus an average of £15,000 per patient, based on NHS list price). There is currently no specific reversal agent licensed for edoxaban. Dabigatran also offers the lowest daily cost of the DOACs, based on NHS list price (current NHS list price is £51.00 per 60 tablets [30 days treatment per pack], equivalent to £1.70 per day).	as part of shared decision making (see recommendation 1.6.2).
SH	Boehringer Ingelheim	Guideline	010	009-010	We support NICE's recommendation not to withhold anticoagulation solely because of a person's age or their risk of falls.	Thank you for your comment.
SH	Boehringer Ingelheim	Guideline	028	026-028	We believe the following statement 'apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran' has the potential to be misleading, as is not consistent with the conclusions of the evidence review G1 which states 'the network meta-analysis evidence was clear that apixaban and dabigatran were superior to the other DOACs'. We would also like to highlight that when using warfarin as the common comparator, dabigatran 150mg had the lowest odds for stroke/systemic embolism of all the DOACs, was the only DOAC to demonstrate a statistically significant benefit for ischaemic stroke, and had the lowest odds for intracranial bleeding.	Thank you for your comment. The recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC and the rationale and impact has been edited.
SH	Boehringer Ingelheim	Guideline	028-029	029 - 002	We have concerns regarding the inclusion of the statement that apixaban has lower rates of clinically relevant non-major bleeding when compared with dabigatran, as dabigatran was not included in the comparison of clinically relevant non-major bleeding (Table 23) of the Evidence Review G1.	Thank you for your comment. The recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC and the rationale and impact has been edited.

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					The comparison for this endpoint in the Lopez-Lopez network meta-analysis uses data from three large phase III trials for apixaban (ARISTOTLE), rivaroxaban (ROCKET AF) and edoxaban (ENGAGE AF-TIMI 48) together with two very small phase II trials for dabigatran (AF-DABIG-VKA-JAPAN and PETRO). The dabigatran phase III trial (RE-LY) did not report clinically relevant bleeding as an outcome measure and was therefore not included for this endpoint. In addition, the trials included for dabigatran (AF-DABIG-VKA-JAPAN and PETRO, 14 and 36 events, respectively), included unlicensed dabigatran doses. In PETRO, patients were randomized to dabigatran 50mg, 150mg, or 300mg twice daily either alone or combined with 81mg or 325mg aspirin once daily; over half of the clinically relevant bleeding events for dabigatran from this study occurred in patients receiving 300mg twice daily (with or without aspirin) (17 of 32 events). In AF-DABIG-VKA-JAPAN, the majority of major and clinically relevant bleeding events occurred in patients receiving concomitant aspirin. This biases the analysis for this endpoint against dabigatran. We propose that this statement is amended to: Indirect evidence from randomised controlled trials suggests that apixaban has lower rates of gastrointestinal bleeding, major bleeding, and myocardial infarction when compared with dabigatran.	
SH	Boehringer Ingelheim	Guideline	General	General	Boehringer Ingelheim welcome the invitation to respond to this NICE NG180 guideline update consultation.	Thank you for your comment.
SH	Boston Scientific	Guideline	016	023-029	We ask the committee to re-consider its endorsement of only laser and RF point by point ablation therapy made in recommendation 1.7.19. Currently the document acknowledges the continued need for cryoballoon ablation but only highlights this in the practice impact statement; '*…this does not mean that other techniques such as cryoballoon are prohibited. Furthermore, if a person's preferences include factors such as avoiding general anaesthetic, cryoballoon may be the ablation technique of choice.'* The committee makes no distinction between technologies and techniques. Thus, technologies such as the cryoballoon and laser balloon are intended only for pulmonary venous isolation and indeed it is impossible to use the laser balloon for anything else. RF technologies are designed to also address modification of atrial fibrillation substate and have greater applicability to AF ablation as opposed to pulmonary venous isolation. As a single shot technology, cryoballoon has been in clinical use for more than a decade and is well established as an efficient and safe technology for achieving pulmonary venous isolation. Currently we estimate less than <1% of PVI ablation cases are performed with laser	Thank you for your comments. Following stakeholder consultation some omissions were identified, new data provided, and issues raised that led to amends to the economic model. These included: -Edits to some of the equipment costs further to stakeholder comments -30% uplift for laser equipment costs from local source used as the base case rather than sensitivity analysis - Reduction in cardiac tamponade risk for cryoballoon (from 1% to 0.4%) -Addition of persistent Phrenic Nerve Palsy risk for laser (1% as with cryoballoon) - Sensitivity analysis on procedural costs for catheter ablation where 'elective' case HRG cost used for RFPP, 'day case' cost used for

					balloon, whilst cryoballoon ablation is performed in approximately 40% of procedures. The laser balloon has achieved very little clinical uptake despite being in the market for some years and this reflects established clinical and patient preferences based on user experience of the technologies. We are surprised that the committee chose to base its decisions on very limited anecdotal cost effectiveness data for the laser balloon and without an understanding of the broader atrial fibrillation field. We believe a more balanced endorsement (in recommendation 1.7.19) of all three therapy options, consistent with the previous guidance, would better reflect current clinical practice both in the UK and globally, ensure limited impact on service delivery and minimise patient risk. The following is presented as rationale for this suggestion. 1. We would encourage the committee to assess the NICOR data at their disposal to confirm current clinical use patterns this and which highlights the danger to what is established clinical practice that may result from this current recommendation. Similarly, we would encourage the committee to consult with the UK's relevant stakeholders such as BHRS and the Arrhythmia Alliance which have leading specialists who are well placed to advise the committee on the flaws in its current evaluations. 2. Ablation activity during the COVID-19 pandemic was significantly impacted (92% decrease in activity)[1] and added to existing waiting list challenges. Cyroablation has operational benefits that are currently not captured in the guidance which may adversely impact service delivery and a hospitals ability to meet this elevated demand if its use in clinical practice declined. Namely; quicker procedure time in cyroballoon therapy vs RF is well documented. Chen et al. (2017) for example, conducted a meta-analysis comparing cyro and RF ablation and reported a 28min reduction (WMD) in pooled cyro data vs pooled RF data[3]. 3. Current guidance is not aligned to elements of the draft NHS commissioning document. In particular, the patient information document provides information to the patient he/she will receive Cyro or RF ablation. We ask the committee to consider if they wish two different National bodies to explicitly endorse 2 different therapies. This further highlights our earlier point that Cyro is an established option in UK practice and we believe	cryoballoon and 'total HRG' used for all other catheter ablation. -Threshold analysis to see what reduction in procedure cost is needed for cryoballoon to become most cost effective. This saving was then compared narratively to savings associated with not having general anaesthesia, savings in staff costs from shorter procedure duration and savings from same day discharge. The latter two sensitivity analyses were considered extreme scenarios as the committee noted that laser and RFPP may also be associated with some of these savings and they are not exclusive to cryoballoon ablation. Overall, the results indicate RFPP is the most cost effective option. The sensitivity analyses around costs do not change the conclusions, although the probability of RFPP being most cost effective does reduce. The threshold analysis for cryoballoon indicates a reduction of £2,913 is required. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge, this equated to £1,289 in savings which is not enough for cryoballoon to become more cost effective than RFPP. A 'consider' recommendation was chosen due to the uncertainty regarding the cross over rate from AAD to ablation, to which the model was sensitive to. Furthermore, the volume and quality of the clinical evidence upon which the model was based was not deemed high enough to make an 'offer' recommendation. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP. The committee considered these people to include those for whom a short procedure time or reduced

					alignment on this topic would minimise any patient and provider confusion on therapy choice. 4. Although the de novo analysis concluded laser was the most cost effective; uncertainties around the cost of laser were highlighted, as was the impact of laser cost on the cost effectiveness outputs detailed in the sensitivity analysis. We share the same concerns highlighted in the published documents that the price estimate for laser, sourced from one centre, is likely not reflective of future National cost. We ask that the committee standardize the use of either local or national reference equipment costs. In addition, we would ask the committee if consideration has been given to the short-term budget impact of broader laser adoption in terms of capital investment and learning curve impact and would urge the committee to consider this alongside the uncertainty of the cost effectiveness model when making such a strong endorsement of laser versus established cyroballoon ablation therapy. ~~5.~~ We would ask the committee to give further scrutiny to the base cost inputs in the economic analysis. When undergoing a sensitivity analysis, the greatest variability in results occur when changing equipment and procedure cost inputs. Hence accuracy and parity when specifying the cost of the device for each technique is vital. As highlighted in the report there is a degree of uncertainty surrounding the base case cost inputs for the various ablation techniques. We would ask the committee to either use local or national price for both laser and cryoballoon ablation, which would be readily obtainable from the many centres using it. This would give more equitable and comparable results from this economic analysis. With regards to the cost of sterilization and reuse, we ask the committee to consider including the labour cost associated with processing in addition to the cost of the sterilising box and to also consider the performance degradation and potential infection risk posed by sterilization and reuse. Furthermore, we ask the committee to reconsider the assumption that all catheter ablation procedures have the same procedure cost taken from the HRGs and to consider including the variability in procedure duration and anaesthetic type between ablation techniques. References: 1. **Rapid cardiovascular data: We need it now (and in the future) NICOR Available at:** https://www.nicor.org.uk/wp-content/uploads/2020/09/NICOR-COVID-2020-Report-	risk of fluid overload from saline irrigated RF catheters was preferred, for example those with a recent history of decompensated heart failure.

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					FINAL.pdf#:~:text=Rapid%20cardiovascular%20data%3A%20We%20need%20it%20now%20%28and,to%20improve%20outcomes%20for%20patients%20with%20cardiovascular%20disease. 2. Chen YH, Lu ZY, Xiang Y, Hou JW, Wang Q, Lin H, Li YG. Cryoablation vs. radiofrequency ablation for treatment of paroxysmal atrial fibrillation: a systematic review and meta-analysis. EP Europace. 2017 May 1;19(5):784-94	
SH	Bristol Myers Squibb and Pfizer Alliance	Guideline	009	011-031	We support the recommendation that Direct-Acting Oral Anticoagulants (DOACs) should be offered first to patients with AF, in preference to warfarin/VKA • Consistent with 2020 European Society of Cardiology guideline (Hindricks G *et al*, 2020). • Supported by evidence from Ruff CT *et al* (Lancet, 2014) which found that the DOACs had a favourable risk-benefit balance when compared with warfarin. • Supported by evidence from the largest observational study of anticoagulants in AF, the ARISTOPHANES study (Lip GYH *et al*, 2018), which found that the DOACs had lower rates of strokes/systemic emboli than warfarin. • Recent evidence support the value of DOACs in the important subgroup of obese patients (Martin AC *et al*, 2020; Deitelzweig S *et al*, 2020). • Yao X *et al* (2020) found that the DOACs appeared to have similar or better comparative effectiveness and safety across the range of kidney function in AF. • A 2020 meta-analysis (Plitt A *et al*, 2020) supports the value of DOACs in patients with co-existing diabetes mellitus and AF.	Thank you for your comment.
SH	Bristol Myers Squibb and Pfizer Alliance	Guideline	010	001-004	We propose that decisions to switch between anticoagulants are underpinned by a clear clinical rationale for the switch, based on an evidence-based assessment of outcomes • Switching stable patients is not supported by the available evidence. • There may be risks to patient safety associated with switching between anticoagulants due to the clinical differences between the medicines. • As a consequence: 1. The clinical rationale and justification for switching between anticoagulants must be evidence-based and documented on a patient-by-patient basis. 2. Decisions to switch between anticoagulants should not be based on the price of each DOAC, given the different indications and supporting clinical data.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted.

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SH	Bristol Myers Squibb and Pfizer Alliance	Guideline	010	Box	We propose that the note on procurement is extended to clarify that any DOAC price changes will have no impact on the clinical recommendations for the DOACs • There are clear and evidence-based differences in the safety profiles of the DOACs (*as described in comment 5 above*) which are not affected by changes in DOAC price. Failure to recognise these could pose a risk to patient safety. • We suggest adding this text, "Any procurement decisions will have no impact on the clinical recommendations in this guideline (sections 1.6.1 to 1.6.9)".	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.
SH	Bristol Myers Squibb and Pfizer Alliance	Guideline	028	024-026	We support the finding that the DOACs perform differently depending on the outcome This is consistent with multiple sources of evidence (both RCT and observational) from a variety of settings. These report differences in safety profiles between the DOACs: • Network meta-analyses of randomised controlled trials (Cohen AT *et al*, 2018; López-López JA *et al,* 2017; Lip GYH *et al,* 2016). • Independent meta-analysis of observational studies (Douros A *et al*, 2019) • Large-scale, US observational data (the ARISTOPHANES study: Lip GYH *et al*, 2018; Yao X *et al*, 2016). • The NAXOS French observational study, which found important differences in safety and effectiveness between the DOACs (van Ganse E *et al*, 2020).	Thank you for your comment.
SH	Bristol Myers Squibb and Pfizer Alliance	Guideline	030	001-006	We propose to incorporate the wider resource use/costs of changing patterns of anticoagulant use, beyond medicine acquisition costs only • If more patients are moved from warfarin to DOACs, drug costs will increase but there is likely to be a reduction in strokes and bleeds with the associated savings in NHS resources (e.g., reduced admissions, bed-days, physician/nurse time) as well as meaningful benefits to patients (e.g., fewer INR monitoring visits). (Cowper PA *et al,* 2013; Schinle P *et al*, 2018). • Any limited increase in drug costs, with the higher use of apixaban over edoxaban and rivaroxaban, is anticipated to be offset by reduced burden/cost of patient management, due principally to fewer bleeding events with apixaban (López-López JA *et al*, 2017).	Thank you for your comment. The 'How the recommendations might affect practice' section is only meant to be a brief summary of the resource impact. A more detailed discussion is available within the chapter in the guideline's discussion of the evidence, particularly regarding the health economic evidence which explicitly captures the costs associated with strokes and bleeds. Furthermore, a separate resource impact assessment report detailing the potential savings associated with DOACs will be published alongside the guideline.

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						The recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC and therefore the last sentence regarding the resource impact of specific DOACs has been removed from this section.
SH	Bristol Myers Squibb and Pfizer Alliance	Guideline	General	General	We support the robust and comprehensive evidence assessment presented in this AF Clinical Guideline, which we believe will enhance the care of patients with AF We are pleased to see the draft NICE AF guideline presenting evidence-based recommendations for the management of patients with AF. We agree with and support the majority of recommendations, based as they are on a robust and critical evaluation of all available evidence. We support the methodological approach taken by the independent academic group to evaluating comparative clinical effectiveness and cost-effectiveness of oral anticoagulants in AF, first commissioned by the Department of Health with NIHR funding (Sterne *et al*, 2017), and updated recently by the authors for this guideline update. Both clinical, and cost-effectiveness, evidence presented here are consistent with published evidence from a wide variety of sources over multiple clinical and geographic settings. We have provided additional evidence summaries in our response (below) to help ensure this guideline makes the most robust, evidence-based recommendations for the clinical care of patients with AF.	Thank you for your comment.
SH	British Association of Stroke Physicians	Guideline	009	029	It could be mentioned that prosthetic heart valves are a contraindication for direct-acting oral anticoagulants; this seems to be one of the few remaining indications along with APL and failed DOAC treatment for warfarin.	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2). This is also being covered by the NICE guideline currently in development on heart valve disease.
SH	British Association of Stroke Physicians	Guideline	010	009	Good that age and falls risk are stated as not being barriers to anticoagulate.	Thank you for your comment.
SH	British Association of Stroke Physicians	Guideline	012	027	I'm not aware of left atrial appendage occlusion being offered if anticoagulation is not tolerated and perhaps defined scenarios such as patients with a high bleeding risk on anticoagulants experiencing ongoing ischaemic events should be used as an example.	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

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SH	British Association of Stroke Physicians	Guideline	General	General	Overall, a comprehensive guideline which covers clinical practice of detection, diagnosis and management of atrial fibrillation. As a general comment, the timing of anticoagulation post stroke is not addressed and perhaps it should be based on 1,3,6,12 ESC guidelines or 4-14 days with the AHA; ie tailored to individual patient, size of stroke, bleeding risk etc. Providing a link to the 2019 stroke guidelines stating aspirin 300mg for 2 weeks then anticoagulate seems rather outdated.	Thank you for your comment. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	British Association of Stroke Physicians	Guideline	General	General	A further point is opportunities for AF screening are missed here. In describing detection, the guidelines state a pulse check, ECG and symptoms but do not talk about considering a pulse check at routine GP appointments / nurse clinics / health centre reviews or patients having flu jabs etc when perhaps they should do.	Thank you for your comment. Opportunistic screening is outside of the remit of this guideline.
SH	British Association of Stroke Physicians	Guideline	General	General	A further area missing is guidance for stopping DOACS around procedures / bridging which perhaps they should do, as it's a not uncommon cause of stroke, considerable variability in practice, and is mentioned in other guidelines	Thank you for your comment. Bridging therapy for surgery was outside of the scope of this update.
SH	British Cardiovascular Society	Guideline	010	001	BCS do not feel that there is sufficient evidence of benefit of one DOAC over another to justify large scale switching of patients already established on one agent. There is clearly a workload resource issue in doing this at scale for primary care teams. There may also be some concern for patients if it is implied that they have been on an inferior treatment.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration
SH	British Cardiovascular Society	Guideline	010	001	We found the wording of 1.6.7 to be ambiguous. Does the guideline recommend switching AF patients on VKA with stable INR to Apixaban/Dabigatran? If so this seems a significant extrapolation of data applying to the whole VKA population (including those with low TTR/ labile INR where ischaemic stroke/ intra-cerebral bleeding rates increase).	Thank you for your comment. Recommendation 1.6.6 has been edited and we now refer to time in therapeutic range when considering switching from a vitamin K antagonist to a DOAC.

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SH	British Cardiovascular Society	Guideline	014	002	Syntax errors. There's a redundant "in".	Thank you for your comment, this has been corrected.
SH	British Cardiovascular Society	Guideline	014	004	Syntax error – redundant "for" or "as".	Thank you for your comment, this has been corrected.
SH	British Cardiovascular Society	Guideline	016	023	The specific recommendation of use of point by point ablation or laser ablation does not appear evidence-based. The head to head evidence between different modalities of ablation is not strong and to choose to mention two specific modalities seems very unusual and inappropriate. RF ablation has been compared with cryoablation in the FIRE and ICE studies. Cryoablation has been shown to be at least equivalent. Centres have reported that, given increased efficiency and throughput when lab time is considered, cryoablation is likely to be more cost-effective than point to point ablation (4 cases per day versus 2). We note that cryoablation is recommended in the ESC guidelines. **BCS would prefer that the guidelines refer either to ablation generically or should also mention cryo ablation.**	Thank you for your comment. Recommendations 1.7.19 and 1.7.20 have been amended. 1.7.20 recommends cryoballoon or laser ablation in people who are assessed as unsuitable for radio frequency point-by-point ablation. The evidence showed that radiofrequency point by point ablation was more cost effective over a lifetime than antiarrhythmic drug treatment and other ablation strategies in people for whom 1 or more antiarrhythmic drug has failed. FIRE and ICE was included in the evidence review. Our de novo model demonstrated that the greater costs of cryoballoon made it less cost-effective in our model. A threshold analysis was conducted where we explored the costs of cryoballoon. The threshold analysis for cryoballoon indicated a reduction of £2,913 in the procedure costs is required for it to become cost effective. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge, this equated to £1,289 in savings which is not enough for cryoballoon to become more cost effective than RFPP.
SH	British Cardiovascular Society	Guideline	016	023	We are unclear why NICE have chosen to specifically mention laser ablation. Very few centres in the UK offer laser ablation and there would be significant start up costs in comparison with the widely established infrastructure for delivering cryo ablation. **BCS feel that implementing this aspect of the guideline would have considerable costs in UK due to start-up/capital costs in establishing this little-used technique more widely**	Thank you for your comment. Recommendations 1.7.19 and 1.7.20 have been amended. 1.7.20 recommends cryoballoon or laser ablation in people who are assessed as unsuitable for radio frequency point-by-point ablation.

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						Capital equipment was not included in the costing as the committee stated that in most cases this is provided free of charge by manufacturers as part of a contractual agreement in exchange for the purchase of a minimum volume of equipment.
SH	British Cardiovascular Society	Guideline	016	026	1.7.20 is a bit vague – "procedure is not always effective and … may not be long-lasting". BCS feel that this is true of the majority of medical interventions. As such it adds little to the guidance.	Thank you for your comment. The committee were aware that some people who are considering ablation are unaware that the procedure is not always long-lasting and that this was a particularly important issue for ablation.
SH	British Cardiovascular Society	Guideline	017	021	BCS would wish NICE to emphasise the importance of obesity in the development of atrial fibrillation and the importance of addressing this when considering treatment. We are aware that success rates of PVI for example are lower in obese patients. BCS would suggest: "Consider antiarrhythmic drug treatment for 3 months after left atrial ablation, alongside lifestyle modification such as weight reduction, to prevent recurrence of atrial fibrillation, taking into account the person's preferences, and the risks and potential benefits."	Thank you for your comment. Lifestyle changes were outside of the scope of this update.
SH	British Cardiovascular Society	Guideline	018	001	1.7.23 is vague - "reassess" in what manner? What are the reasons for continuing antiarrhythmics beyond three months, assuming the patient is in SR? **BCS suggests: "Do not routinely offer treatment beyond three months"**	Thank you for your comment. There was no evidence for stopping treatment at three months and the committee agreed that the decision should be made on an individual basis.
SH	British Cardiovascular Society	Guideline	018	003	1.7.24 BCS would welcome guidance on the role for pace and ablate strategy. In patients with LVSD, what is the place of VVIR single chamber pacing v CRT-P therapy in patients with impaired LV function (as in BLOCK-HF)?	Thank you for your comment. This recommendation was not reviewed as part of this update. We have passed your comment to the surveillance team to ensure the guideline is up to date.
SH	British Cardiovascular Society	Guideline	022	005	A clinical risk exists where patients with post-operative AF are discharged with Amiodarone. Please consider adding 'Reassess the need for AAD at 3 months after cardiothoracic surgery'- i.e. analogous to 1.7.23 above.	Thank you for your comment. We have edited the recommendation and added 're-assess at a suitable time point'. There is variation in practice on when this should be done and committee were unable to reach consensus.
SH	British Cardiovascular Society	Guideline	023	General	Further research suggestions: Risk thresholds in device-detected PAF (what constitutes a significant amount of AF sufficient to justify anticoagulation). Studies to describe patient therapy preferences, perception of risk, and how the format of information provided influences these.	Thank you for your comment. The research recommendations were based on the evidence reviews conducted as part of this update or carried over from previous versions of the guideline. As risk thresholds were not specified in the protocol

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						we are therefore unable to include them in the research recommendation
SH	British Geriatrics Society (Cardiovascular Special Interest Group)	Guideline	014	004	There is some emerging evidence that digoxin may be more suitable for rate control in a wider proportion of older adults than this statement, notably from the RATE-AF randomised trial (presented at European Society of Cardiology Congress 2020, currently unpublished) which reported improved quality of life, symptom control and reduced adverse drug events for patients on digoxin compared to beta-blockers. Even going back to the original AFFIRM trial in 2004, adequate rate control was achieved in a similar proportion of patients on digoxin and beta-blockers, both at rest and during exertion. This guideline statement may need to be moderated to reflect increasing uncertainty of the benefit of beta-blockers over digoxin in more patient groups with AF (without heart failure), rather than just sedentary patients with undefined comorbidity.	Thank you for your comment. The committee were aware that digoxin is sometimes used for rate control. The recommendation in the previous version of the guideline was updated to also cover those where other rate control drugs are ruled out due to comorbidities or the person's preferences. However, the evidence comparing digoxin with other rate control drugs was too limited to be able to expand its use to further groups of people.
SH	British Geriatrics Society (Cardiovascular Special Interest Group)	Guideline	023	018	Chronic atrial fibrillation management is overwhelmingly undertaken in older adults, reflecting our ageing population. The easier administration of direct anticoagulants such as apixaban has increased anticoagulation rates compared to warfarin. However, it would seem that when we come to assess the bleeding risks of therapy, we are largely relying on evidence generated from a different era of prescribing, that does not necessarily reflect recent trends towards anticoagulant prescribing in much frailer individuals. A pragmatic suggestion for future research would be to understand the real-world safety and efficacy of novel anticoagulant therapy in frailer patients, with greater interacting comorbidity, more concomitant prescribed drugs and potentially higher falls risk.	Thank you for your comment. The research recommendations were based on the evidence reviews conducted as part of this update or carried over from previous versions of the guideline. As RCTs were specified in the review protocol we are unable to formulate a research recommendation on real world evidence. However, NICE is currently exploring how NICE guidelines can utilise such evidence when making recommendations
SH	British Geriatrics Society (Cardiovascular Special Interest Group)	Guideline	025	004	The suggestion here for further future research into the optimum rate control strategy in older patients is welcome. However, the somewhat arbitrary age-based threshold of >75 years old is less likely to yield clinically helpful data for future guidelines. The increasing healthcare challenge for managing AF is in patients with frailty and multimorbidity where treatment decisions are more complex. This recommendation to the research community would be better framed around frailty and multimorbidity than by age thresholds.	Thank you for your comment. As this recommendation was made as part of the 2014 update we are unable to change it.
SH	British Society of Haematology and Royal College of Pathologists (joint response)	Guideline	010	001-004	We note that apixaban and dabigatran are preferred over other DOACs on the basis of the cost-effectiveness analysis even though there has not been a head-to-head analysis. We feel that this is a major limitation when recommending one drug over another. Both apixaban and dabigatran are taken twice daily while rivaroxaban and edoxaban are once a day. Experience from anticoagulation clinics is that patients prefer a daily to twice daily regimen and patient choice should be the key factor here. Anticoagulation clinics will not follow a recommendation to switch drugs when this goes against patient preference and there is no clinical advantage to doing so.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted.
SH	British Society of	Guideline	011	002-008	We agree that more focus should be on TTR rather than single INR readings. This is expected to improve control for patients on warfarin. This may be challenging for some anticoagulation	Thank you for your comment. These recommendations were not reviewed as part of this

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	Haematology and Royal College of Pathologists (joint response)				clinics that are not used to focusing on the TTR. There may be a need for more education in primary care anticoagulation clinics, particularly those using point-of-care testing.	update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	British Society of Haematology and Royal College of Pathologists (joint response)	Guideline	020	004-008	We are concerned that the recommendation to use heparin at initial presentation is not based on any data that shows this approach to be of benefit. In fact there is data that shows it is not of value.	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	Care Quality Commission	Guideline	010 - 019	General	We are concerned that these recommendations are being based on studies referenced on pages 10-19 in which the impact of prevailing levels of renal function is cited as being unclear. The conclusions drawn from these papers may result in the potential risk that patients are treated with Direct Oral Anticoagulants (DOAC) medicines when this may not be in their best interest.	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2) including renal function.
SH	Care Quality Commission	Guideline	020 - 038	General	We are concerned that the level of quality of the majority of the papers cited and used to inform this guideline are rated as being of low or very low quality and hence call into question the conclusions drawn and recommendations made. The CQC has been made aware of data which has been made available covering the real-world current outcomes for over 20 million patients in British General Practice. The information is attached to this document as Appendix 1. We believe that this data should be taken into consideration, referenced and included in the decision- making process for this guideline. NICE Chief Executive, Professor Gillian Leng, and NICE Director of the Centre for Guidelines, Dr Paul Chrisp, are both identified as key stakeholders in the attached data pack. **Appendix 1:**  PSL - Data Pack - Anticoag (Aug 20) V2.	Thank you for your comment. The quality of evidence is graded using GRADE criteria, according to 4 criteria: risk of bias, indirectness, imprecision and inconsistency. The committee took these ratings into account when interpreting findings, with implications for the strength of recommendations made. The committee's pre-hoc decisions on the type of evidence to be sought for each review question is based on their agreement regarding the most appropriate type of data (for example, randomised controlled trial data). This decision is, of course, made prior to any knowledge of the quality ratings of the evidence (which is only known after the papers have been reviewed) and so the quality ratings can only be used to assist interpretation of the evidence rather than to alter the choice of the evidence sought.

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						These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	Clinical Leaders of Thrombosis (CLOT)	Guideline	074	020	We are concerned regarding the recommendation that Apixaban and Edoxaban should be used due to cost effectiveness of the drugs. The drug of choice should be based on the best option and prevention outcome for the patient. This recommendation may cause commissioners to use a blanket approach for anticoagulation which would ignore the specific need of a patient. This may lead to non-compliance and reduced efficacy. The clinician should base the anticoagulation choice on the best treatment to suit the need of the patient whether this be warfarin, Edoxaban, Apixaban, Rivaroxaban or Dabigatran. As a committee we agree clinicians should be free to exercise their own judgement based on individual patient need to ensure efficacy and safety for the patient.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.1 refers to patient preferences when discussing the risks and benefits of anticoagulation treatment. We refer to shared decision making when choosing anticoagulant treatment in recommendation 1.6.2.
SH	College of Paramedics	Guideline	General	General	Community detection of presumed new onset AF An addition to the guidelines to cover onwards referral to primary care for follow-up, further assessment and treatment if untreated/undiagnosed AF is detected in the community (by for example, ambulance clinician, district nurse or other clinicians) and the patient is not being conveyed to a healthcare setting/started on treatment at that time.	Thank you for your comment. Patients with AF detected in the community should be referred to primary care and the recommendations on diagnosis are aimed at primary care. Treatment can then be initiated for example on stroke prevention or ablation.
SH	Daiichi Sankyo UK Limited	Guideline	009 010	011 - 028 001 - 004	1.0 RECOMMENDATION IS ONE THAT IS PROPERLY MADE VIA A MULTIPLE TECHNOLOGY APPRAISAL UNDER REGULATION 7 OF THE 2013 REGULATIONS The lawful route for revising the current recommendation of parity between treatments, which would take place at the same level of rigour as the prior HTAs would be a Multiple Technology Appraisal ("MTA"), which could properly evaluate the DOACs in Atrial Fibrillation. The process for developing Guidelines under regulation 5 of the 2013 Regulations (as opposed to Technology Appraisals under regulation 7) is a separate process – however this Guideline seeks to cover similar ground. In our view it therefore contradicts NICE's own guidance on the circumstances in which an MTA is appropriate, and therefore is outside the scope of its statutory powers under the 2013 Regulations, in seeking to supplant a recommendation under regulation 7 with a recommendation made under regulation 5. Paragraph 1.6 of the document entitled '*Guide to the processes of technology appraisal*' dated 2 September 2014 states that Technology Appraisals '*are designed to provide*	Thank you for your comment. The recommendations have been developed in accordance with the guidance in the NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction. The manual provides guidance on how interventions (including pharmaceutical) can be compared against each other including conducting a network meta-analysis. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA

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					recommendations, in the form of NICE guidance, on the use of new and existing medicines, products and treatments in the NHS'. In our view the type of recommendation, displacing parity between DOACs, clearly falls within the stated remit of an MTA. We consider that this document constitutes an established process under paragraph (9) of regulation 7 of the 2013 Regulations, which NICE is required to adhere to. Conversely, paragraph (11) of regulation 5 states that *'for the purposes of this regulation, a "recommendation" does not include a technology appraisal recommendation'*. The scope of NICE's power under regulation 5 is therefore confined to what is not covered by regulation 7. As evidenced by NICE's own established processes, recommendations about the use of specific treatments are within the statutory 'field' of regulation 7. It follows that a Guideline should complement recommendations made in a Technology Appraisal, not pre-empt or seek to replace them. Recommendations such as those made at paragraphs 1.6.3 – 1.6.5 (page 9, line 11-28) and 1.6.7 (page 10, lines 1-4) of the draft Guideline, can only properly be made following the more rigorous analysis which would be conducted under a Multiple Technology Appraisal. This is the process envisaged under the statutory scheme.	estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. Recommendation 1.6.3 and 1.6.4 now recommend any licensed DOAC.
SH	Daiichi Sankyo UK Limited	Guideline	009	024	2.0 HANDLING HETEROGENEITY AND UNCERTAINTY WHEN CONSIDERING THE RELATIVE CLINICAL EFFECTIVENESS BETWEEN DOACs DSUK has significant concerns about the Sterne et al. analysis, reported in Evidence Review G2 Adequately adjusting for heterogeneous analysis ("Evidence Review 6"), which underpins the clinical and cost-effectiveness evidence used to develop the DOAC recommendations Guideline section 1.6.3, 1.6.4, 1.6.7. The Sterne et al. NMA is a post-hoc analysis which derives its results from a range of existing and heterogenous clinical trials. Its conclusions are based on direct comparisons between secondary, indirect evidence. The NMA itself fails to acknowledge the significant differences in the study design, patient populations and endpoint definition for each of the trials which it seeks to compare. In our view it is not therefore reasonable for the trials to be 'compared as equals' in the way that the NMA purports to do. In largely adopting the conclusions of the NMA without scrutiny of these differences, NICE therefore also fails to take account of such methodological differences between the trials compared within the NMA. While we acknowledge that it is open to NICE to reach its own view on the limitations of NMAs, including the NMA referenced in Evidence Review 6, we do not think a rational conclusion can be reached if the limitations outlined in this response are not acknowledged, analysed or explained in the decision-maker's explanatory reasoning.	Thank you for your comments. On further discussion, the committee agreed that the NMA by Sterne / Lopez Lopez was probably not able to adequately adjust for the differences between treatment comparisons in terms of population characteristics that could affect outcome. Initially we had felt that the meta-regressions used were adequate, but after consideration of the numbers of studies involved it does seem unlikely that the meta-regression would have been able to make realistic adjustments to effect that were sufficient to negate inter-comparison differences in prognostic characteristics. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.

For example, it is well documented that methodological differences exist in the study design, patient populations and endpoint definitions used across the four pivotal DOAC randomised controlled trials (RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48) (Ruff CT et al., 2014). Differences include, but are not limited to:

- The ARISTOTLE and RE-LY trials enrolled patients who had a $CHADS_2 \geq 1$, whereas ROCKET-AF and ENGAGE AF-TIMI 48 enrolled patients with $CHADS_2 \geq 2$. Mean $CHADS_2$ scores were higher in the ROCKET-AF and ENGAGE AF-TIMI 48 trials than in the ARISTOTLE and RE-LY trials and the distribution across $CHADS_2$ score differed
- Median time in therapeutic range (TTR) for the warfarin arm was higher in the ENGAGE AF-TIMI 48, ARISTOTLE and RELY trials than in the ROCKET-AF trial
- The ARISTOTLE, ROCKET-AF, and ENGAGE AF-TIMI 48 trials were double-blind, double dummy trials, whereas the RE-LY trial administered warfarin as an open-label treatment
- Median follow-up for the ENGAGE AF-TIMI 48 trial was 2.8 years, longer than median follow-up in the other trials 1.8 years (ARISTOTLE); 1.9 years (ROCKET-AF); 2.0 years (RE-LY).

The differences amongst the trials have been discussed extensively in published literature and previously published NICE Technology Appraisals for the DOACs with the conclusion that direct comparison of study results across DOAC RCTs and through meta-analyses is challenging and potentially misleading (Camm J et al., 2018). The table below captures the trial characteristics used to conduct the NMA and highlights some of the differences.

Table 1: Summary of the pivotal DOAC trial characteristics used to inform the Sterne et al. NMA

	Treatment (& dose)	Trial design	Patient population	Mean age (SD) or Median age (IQR)	% Male	Mean $CHADS_2$ score	Mean % TTR	Number of randomised patients	Trial length (years) median FU
ENGAGE AF-TIMI 48	Edoxaban 60 mg od (60 mg/ 30 mg DR)	Randomised double-blind, double dummy	Adult patients ≥20 years old with NVAF and a $CHADS_2$ ≥2	72 (64-68)	62.1	2.8	n/a	21,105	2.8
	Edoxaban 30 mg od (30 mg/ 15mg DR)			72 (64-78)	61.2		n/a		
	Dose adjusted warfarin (INR 2.0-3.0)			72 (64-78)	62.5		64.9%		

ARISTOTLE	Apixaban (5mg bd)	Randomised, double blind, double dummy	Patients with AF and a $CHADS_2$ score ≥1	70 (63-76)	64.4		2.1	n/a	18,201	1.8
	Dose adjusted warfarin (INR 2.0-3.0)			70 (63-76)	65.0			62%		
RE-LY	Dabigatran 110 mg bd	Randomised, two doses of dabigatran administered in a blinded fashion, open-label use of warfarin	Patients with AF and a $CHADS_2$ ≥1	471·4 (8·6)	64.3		2.1	n/a	18,113	2
	Dabigatran 150 mg bd			71·5 (8·8)				n/a		
	Dose adjusted warfarin (INR 2.0-3.0)			71·6 (8·6)				64%		
ROCKET-AF	Rivaroxaban 20 mg od	Randomised, double blind, double-dummy	Patients with NVAF and a $CHADS_2$ ≥2	73 (65–78)	60.3		3.6	n/a	14,262	1.9
	Dose adjusted warfarin (INR 2.0-3.0)			73 (65–78)	60.3			55%		

(Abbreviations: bd = twice daily; DR = dose reduction; FU = follow up; INR = international normalised ratio; mg = milligrams; NVAF = non-valvular atrial fibrillation; od = once daily)

Further, consecutive NICE Technology Appraisal Committees have reached the same view regarding heterogeneity across DOAC trials. In NICE TA355, the Technology Appraisal Committee noted (our emphasis)::

4.8 The Committee discussed the data for edoxaban compared with rivaroxaban, apixaban, dabigatran etexilate (110 mg twice daily and 150 mg twice daily) and rivaroxaban, that were used in the company's network meta-analysis. The Committee noted that the trials included in the network meta-analysis were not directly comparable; for example, they had different baseline risks of stroke (with different $CHADS_2$ inclusion criteria and mean $CHADS_2$ scores) and differences in time in the therapeutic range in the warfarin groups.
...The Committee concluded that the network meta-analysis results should be interpreted with caution, but edoxaban is unlikely to be different from rivaroxaban, apixaban and dabigatran etexilate in clinical practice.

Section 1.3.3 of the 'Method' document accompanying the consultation states that TA355 is 'incorporated in this guidance'. However, there is no consideration or analysis of the interaction between the directly contradictory statements in the draft guideline, and TA355.

					Similarly, we see that this is the case with previous NICE Technology Appraisal Committees in other disease areas when exploring differential effectiveness within a class of drugs, in the absence of direct clinical evidence. For example, the appraisal committee for the Multiple Technology Appraisal NICE TA375 (Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs (DMARDs) or after conventional DMARDs only have failed) discussed whether the clinical evidence suggested that one biological DMARD might be more effective than the others. The committee "*considered that for all of the biological DMARDs there were similar results for both ACR and EULAR response, and that the overlapping credible intervals were often wide, indicating uncertainty in the true estimate of effect. The Committee concluded that the evidence of greater clinical effectiveness for biological DMARDs compared with conventional DMARDs was more compelling in disease previously treated with methotrexate and that the evidence did not suggest differential effectiveness between the biological DMARDs. The clinical experts confirmed that this was their view too.*" (Abbreviations: ACR = American College of Rheumatology; EULAR = European League Against Rheumatism) 2.1 Published evidence on treatment effect modification Published evidence indicates that baseline characteristics can play an important role in effect modification. A NMA combining individual patient data from the four pivotal trial of DOACs, concluded that for age, body weight and creatinine clearance there was evidence of statistical interaction regarding treatment effect for various outcomes (Carnicelli A et al., 2020). For example, the benefit of DOACs over warfarin with respect to major bleeds was more pronounced in patients with higher age (ibid). In a similar analysis using the HOKUSAI-VTE data, Van Hout B et al. (2020), investigated the impact of age, body weight and creatinine clearance on the recurrence of venous thromboembolic event (VTE) and clinically relevant bleeding. It was demonstrated that there is a significant modification of the treatment effect by age for those taking warfarin. The hypothesis of effect modification due to age for patients on warfarin is further confirmed by an analysis of the ENGAGE AF-TIMI 48 trial (Le Moine et al., 2020) (Academic in confidence). The modification of treatment effect by age for patients on warfarin might bias estimates of comparative effectiveness among DOACs if vitamin K antagonists (VKA)s are the reference treatment. The findings from a study by Caldeira D et al. (2019) also support the importance of age as an important treatment modifier. The study found stroke risk reduction to be significantly higher in elderly patients with NVAF (age ≥75 years) than in younger adults (<75 years). Furthermore, edoxaban and apixaban, individually, were found to demonstrate a significant reduction in the risk of major bleeding in both elderly and younger patients, whilst dabigatran only demonstrated a significant reduction in risk of major bleeding in the younger patient group. Stratifying patients by stroke risk was also observed to be important effect modifiers by Ruff CT et al. (2014) and De Groot et al. (2020). In a recent publication, Bakhai et al. (2020), investigated real-world data on the incidence, mortality and cost of ischaemic stroke and major bleeding events among NVAF patients in England. The authors explored CHA_2DS_2-VASc score as an effect modifier. Patients with lower baseline CHA_2DS_2-VASc scores had lower rates of ischaemic stroke and major bleeding, irrespective of treatment post-index, reflecting the impact that CHA_2DS_2-VASc scores have on event outcomes. This highlights the important of CHA_2DS_2-VASc as a potential treatment effect modifier with heterogeneously reported data and the need to appropriately assess this covariate. We see no evidence, aside from the attempted meta-regression, that the potential of stroke risk to modify the effect of treatment across the different trial populations compared in the NMA has been considered or weighed against other factors.	

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					Whilst acknowledged to be important, clinical differences in baseline characteristics were not adjusted for in the NMA by Sterne et al. (see further specific comments in response sections 1.2 and 1.3 below). Therefore, the small numerical treatment differences between DOACs could be due to variability in baseline characteristics. In fact, Evidence Review 5 (Section 1.7.1.3, page 71. Line 35) highlights that "*due to model limitations such as the uncertain utility data and reliance on indirect treatment effect evidence, the uncertainty was likely to be even higher than estimated."* The NMA, and by extension, the NICE recommendations made as a result, appear to disregard this evidence entirely in reaching their conclusions. DSUK believes that the Sterne et al NMA results should, in accordance with the recommended approach to NMAs in the academic community, be interpreted with additional caution because of these significant differences in patient characteristics and trial design that exist between the four pivotal trials. However, as above, there is no acknowledgement of this issue, nor any evidence that NICE has taken it into account in its reasoning, instead proceeding to draw definitive conclusions undermining parity between DOACs, while ignoring these significant limitations.	
SH	Daiichi Sankyo UK Limited	Guideline	009	024	2.5 DSUK advises caution in interpretating findings due to heterogeneity and uncertainty DSUK has concerns about the draft guideline's reliance on the Sterne et al. NMA to inform the comparative effectiveness of the DOACs.The heterogeneity present between these studies further contributes to the uncertainty in the between treatment comparisons of the results of any network meta-analysis. DSUK understands that the use of a NMA is necessary, but it is important to highlight that any uncertainty intervals calculated as a result of a NMA assume that the data from the trials included are exchangeable. As described by Professor John Camm and colleagues (2018), the data are unlikely to be fully exchangeable. As a consequence, the level of uncertainty reported for the NMA that is the basis of the draft NICE recommendations should be considered the most optimistic case – in reality we believe the confidence intervals should be wider. In the absence of head-to-head RCTs or any matched-adjusted analysis using individual patient level data, it will be a challenge to conclusively differentiate between the DOACs. The draft clinical guideline in its current format limits patient choice to NICE-recommended treatments. All four DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) have been assessed rigorously in previous NICE STAs and have been deemed by the NICE Technology Appraisal Committee to be a cost-effective use of NHS resources. These recommendations were based on data from RCTs comparing DOACs with warfarin. There has not been a Multiple Technology Appraisal (MTA) evaluating the DOACs in Atrial Fibrillation and the development of a NICE Clinical Guideline follows a different process compared with a NICE Technology Appraisal.	Thank you for your comments. On further discussion the committee agreed that the NMA by Sterne / Lopez Lopez was probably not able to adequately adjust for the differences between treatment comparisons in terms of population characteristics that could affect outcome. Initially we had felt that the meta-regressions used were adequate, but after consideration of the numbers of studies involved it does seem unlikely that the meta-regression would have been able to make realistic adjustments to effect that were sufficient to negate inter-comparison differences in prognostic characteristics. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.

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					DSUK considers that, in the absence of head-to-head trials, an analysis could be conducted utilising individual patient data from the existing DOAC RCTs as such an analysis would allow the selection of comparable participants from across the trials and this data could be used in a series of NMAs to improve the estimation of relative clinical effectiveness, cost-effectiveness and safety between the DOACs and other treatment options. Population-adjusted indirect comparisons such as Matching-Adjusted Indirect Comparisons (MAIC) are increasingly being used in STA submissions to NICE, particularly when there is access to individual patient data, in order to adjust for between-trial differences (NICE Decision Support Unit, 2016). Differences in trial study design and endpoint definition can only be addressed in a head-to-head trial. Additionally, from TA355 it appears that the constant hazards assumption does not hold for any of the four pivotal DOAC trials. The impact of these violations of the proportional hazards assumption on the size of NMA outputs is not known. DSUK recognizes that the assumption of proportional hazards is a necessity in order to conduct reliable comparisons that will inform decision making. However, in situations like this where the proportional hazard assumption does not hold, whilst useful, it further increases the uncertainty of comparative effectiveness. For this reason, the estimates from the model assuming constant hazards by Sterne et al. should be interpreted with caution as it is likely that the credible intervals should be wider than presented. It is worth acknowledging that whilst there are extensions to the modelling that would relax these strong assumptions, there is unlikely to be sufficient data to model these extensions. For this reason, the approach presented by Sterne et al. may be the optimal approach in this case but the limitations, and therefore output, need careful consideration when using them to make decisions on superiority. At the very least, NICE is required to acknowledge the potential presence of such flaws with Sterne et al. NMA, explain its reasoning in relation to them, and either justify its disregard for such flaws or take them into account in modifying the recommendation.	
SH	Daiichi Sankyo UK Limited	Guideline	009	024	4.0 LACK OF CONSIDERATION OF NON-RCT DATA Edoxaban has been studied in the largest and longest NVAF DOAC RCT to date (ENGAGE AF-TIMI 48) and has demonstrated consistent stroke/SEE prevention and reduction in risk of major bleeding versus well-managed warfarin across age groups with an elderly population that broadly reflects patients seen in UK clinical practice. These findings were supported by a subgroup analyses from ENGAGE AF-TIMI 48 trial, which included the largest number of elderly patients enrolled within a DOAC RCT, including high risk patients and those with multiple comorbidities (Kato ET et al., 2016).	Thank you for your comment. It may be argued that broader sources of data can help determine the “real-world” effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT

					The analysis by Sterne et al., focussing only on RCTs, underpins the clinical and economic evidence for the DOAC recommendations in the draft guidance. These findings are used to base conclusions on the clinical and cost-effectiveness differences between the DOACs. Such significant conclusions, with wide-ranging consequences for patients and market participants, cannot reasonably be based on secondary inferences restricted to one kind of data (RCTs). DSUK therefore suggests that an additional flaw in NICE's reliance on an NMA study in this instance is the fact that its evidence base does not include any other types of studies such as routine clinical practice or real-world evidence (RWE) studies should be considered as part of the evidence base. It is widely accepted that randomised trials are the gold standard for ascertaining the efficacy and safety of a given therapy and, as stated above, prospective head to head RCTs to assess differences between DOACs would be required in order to properly establish any differences between them. However, in a context where reliance is entirely placed on an NMA study, data entirely derived from pre-existing RCTs cannot be fully representative of an unselected real-world population due to their highly controlled settings. For this reason, DSUK considers that routine clinical practice or Real-World Evidence (RWE) studies should be considered as part of the evidence base, if seeking to rely on indirect data alone. For example, patients with very high bleeding risk can be largely excluded resulting in paucity of data on these patients. Additionally, the patient population specified in the label is usually broader than the key inclusion criteria of pivotal trials (De Caterina R et al., 2019). The potential for RWE studies to provide evidence of estimation of the usage, dosing and clinical effectiveness of DOACs in routine clinical practice cannot and should not be overlooked. RWE studies are also fundamental to detect rare/unexpected side effects. For this reason, it is important to provide high quality, preferably prospective data on the routine practice performance on a DOAC. 4.1 ETNA-AF ETNA-AF-Europe is a multinational, multicentre, EMA authorised PASS study, conducted in 825 sites in 10 European countries. A total of 13,980 patients were enrolled and will be followed up for up to four years (De Caterina R et al., 2019). Baseline characteristics for ETNA-AF-Europe and the European cohort of ENGAGE AF-TIMI 48 were broadly similar and efficacy and safety findings were also largely similar according to a poster presented at ESC 2019 by De Caterina R et al. Of note, compared with the ENGAGE AF-TIMI European cohort, lower rates of major bleeding and stroke/systemic embolic events were observed in 12,500 unselected, mostly elderly AF patients in routine clinical practice in ETNA-AF after 1-year follow up (De Groot JR et al., 2020). Further observations from ETNA-AF-Europe confirm that	evidence on the effectiveness of anticoagulants to support decision-making.

					edoxaban is used in the vast majority of patient in line with the SmPC and that the results from ENGAGE AF-TIMI 48 can be translated in routine practice (De Groot JR et al., 2020). There is no evidence that these data were taken into account by NICE in developing the draft Guideline. 4.2 Other relevant RWE In addition, there are also routine practice studies that compare VKA with DOACs and DOACs between each other. A recent German study including 837,430 patients showed that edoxaban was the only DOAC that did not show an increased stroke risk vs VKA (Paschke LM et al., 2020). There is no evidence that the latter was taken into account by NICE in developing the draft Guideline. Although RWE studies might report different findings from the pivotal trials, they can be a robust indicator of patient outcomes in routine practice where other factors such as patient adherence, persistence and dose selection play a role. Another routine practice study that included 61,568 DOAC-naive patients with non-valvular AF, showed that edoxaban, among all DOACs, had the lowest matched risk of major bleeding, fatal recurrent stroke, fatal composite outcome and all cause death versus warfarin (Park J et al., 2019). Again, there is no evidence that this was taken into account by NICE in developing the Guideline. An analysis on a German database presented at ESC 2020 showed that edoxaban was associated with a significant lower risk of systemic embolism and stroke separately compared to apixaban, dabigatran, rivaroxaban and VKA, a significant lower risk of all major bleeding compared to dabigatran, rivaroxaban and VKA and a similar major bleeding risk to apixaban (Marston X et al., 2020). A recent UK observational study by Vinogradova et al. (2018) has identified increased mortality with apixaban and rivaroxaban. This is noteworthy as mortality is an important clinical input into the cost effectiveness model impacting on both costs and QALYs. It should be noted that the same study reports a significantly higher ischaemic stroke HR for dabigatran 150mg (1.37 vs warfarin) compared to that used in the NICE economic model. Based on these findings and the importance of routine practice data, and given the significance of the departure from the previous position apparently under consideration, we suggest that non-RCT data such as ETNA-AF should be considered in developing the final NICE CG180 recommendations.	

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SH	Daiichi Sankyo UK Limited	Guideline	010	001 - 004	13.0 DOAC SWITCHING AND PATIENT SAFETY DSUK considers the recommendation (in Section 1.6.7) to discuss the switching of patients who are already stable on their anticoagulation treatment to apixaban or dabigatran on the basis of cost-effectiveness is wholly unacceptable. This recommendation is based on limited evidence and risks compromising patient safety. The recommendation to discuss the switching of stable patients is not supported by strong evidence and the DOAC treatments are not bioequivalent and should not be considered as routinely interchangeable. Further, the recommendation is an unjustified departure from established clinical practice, which fails to properly take into account patient safety. In summary, recommendation 1.6.7: • is a departure from an established norm which is not supported by the rigorous analysis necessary to justify such a departure; and • fails to acknowledge or take into account specific risks, such as the difference between once daily and twice daily dosing outlined below. Furthermore, Evidence Review 5 (page 71, line 38) describes some of the considerations on patient safety *"The committee discussed the patient experience of using apixaban and dabigatran, and described how dabigatran may lead to more upper GI side effects, and also possibly less compliance because of the greater number of doses per day."* Apart from the accepted rule in general medicine that a medication that is effective and well tolerated by the patient should not be switched to an alternative treatment, there are important potential hazards for the patient if required to switch from edoxaban or rivaroxaban to apixaban or dabigatran. For example, there may be issues with underdosing if patients, who are used to taking once-daily DOAC regimens are switched to twice-daily medications but are unable to comply with the change of dosing frequency. In such cases, patients will be put at greater risk of stroke. Both apixaban and dabigatran, which are recommended as first line DOACs in the draft clinical guidelines, are administered twice daily, which can lead to issues regarding compliance, adherence, and persistence. Several publications support the superior adherence of once daily over twice daily drugs. Patients suffering from AF are usually elderly, so a deviation from the medication they are used to may present a significant patient safety risk. It might even lead to severe underdosing when a twice daily drug is wrongly taken once daily over a period of time. This might be especially problematic with apixaban which is often not prescribed according to the label and dose reduced to 2.5 mg bd without meeting the dose reduction criteria within the Summary of Product Characteristics (SmPC). Finally, most patients with AF prefer once daily dosing over bd (Wilke T et al., 2019), an important point which needs to be considered. The importance of patient preference is underlined by the recent ESC guidelines 2020. Further, patients may experience specific off target side effects when switching from a well-tolerated medication to an alternative drug. A common side effect of dabigatran is gastrointestinal (GI) upset which may lead to the patient stopping the drug with potentially serious consequences.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted

					The practicalities of switching from edoxaban and rivaroxaban is not straightforward for several reasons and when considering this could involve >500,000 patients, putting significant strain on the NHS during the time of already considerable pressure amidst a national pandemic. It requires detailed knowledge of the dosing criteria to avoid dosing errors. Dose selection criteria differ markedly between DOACs. Rivaroxaban and edoxaban have clear dosing criteria stated within their SmPCs, it is more complicated for apixaban (2 out of 3 criteria) and for dabigatran no clear criteria exist. The recommendation for dabigatran is solely based on the 150 mg bd dose data, however, 55% of AF patients in the UK receive the 110 mg dose that is not different from warfarin with respect to protection for ischaemic stroke. Switching exposes patients to an unnecessary risk for a devastating cardioembolic stroke (if underdosed) or life-threatening bleed (if overdosed). The significance of these risks to patient safety justify the application of a higher degree of scrutiny to any decision which might increase them or further expose patients to them. Furthermore, all DOACs differ with respect to certain contraindications, e.g. dabigatran is contraindicated in patients with CrCl <30 ml/min, also it should not be given with concomitant dronedarone, a frequent co-medication in patients with AF. There are also pharmacologic interactions with other CV medications that need to be taken into account when switching between DOACs. All DOACs vary regarding metabolism and excretion. Apixaban is metabolised to a considerable extent bycytochrome P450 (CYP), dabigatran is excreted to 80% by kidneys. In contrast, edoxaban has a very balanced metabolism/excretion (<4% CYP, 50% kidney). Elderly patients often take many concomitant medicines that may interfere with apixaban leading to hard to predict exposure levels, which may result in anti-factor Xa (anti-FXa) activity different from the prior medication. According to the SmPC, apixaban should not be co-administered with strong inhibitors of both CYP3A4 andP-glycoprotein (e.g. ketoconazole) as it leads to a 2-fold increase of exposure. Edoxaban requires only dose reduction to 30 mg once daily when given with ketoconazole since it is not metabolised by CYP enzymes in a clinically relevant way. This illustrates that switching requires very detailed knowledge of the SmPC to avoid dangerous over- or under-exposure of the patient. Essentially, the 'one size fits all' nature of the recommendation is particularly irrational in light of the clearly different circumstances of the patient groups likely to be affected. We see no evidence that such nuances (which are impactful nonetheless) have been taken into account in developing the Guideline. DOACs show quite high inter-individual variations in exposure (EHRA guidelines, 2018), even if all precautions listed in the various SmPCs are carefully considered, it is by no means guaranteed that the alternative DOACs provides the same balance between efficacy and safety as the original one. Side effects that may not be clinically relevant like nuisance bleeds may cause a patient to stop the new DOAC putting them at high risk for serious consequences. In conclusion, switching a stable patient on edoxaban or rivaroxaban to apixaban or dabigatran without a clear clinical rationale results is an unnecessary risk for potentially serious consequences for this patient and is not evidenced based. DSUK is seriously concerned about the draft recommendation to discuss switching stable patients between DOACs, all of which have been NICE recommended and individually deemed to be clinically effective and a cost-effective use of NHS resource, and would urge for this recommendation to be completely removed from the final guideline.	

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SH	Daiichi Sankyo UK Limited	Guideline	028	026-028	18.0DOCUMENTATION ERRORS We would like to point out that edoxaban has been omitted completely from this section: "*Results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran.*"	Thank you for your comment. The recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC and the rationale and impact has been edited.
SH	Daiichi Sankyo UK Limited	Guideline	General	General	EXECUTIVE SUMMARY Daiichi Sankyo UK Limited ("DSUK") would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to comment on the draft "Atrial Fibrillation: Management" consultation document. In general, DSUK considers the document to be well written and it contains important information on the diagnosis and management of atrial fibrillation (AF). The overarching strategy for the National Health Service (NHS), the NHS Long Term Plan (LTP), has recognised that too many people in England are living with undetected, high-risk conditions that cause cardiovascular disease (CVD), such as AF. The NHS Long Term Plan committed to preventing up to 150,000 heart attacks, strokes and dementia cases over the next ten years by improving early detection and treatment of CVD risk factors. Updating clinical guidelines play an important part in ensuring that healthcare professionals adopt best practice in the management of conditions such as atrial fibrillation, and thus the prevention of CV events. For CVD objectives in the NHS LTP to be met, Health Care Professionals (HCPs) need a wide range of clinically effective and cost-effective treatment options in order to offer effective and sustainable management to patients and improve population health. DSUK would like to make NICE aware of our strong concerns regarding the draft recommendations in relation to the sequential use of direct-acting oral anticoagulants (DOACs) detailed in section 1.6 of the draft guideline. More specifically, DSUK's position is that recommendations 1.6.3 – 1.6.5 (at lines 11 – 28 of page 9), and paragraph 1.6.7 (at lines 1 – 4 of page 10), should be struck out of the guidance, with corresponding consequential changes made to the narrative at lines 22 – 29 on page 28 and lines 1 – 6 on page 29. In DSUK's view, the heterogeneity between DOAC randomised control trials (RCT)s has not been adequately taken into account or addressed by the Guideline Committee. We believe	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals were wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore were no longer confident to recommend a specific DOAC or DOACs. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Responses to the comments relating to the health economic model have been provided in the individual comments sent by DSUK. Please refer to these for more information.

					that the draft recommendations do not reflect the uncertainty in clinical and cost-effectiveness estimates between DOACs and that they are based on potential over-interpretation of, or undue weight given to the indirect comparison results reported by Sterne et al. The differences amongst the DOAC RCTs have been discussed extensively and there is broad consensus in the literature that such differences pose challenges on any direct comparison of study results across the trials. In the absence of head-to-head RCTs, or matched-adjusted analysis using individual patient level data, it is not possible to conclusively differentiate between the DOACs and any attempts to do so through NMAs of heterogenous trials would be misleading. Sequential DOAC recommendations, as stated in these draft guidelines, are not consistent with other referenced International AF Guidelines nor the current NICE CG180 (2014). The recent European Society of Cardiology (ESC) '2020 Guidelines for the diagnosis and management of atrial fibrillation' recommend all DOAC options as parity options within their licensed indication (ESC, 2020). A recent European Medicines Agency (EMA) report, based on the findings from an EMA-funded real-world study found there to be insufficient data to allow robust conclusions to be drawn on comparisons between the DOACs (EMA, 2020). Furthermore, all four DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) have been assessed rigorously in previous NICE Single Technology Appraisals (STAs) and have been deemed by the NICE Technology Appraisal Committee to be a cost-effective use of NHS resources. The draft NICE CG180 in its current format appears to contradict the recommendations in these appraisals and guidelines and limits patient choice to NICE-recommended treatments. As further set out below, we consider that NICE has failed to take into account multiple material factors – there is no acknowledgment or attempt to address and weigh these factors against those which *are* taken into account in order to reach a rational, proportional and balanced outcome. Furthermore, we want to draw attention to several potential material mistakesand inaccuracies that DSUK has identified in its review of the Sterne et al. cost-effectiveness analyses and the R model. These include potential modelling errors, limitations in the way that heterogeneity was accounted for in the analyses, issues with the way that healthcare state costs are estimated and coded in the model, concerns with the validity and accuracy of generating model inputs via a competing risks network meta-analysis (NMA) which is not clearly documented, and failure to consider the impact of pricing schemes, thus, producing results that are not based on actual NHS drug acquisition costs. There is also a clear omission of published transient ischaemic attack ("TIA") evidence relating to edoxaban which we believe would significantly improve edoxaban's cost effectiveness. In addition, DSUK is concerned	

					with the Committee's use and interpretation of evidence from Cost Effectiveness Acceptability Curves (CEACs) which appear to have been used to compare and rank multiple interventions to decide on the optimal intervention – this is not considered methodologically appropriate and is misleading in this context. DSUK has conducted exploratory analyses to address key limitations and assess robustness of the base case results, namely changing the treatment effect outcomes to reflect an updated NMA which takes into account patient stroke risk, correcting the hazard ratio for edoxaban in respect of TIA, updating stroke acute costs and correcting a potential coding error for stroke management costs. The results generated (see response section 11 below) highlight the significant impact on cost-effectiveness results. Addressing these parameters changes the sequential order of DOACs in terms of their cost-effectiveness and thus calls into question the robustness of the recommendations in the draft guidelines. Details of our concerns relating to these aspects and other concerns, are detailed within our response below. Despite the conclusions derived from our exploratory analyses, DSUK agrees with the general consensus in the literature as well as other published clinical guidelines, that there is insufficient evidence to conclude that any DOAC is superior to another. We would encourage the Committee to amend the draft guidelines and to recommend all four NICE approved DOACs as equal options in accordance with their respective NICE Technology Appraisals. The choice of DOAC should be based on discussions between patient and prescriber and taking into consideration all relevant clinical and individual patient factors. As such, we believe that recommendations 1.6.3 – 1.6.5 (page 9, lines 11-28) and recommendation 1.6.7 (page 10, lines 1-4) should therefore be struck out, and corresponding changes made to the relevant explanatory sections. DSUK considers that the current draft recommendations in section 1.6.3, 1.6.4, 1.6.7, (page 9 line 11 to page 10 line 4) if made final, would be unreasonable, unfair, and likely unlawful, in light of the available evidence. Based on issues raised in this response,, including identified potential modelling errors and previous conclusions from the NICE Technology Appraisal Committees, the decision would very likely be considered irrational by any reviewing court. DSUK continues to take advice on this issue and its rights are fully reserved at this time. In conclusion, DSUK has significant concerns relating to the validity and reliability of Sterne et al's findings to differentiate between the four DOACs. In this response, we have highlighted various potential errors and limitations with the methodology and the R model which should be taken into consideration by the NICE Guideline Committee. Furthermore, DSUK would recommend that an independent group be commissioned to review and critique the research conducted by Sterne et al. before it is used for decision making purposes. Any decision to	

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					issue the guidelines in their current form, without taking into account these additional factors and the weaknesses of the evidence will therefore be outside of the range of reasonable responses to the evidence available to any rational decision-maker. *Note: For the purpose of this response, "Sterne et al." refers to Jonathan Sterne and his research team who conducted the NMA and cost-effective analyses that underpin the draft CG180 clinical guidelines. "Sterne JAC et al. (2017)" relates specifically to the NIHR Health Technology Assessment report published in March 2017. "Lopez-Lopez (2017)" relates specifically to the BMJ publication of the Sterne et al. research and its findings.*	
SH	Daiichi Sankyo UK Limited	Guideline	General	General	SECTION OVERVIEW The points set out above form the basis for DSUK's overall concerns with the recommendations made in the draft Guideline. In order to explain and evidence these concerns, we have addressed them according to key passages and themes in the draft Guideline and other documents supporting the consultation. The areas covered are as follows: 1. Use of Guideline instead of MTA process 2. Handling heterogeneity and uncertainty when considering the relative clinical effectiveness between DOACs 3. Conclusions of superiority driven by differences in clinical outcomes – overinterpretation of the evidence 4. Lack of consideration of non-RCT data 5. Dosing of apixaban and dabigatran in UK clinical practice 6. Exclusion of published TIA data for edoxaban 7. Potential errors in model costs for ischaemic stroke and intracranial haemorrhage 8. Methodologist review and model critique 9. Lack of transparency and reporting of R economic model 10. Inappropriate use of CEACs to compare multiple interventions 11. Exploratory alternative modelled scenarios 12. Lack of consideration of practical factors and patient preference 13. DOAC switching and patient safety 14. DOAC pricing DSUK will discuss each of these key aspects in turn as part of this response.	Thank you for your comment. We have addressed your comments separately.

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					Additionally, the following additional sections have also been put forward for your review and consideration 15. Response to Question 2 16. Response to Question 3 17. Scientific accuracy of data included 18. Documentation errors	
SH	Daiichi Sankyo UK Limited	Guideline	General	General	In conclusion, DSUK has significant concerns relating to the validity and reliability of Sterne et al's findings to differentiate between the four DOACs. In this response, we have highlighted a number of potential errors and limitations with the methodology and the R model which should be taken into consideration by the NICE Guideline Committee. Furthermore, DSUK would recommend that an independent group be commissioned to review and critique the research conducted by Sterne et al. before it is used for decision making purposes. DSUK would encourage the Committee to amend the draft guidelines and to recommend all four NICE approved DOACs as equal options in accordance with their respective NICE Technology Appraisals. The choice of DOAC should be based on discussions between patient and prescriber and taking into consideration all relevant clinical and individual patient factors.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles of shared decision making and supporting adherence in the NICE guidelines on medicines adherence, medicines optimisation and patient experience in adult NHS services.
SH	Daiichi Sankyo UK Limited (Contains conf comments)	Guideline	028	024-028	3.0 CONCLUSIONS OF SUPERIORITY DRIVEN BY DIFFERENCES IN CLINICAL OUTCOMES – OVERINTERPRETATION OF THE EVIDENCE As noted above, it is accepted within the academic community that caution must be exercised when relying on indirect evidence such as Sterne et al in making such strong claims of superiority and sequential recommendations. We consider that there is additional evidence that, when taken into account, further undermines the conclusions derived by the Committee from the Sterne et al. NMA. We have set out below the additional evidence which we consider should inform NICE's reasoning in reconsidering the Guideline (as suggested in the NICE factsheet "Developing NICE Guidelines: how to get involved"). The draft recommendations, based on the findings from Evidence Review 6, report cost-effectiveness differences between the DOACs. It states that "*Results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants*	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). Please note that the uncertainty in the NMA was propagated into the economic model. We acknowledge in our interpretation of the incremental costs, QALYs, and net monetary benefit (and using the CEACs) that the results are uncertain. The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals were wider and the results

					performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran." **3.1 Clinical effectiveness differences between DOACs** The updated report by Sterne et al. includes the results of a NMA across multiple clinical outcomes. The authors interpret each set of results on a particular clinical outcome in turn, noting where they have found evidence for superiority for DOACs versus warfarin, or where they found evidence that one DOAC appears superior to another. Across the majority of outcomes in the NMA, it is worth noting that there was weak or no evidence to differentiate between DOACs. In other words, the estimated treatment effects for pairwise comparisons between DOACs included the point of no difference. The authors explored meta-regression but did not conduct any subgroup analyses – for example to explore the impact on treatment effect estimates of differences across DOAC trial populations. In contrast, a separate NMA conducted by Leicester University (Data on file; academic in confidence) did explore the impact of differences across trial populations. The Leicester University NMA conducted a subgroup analysis to explore differences across DOAC trial populations based on baseline stroke risk ($CHADS_2$ score). This NMA subgroup analysis estimated treatment effects for patients with a high risk of stroke at baseline, as defined by a $CHADS_2$ score ≥2. The subgroup analyses found that once differences across trial populations (in terms of $CHADS_2$ score) had been adjusted for, the evidence for differences between DOACs was more uncertain. For example, for the outcome SSE, in the $CHADS_2$ ≥2 subgroup, there was no evidence of a difference in treatment effect between any pair of DOACs, in contrast to the Sterne et al. NMA in the overall trial population. These findings are similar to a previously published NMA (Fernandez et al., 2015). Table 2: Comparative efficacy of DOACs for SSE: results from Sterne et al. vs Leicester $CHADS_2$ ≥2 subgroup | | Sterne et al. NMA (OR, 95% CI) | Leicester subgroup NMA (OR, 95% CI) | | --- | --- | --- | | Dabigatran (150 mg bd) vs Apixaban (5 mg bd) | 0.82 (0.62, 1.08) | [redacted] ([redacted], [redacted]) |	more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore were no longer confident to recommend a specific DOAC or DOACs. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.

Edoxaban 60 mg od vs Apixaban (5 mg bd)	1.09 (0.87, 1.39)	[redacted]
Rivaroxaban (20 mg od vs (Apixaban (5 mg bd)	1.11 (0.87, 1.41)	[redacted]
Edoxaban (60 mg od) vs Dabigatran (150 mg bd)	1.33 (1.02, 1.75)	[redacted]
Rivaroxaban (20 mg od) vs Dabigatran (150 mg bd)	1.35 (1.03, 1.78)	[redacted]
Rivaroxaban (20 mg od) vs Edoxaban (60 mg od)	1.01 (0.80,1.27)	[redacted]

(Abbreviations: bd = twice daily; CI = confidence interval; mg = milligrams; od = once daily; OR = odds ratio)

Furthermore, pairwise comparisons from the Leicester University NMA subgroup show significant differences between the DOACs with regards to major bleeding whilst Sterne et al.'s overall population findings did not. Table 3 below shows that only edoxaban and apixaban were superior to warfarin and to the other DOACs, dabigatran and rivaroxaban for reduction of major bleeding. It should be noted that the Leicester NMA only explores heterogeneity due to baseline stroke risk (for which there were data availability limitations), and that there remains other notable differences across trials which could not be adjusted for due to lack of data.

Table 3: Comparative safety of DOACs for major bleeding: results from Sterne et al. vs Leicester $CHADS_2$ ≥2 subgroup

	Sterne et al. NMA (OR, 95% CI)	**Leicester subgroup NMA (OR, 95% CI)**
Dabigatran (150 mg bd) vs Apixaban (5 mg bd)	1.33 (1.09, 1.62)	[redacted]
Edoxaban 60 mg od vs Apixaban (5 mg bd)	1.11 (0.92, 1.35)	[redacted]
Rivaroxaban (20 mg od vs (Apixaban (5 mg bd)	1.45 (1.19, 1.78)	[redacted]
Edoxaban (60 mg od) vs Dabigatran (150 mg bd)	0.84 (0.69,1.02)	[redacted]

Rivaroxaban (20 mg od) vs Dabigatran (150 mg bd)	1.10 (0.90, 1.34)	[redacted] ([redacted], [redacted])
Rivaroxaban (20 mg od) vs Edoxaban (60 mg od)	1.31 (1.07, 1.59)	[redacted] ([redacted], [redacted])

(Abbreviations: bd = twice daily; CI = confidence interval; mg = milligrams; od = once daily; OR = odds ratio)

3.2 Cost effectiveness differences between the DOACs

Cost-effectiveness results in the analyses are driven by the clinical endpoints from the competing risks NMAs conducted by the Sterne et al. However, as noted above, findings from the Leicester University NMA subgroup analysis produces some notable differences in estimated treatment effects. DSUK believes that a cost-effectiveness analysis that has failed to take account of important differences in populations across clinical trials, cannot provide a reasonable basis for any decision to adopt the draft Guideline.

To illustrate this point, we draw reference to the clinical outcome intracranial haemorrhage (ICH), which is included explicitly as a health state in the Sterne et al. economic model. In the Sterne et al. NMA dabigatran 150 mg has the highest impact of all the DOACs in terms of reducing ICH compared to warfarin 0.36 (0.26, 0.49). However, the Leicester University subgroup NMA estimated a smaller treatment effect and a greater degree of uncertainty for this outcome [redacted] ([redacted], [redacted]). Indeed, the treatment effect for dabigatran in the subgroup is very similar to that for apixaban [redacted] ([redacted], [redacted]) and edoxaban [redacted] ([redacted], [redacted]). Rivaroxaban has a numerically smaller treatment effect than other DOACs [redacted] ([redacted], [redacted]).

DSUK believes it to be fundamentally important that treatment effects incorporated in the cost-effectiveness analysis take account of differences in DOAC trial populations and reduce underlying heterogeneity. The Leicester University NMA should be considered as exploratory and has limitations to inform the economic model due to significant data availablity challenges for the $CHADS_2$ subgroup across all endpoints and treatments. However, DSUK considers it builds upon the Sterne et al NMA for decision-making. Treatment effects for comparable trial populations should be included in the Sterne et al. model.

Importantly, subgroup analyses to take account of stroke risk were not conducted by Sterne et al. and we would therefore query both (1) the relevance of their findings to NVAF patients who would be at risk of stroke and more likely to be treated with DOACs, and (2) the limitation of their methodology to explore heterogeneity due to differences in patient characteristics.

					Whilst the NMA by Leicester University yielded useful findings, DSUK would still urge caution in utilising the results from any NMA, including the Leicester University and Sterne et al. work, in drawing strong conclusions on the differences between the DOACs. DSUK has explored alternative cost-effectiveness model scenarios reflecting changes to the base case model. This includes replacing the clinical outcome hazard ratios with data from the Leicester University NMA subgroup analysis, where available. For endpoints where data was not available, the model utilised results from Sterne et al. where there were still gaps in the data (e.g. data for TIA, systemic embolism and other CRB were sourced from the Sterne et al. Health Technology Assessment report (2017). Thus this approach remains conservative for edoxaban. The cost-effectiveness results from this exploratory exercise are available in response section 11.0 below. **3.3 Overinterpretation of indirect evidence** DSUK believes that the results of the Sterne et al. 2017 analysis are likely overinterpreted. Looking at tables 18-25 of the draft guidance, the point estimates of the odds ratio of each treatment for each outcome showcase the fact that no treatment consistently dominates in terms of outcomes and additionally that they are comparable in terms of size of effect. As an example of overinterpretation, when comparing the mean quality-adjusted life year (QALY) differences across treatments compared to warfarin in the forest plot presented in Figure 1, one can see that the mean differences are nearly the same for all four treatments. The slight differences in the four treatments below should not be overinterpreted as important differences between drugs in this class. Similarly, the forest plot of the mean total cost differences relative to warfarin in Figure 2 and the forest plot of the net monetary benefit of each treatment in Figure 3 do not show evidence of difference across treatments, providing evidence of class effect for the four DOACs. This evidence demonstrates that rather than giving rise to definitive conclusions in relation to preferences between different DOACs in a clinical setting, a range of interpretations is possible, and therefore the range of rational responses to the Sterne et al. NMA does not include the definitive conclusions purported to be drawn from them in the draft Guideline. Figure 1: Forest plot - mean QALY differences*	

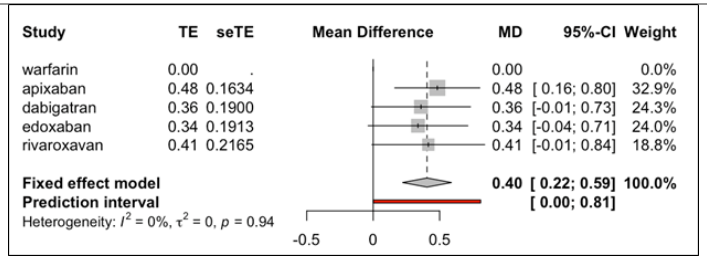

*Figure 1 was produced using the ''total_qalys'' dataset produced from the R code

Figure 2: Forest plots of total costs relative to warfarin*

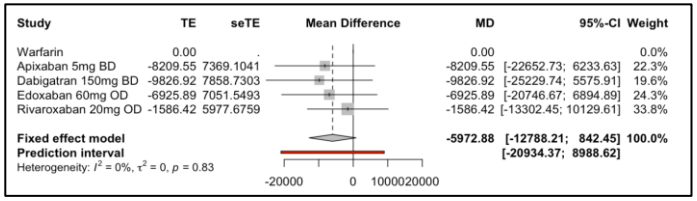

*Figure 2 was produced using the ''total_costs'' dataset produced from the R code

Figure 3: Forest plots of net monetary benefit*

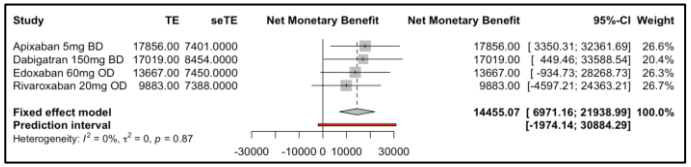

*Figure 3 was produced using the ''total_costs'' dataset and ''total_qalys'' dataset produced from the R code

The marginal numerical differences in the four treatments should not be overinterpreted as important differences between drugs in this class. Similarly, the forest plot of the mean total cost differences relative to warfarin in Figure 2 and the forest plot of the net monetary benefit

					of each treatment in Figure 3 do not show evidence of difference across treatments, providing evidence of class effect for the four DOACs. The forest plots (Figures 1-3) are developed as illustrative since the fixed effect model estimate has not adjusted for the correlation between studies (the model outputs were used). The costs per day of each intervention differ at most by £0.20. Given the fact that per day costs are nearly indistinguishable, in addition to the fact that the odds ratios for each treatment for each outcome are approximately equivalent, DSUK believes that the guidance that is given is based on an overinterpretation of the results as presented – the guidance that two of the treatments should be preferred to the others is misplaced when taking into account the data and the results of the modelling. Based on the above, it appears that NICE has accorded manifestly inappropriate weight to what are demonstrably very minor differences in odds ratios for each treatment for each outcome and per day treatment costs, thereby extrapolating preferences between DOACs. DSUK consider that such extrapolation is not within the range of reasonable responses to the data. DSUK has concerns that the draft NICE clinical guidance is based on an overinterpretation of the results as presented in Evidence Review 6 analysis. Claims of superiority between the DOACs and the recommendations for sequential DOAC usage, are founded upon NMA findings that cannot be compared for reasons of vast heterogeneity (as mentioned previously) and overinterpretation/generalisation of statistical evidence provided in Sterne et al.'s analyses. DSUK believes there is strong evidence to support an argument for a class effect in favour of all DOACs over warfarin, supported by direct trial evidence, but weak or no valid evidence to suggest superiority within the DOACs and any recommendations to support sequential DOAC usage. Such claims would rely on the findings from head-to-head trials between the DOACs or individual patient data from the existing DOAC RCTs, adjusted for patient and study differences, to enable direct comparison of efficacy, safety and cost-effectiveness.	
SH	Daiichi Sankyo UK Limited	Guideline	General	General	FAILURES IN NICE'S DECISION-MAKING PROCESS	Thank you for your comment. The limitations of the model are fully discussed in section 12.2.2 of evidence report G2 and in the

					DSUK considers that the issues summarised above (and set out in detail in the remainder of our response) give rise to the following failures in the process followed by NICE in deciding to make the recommendations in the draft Guildeine: • NICE has misinterpreted section 9.1 of its Manual on Developing NICE guidelines (PMG20) (pages 164-171), by making recommendation 1.6.3 'strong' on the basis of uncertain and weak (by its own admission) evidence; • the draft Guideline irrationally and unlawfully purports to substitute the established (and evidentially robust) method of comparing similar treatments, namely the Multiple Technology Appraisal ("MTA") process with an alternate process of comparative recommendation; • the draft Guideline is beyond the scope of NICE's power to issue non-binding Guidelines, given that it would have the effect of making recommendations properly reserved for the HTA and comparative MTA procedures (as is made clear in NICE's published procedures under regulations 5 and 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013/259 ("the 2013 Regulations"); • it follows that NICE has potentially erred in seeking to issue a recommendation of the kind covered by the HTA process (or the MTA process), the power for which is provided under regulation 7 of the 2013 Regulations, which properly 'occupies the field' in relation to specific treatment recommendations – the draft Guideline is ultra vires the powers vested in NICE under the relevant statutory scheme; • issuing the guideline in its current form will be a breach of DSUK's legitimate expectation of being able to continue to trade in the UK on the basis of the edoxaban HTA published by NICE (last reviewed in 2018), which directly contradicts the draft Guideline while being based on the same underlying data; • as a result of the above, DSUK considers that any decision to issue the Guideline would ultimately result in a breach of DSUK's Article 1, Protocol 1 rights under the Human Rights Act 1998, and • DSUK consider that recommending apixaban in preference to other drugs in the Guideline without necessary justification would facilitate the abuse of a market position by a dominant player in such a way as to infringe article 106 of the Treaty on the Functioning of the European Union. These assertions are, in turn, based on the following defects in the decision-making process followed by NICE in developing the draft Guideline. *Unreasonable process used to reach decision*	committee's discussion of the evidence in evidence report G1. The committee agreed that it was highly unlikely that the resources allocated to performing a new NMA based on our own data would be justified by any gains over Lopez-Lopez, and therefore that using Lopez-Lopez might be preferable to carrying out our own NMA. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.4.2 refers to following the principles of shared decision making and supporting adherence in the NICE guidelines on medicine adherence, medicines optimisation and patient experience in adult NHS services, which would include taking into account personal preferences such as dose frequency. It may be argued that broader sources of data can help determine the "real-world" effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making. We have reviewed and re-worded the section in section 1.5.2, and have removed the statement by one member of the committee about the quality of the Lopez-Lopez NMA. The decision to use Lopez-Lopez was based on reasons other than this statement, as section 1.5.2 hopefully now makes clear.

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					First, we consider that relying on the Sterne et al NMA alone in reaching the decision to publish the draft Guideline is irrational: NICE has placed manifestly disproportionate weight on the Sterne et al. NMA at the expense of all other relevant considerations including Real World Evidence (RWE) and practical patient factors. The acknowledgment of limitations in the Sterne et al NMA is absent form NICE's analysis. In addition, as discussed at Comment 16 below, the Committee appears to have placed undue weight on one single Committee member's viewpoint, rather than exercising its decision-making power collectively, and subjecting individual Committee member's views to reasonable objective scrutiny. At the very least, when seeking to rely on a single NMA to make preferential recommendations, a reasonable decision-maker must undertake some form of secondary analysis in relation to that proposed course (such as independent assessment by experts in NMA methodology within Bayesian frameworks as further described below), rather than forgoing further rigorous review on the basis of a single Committee member's view. *Misapplication of own guidance in relation to Guidelines made under regulation 5 of the 2013 Regulations* Second, NICE's own published guidance on its process for developing Guidelines (PMG20: Developing NICE guidelines: the manual, last updated 15 October 2020 – the "Guidelines Manual") cautions against the risks of relying on secondary evidence such as NMAs. The manual further warns (again in section 9.1): *'The use of indirect evidence must be considered carefully by the committee, with explicit consideration of the features of the condition or interventions that allow extrapolation to a different context or population. This also applies when extrapolating findings from evidence in different care settings (for example, between primary and secondary care). The committee should consider and document any similarities in case mix, staffing, facilities and processes, and any limitations.'* The risks inherent with reliance on such indirect evidence to base preferential recommendations for the DOACs were not explicitly considered by the committee. In further misapplication of the Guidelines Manual, NICE proceeds to make a 'strong' recommendation to offer apixaban or dabigatran in preference to other DOACs, at paragraph 1.6.3 Guideline (by using the word 'offer'), despite its own acknowledgement at section	The NICE methods manual (https://www.nice.org.uk/process/pmg20/chapter/introduction) states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. Responses to the other comments relating to the health economic model have been provided in the individual comments sent by DSUK. Please refer to these for more information.

					1.7.1.3. (page 70 line 25 to page 72 line 17) of Evidence review G1: Anticoagulant Therapy for stroke prevention in people with atrial fibrillation, that 'due to model limitations such as the uncertain utility data and reliance on indirect treatment effect evidence, the uncertainty was likely to be even higher than estimated'. For the avoidance of doubt, based on these evidence limitations, and in conjunction with the other issues listed throughout our consultation document, we do not consider that a rational decision-maker could proceed to make any recommendation, whether to offer, consider or discuss, apixaban or dabigatran in preference to other DOACs . We consider that the Guidelines Manual constitutes an established procedure for the giving of advice or guidance under paragraph (4), Regulation 5 of the 2013 Regulations, which NICE is therefore required to adhere to. *Failure to take into account relevant factors* Third, it is clear that in reaching its conclusion, NICE failed to take into account a number of plainly material factors in its reasoning. While we accept that Parliament has afforded NICE a measure of discretion (within the statutory scheme applicable to it) to reach its own conclusions on each relevant factor, we do not accept that a decision that entirely ignores and fails to engage or explain its reasoning in relation to clearly relevant factors can be sound as a matter of public law. Relevant factors that NICE has failed to take into account in its decision-making process are, in summary, as follows: • the reported differences between the underlying DOAC RCT studies, which the NMA seeks to compare on an equal footing, thus drawing its entire conclusion from a demonstrably flawed point of comparison (Camm et al 2018); • the uncertainty in clinical and cost-effectiveness estimates between DOACs; • the inherent risk (which in our view is crystallised here) of over-interpretation of the indirect comparison results reported by the NMA; • the recognised flaws in the use of Cost Effectiveness Acceptability Curves ("CEACs") to compare multiple interventions and “rank” treatments, which has been criticised as potentially misleading (for example in Fenwick E et al. (2001)); • sequential DOAC recommendations, as stated in these draft guidelines, are not consistent with other referenced International Atrial Fibrillation (AF) Guidelines nor the current NICE CG180 (2014), including:	

					○ the recent European Society of Cardiology (ESC) '2020 Guidelines for the diagnosis and management of atrial fibrillation', which recommend all DOAC options as parity options within their licensed indication (ESC, 2020); and ○ a recent European Medicines Agency (EMA) report, based on the findings from an EMA-funded real-world study, which also support parity between the DOACs and found there to be insufficient data to allow robust conclusions to be drawn on comparisons between these medications (EMA, 2020); • the limitations of meta-regression methods when data is sparse in assessing and adjusting for treatment effect modifiers, and the potential value of sub-group analyses to assess the robustness of model findings; • ERG comments in an earlier NMA used in Edoxaban's Technology Appraisal explicitly acknowledged by NICE, which also arise in relation to this NMA; • a range of recent non-RCT studies showing, variously, that edoxaban was the only DOAC that did not show an increase of stroke risk vs VKA; that edoxaban among all DOACs had the lowest matched risk of major bleeding, fatal recurrent stroke, fatal composite outcome and all cause death versus warfarin; and other significant outcomes, which further described below; • a number of studies relating to inappropriate low dosages of apixaban in clinical practice; • disregarded published Transient ischemic attack ("TIA") evidence from ENGAGE AF-TIMI 48 in relation to edoxaban; • patient preference for once daily doses as opposed to twice daily, including evidence of reduced compliance with more frequent dosage requirements; • improvements in stroke outcomes since 2014 which have reduced the costs associated with stroke; *Mistakes of fact* Fourth, NICE has made a number of mistakes as to the facts underlying the decision, which ought to have been within its knowledge. Based on the documents supporting the consultation, a number of these played a material part in NICE's reasoning, while some played a decisive part. These are in summary: • the omission and material disregard of, the published TIA evidence from ENGAGE AF-TIMI 48 as part of the cost-effectiveness model (see in particular Comment 13 below);	

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					• the wrongful assumption as to the comparability of the data from the trials referred to in the NMA; • potential errors in the R model such as in the calculation of stroke costs – model cycles are 3 months in duration, however, the model assigns a full year's worth of costs per 3 month cycle (a decisive factor); *Use of regulation 5 process to undermine recommendation made under regulation 7* Fifth, the draft guideline contradicts prior recommendations and comments by NICE in relation to all four DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) that have been assessed in previous STAs and deemed to be a cost-effective use of NHS resources. As mentioned above, in our view this unlawfully overreaches beyond the scope of NICE's powers under regulation 5 of the 2013 Regulations by seeking to effectively substitute a recommendation made under regulation 7 with a recommendation under regulation 5. It is therefore unlawful for NICE to make a recommendation pursuant to regulation 5 that undermines a regulation 7 recommendation, particularly where the regulation 5 recommendation has been reached on a less rigorous evidential basis than the regulation 7 recommendation (that provides the basis for a rigorously evidenced recommendation to fund treatments).	
SH	Department of Cardiology, Northumbria Healthcare NHS Foundation Trust	Guideline	009	6-22	Section 1.6.2 appears to be at odds with the subsequent section restricting use of NOAC/DOACs. It also conflicts with the technology appraisals quoted. If they are all recommended options why restrict in 1.6.3?	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.
Stake holder	Department of Cardiology, Northumbria Healthcare NHS Foundation Trust	Guideline	010	001	There is a recommendation to switch patients on other anticoagulants (including NOACs) to either Apixaban or Dabigatran. This is not clinically sensible when a patient is tolerating an effective drug; it is generally best left alone. In addition there is an actual real increase in cost entailed in a switch eg. Edoxaban to Apixaban. This would lead to a tangible increase in their prescribing costs and workload. The patients would be switched from a treatment NICE endorses as appropriate and cost effective in its technology appraisals, to another similar drug which is also appropriate but more expensive.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted.
Stake holder	Department of	Guideline	013	022	A long acting rate limiting calcium channel blocker is generally felt to be appropriate. There is no evidence either way but expert consensus would support this. Similarly a cardio selective	Thank you for your comment. The committee agreed that the evidence reviewed did not allow a

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	Cardiology, Northumbria Healthcare NHS Foundation Trust				beta blocker (BB) is most appropriate. BB are similarly not usually licenced for AF rate control but widely used. It makes sense to recommend what expert consensus supports.	preference to be made between calcium channel blockers and beta-blockers and that there was not consensus in this area to be able to make consensus recommendations. In addition, the review did not include within-class comparisons, meaning a preference for particular types of beta-blockers or calcium channel blockers could not be made.
Stake holder	Department of Cardiology, Northumbria Healthcare NHS Foundation Trust	Guideline	014	004	Typo: “as” or “for”	Thank you for your comment, this has been corrected.
Stake holder	Department of Cardiology, Northumbria Healthcare NHS Foundation Trust	Guideline	020	009	This is not clear. An individual with CHADSVaSc of 0 does not necessarily require anticoagulation if “*stable sinus rhythm is not successfully restored within the same 12 48-hour period after onset of atrial fibrillation or there are factors indicating a high risk of atrial fibrillation recurrence ……”* The guidance suggests this is in itself an indication and is generally confusing. We do support a strategy of “generous” anticoagulation in patients who have single episodes of AF with raised stroke risk but not in those with low risk, even if recurrent episodes are likely. This section isn’t very clear.	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Stake holder	Department of Cardiology, Northumbria Healthcare NHS Foundation Trust	Guideline	022	013	The wording of this section is confusing. “AF is no longer detectable”. Presumably this means if the patient is in sinus rhythm at the time of the assessment as AF may be paroxysmal and stroke risk is still elevated. This would be much clearer wording. Also, from the comments it is clear that the authors wish this to be applied to individuals after apparently successful AF ablation but this isn’t made explicit.	Thank you for your comment. These recommendations do apply to people post-DC cardioversion and ablation. The recommendations state that discussions about whether to stop anticoagulation should be based on stroke and bleeding risk scores and not whether or not AF is no longer detectable. We have edited the discussion in the rationale and impact section to make this clearer.
SH	Guildford and Waverley ICP	Guideline	010	005	We are very concerned about the recommendation, “For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist and are stable, discuss the option of switching treatment at their next routine appointment”.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs

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					Our local health economy has invested considerable effort and money to ensure that the anticoagulants prescribed for individual patients have been accompanied by the appropriate counselling and monitoring, with special attention to renal function, The recommendation to switch patients would either require considerable additional investment (the evidence review does not demonstrate savings sufficient to justify this) or a loss of safety.	has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.
SH	Icentia	Guideline	24	1-4	Recommendation for research - Tests to Diagnose Paroxysmal Atrial Fibrillation: Do self-administered, home-based ECG monitoring solutions for detection and diagnosis of AF have sufficient effectiveness and accuracy?	Thank you for your comment. The research recommendation would include home-based technologies.
SH	Johnson & Johnson Medical Limited	Guideline	016	023	Overall, Johnson & Johnson Medical is supportive of NICE's methodological approach to the evidence review and cost-effectiveness analysis. However, the assumptions used for the laser ablation equipment costs in the cost-effectiveness analysis, that has led to the recommendation for laser ablation, should be re-examined (see comment 21 for full details).	Thank you for your comment. Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 17.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.
SH	Johnson & Johnson Medical Limited	Guideline	016	023	Johnson & Johnson Medical supports recommendation 1.7.19 for radiofrequency point by point (RF PP) ablation. RF PP ablation is the most established type of ablation treatment as demonstrated by the number of studies included in the systematic literature review, which span the last 15 years. We agree that the evidence confirms that RF PP provides a more favourable reduction in AF recurrence rates as compared to other technologies and that this has played a key role in the results of the cost-effectiveness analysis.	Thank you for your comment.
SH	Johnson & Johnson	Guideline	031	019	The ablation equipment costs associated with laser ablation used in the primary cost-effectiveness analysis are likely underestimated and therefore inaccurate. We believe that the	Thank you for your comment.

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	Medical Limited				committee's sensitivity analysis (SA21), which uses a 30% increase in costs for laser ablation, provides a more accurate depiction of the true costs associated with laser ablation procedure. The costs in the current base case analysis may be underestimated because: - It is missing a circular mapping catheter that is required to perform a laser ablation procedure (see comment 5 for full details) - It uses an inconsistent methodology for laser ablation equipment cost (expert opinion) vs. other ablation technology costs (NHS catalogue price) (see comment 17 for further details) If the sensitivity analysis which increased the total equipment costs for laser by 30% was the primary analysis, laser ablation would be less cost-effective than RF PP.	Following stakeholder consultation some omissions were identified, new data provided, and issues raised that led to amends to the economic model. These included: -Edits to some of the equipment costs further to stakeholder comments (including addition of circular mapping catheter and cable) -30% uplift for laser equipment costs from local source used as the base case rather than sensitivity analysis Overall, the results indicate RFPP is the most cost effective option and the recommendation has been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP. The committee considered these people to include those for whom a short procedure time or reduced risk of fluid overload from saline irrigated RF catheters was preferred, for example those with a recent history of decompensated heart failure.
SH	Johnson & Johnson Medical Limited	Guideline	032	022	The choice of sedation method is not technology specific, but rather reflects hospital resources, clinical judgement and patient preference. We would like to clarify that evidence demonstrates the safety and efficacy of conscious sedation with RF PP technology. This is supported by the RF PP studies selected by NICE for the analysis, which include use of general anaesthesia and conscious sedation. Studies within the NICE systematic literature review that use conscious sedation in both arms include: Hunter 2015, Koch 2012, Podd 2015, Schmidt 2013, Ucer 2018, Watanabe 2018. In addition, there are many other studies which demonstrate the safety and efficacy of conscious sedation during RF PP procedures, including: Chikata A, Kato T, Yaegashi T, et al. General anesthesia improves contact force and reduces gap formation in pulmonary vein isolation: a comparison with conscious sedation. Heart Vessels. 2017;32(8):997-1005. Tang RB, Dong JZ, Zhao WD, et al. Unconscious sedation/analgesia with propofol versus conscious sedation with fentanylmidazolam for catheter ablation of atrial fibrillation: a prospective, randomized study. Chin Med J (Engl). 2007;120(22):2036-2038 Cho JS, Shim JK, Na S, Park I, Kwak YL. Improved sedation with dexmedetomidine-remifentanil compared with midazolamremifentanil during catheter ablation of atrial fibrillation: a randomized, controlled trial. Europace. 2014;16(7):1000-1006.	Thank you for your comment. We acknowledge that RF point-by-point is also performed under conscious sedation in the committee's discussion of the evidence in evidence review J1.

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					Moravec, O., et al. General anesthesia or conscious sedation in paroxysmal atrial fibrillation catheter ablation. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2020 Apr 6. 2020.	
SH	Kent Surrey Sussex Academic Health Science Network	Guideline	010	001	In any normal times, we believe it would not be appropriate to switch drugs within a class where patients are stable and has previously expressed a preference for edoxaban or rivaroxaban. We are however, not in normal times but instead in the middle of the COVID19 pandemic with major pressures on healthcare. There is very high workload in primary care and significantly less face to face contacts. Advising GPs to use the next routine appointment to discuss switching drugs in unnecessary and those appointments could be used in a much more useful way for monitoring of all long-term conditions. Switching from Edoxaban or Rivaroxaban is likely to require additional blood testing for renal function before switching. It is inappropriate to undertake any unnecessary change in medical therapy that might require more face to face appointments and as a result an increased risk of contracting COVID19 in a high-risk population. Hopefully this will only be significant or the next few months, but NICE need to consider that the country may still be having to deal with COVID19 for the next year or longer. The first priority in this health emergency should be patient safety and changing stable medication at this time is inconsistent with that priority.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted.
SH	Kettering General Hospital NHS Foundation Trust	Guideline	009	011 - 028	*Offer anticoagulation with either apixaban or dabigatran to people with atrial fibrillation and a CHA2DS2-VASc score of 2 or above, taking into account the risk of bleeding. ...* *Consider anticoagulation with either apixaban or dabigatran for men with atrial fibrillation and a CHA2DS2-VASc score of 1, taking into account the risk of bleeding. ...* *If apixaban and dabigatran are not tolerated in people with atrial fibrillation, offer anticoagulation with either edoxaban or rivaroxaban.* Current risk scores (including Orbit) do not take full account of every important comorbidity associated with increased thromboembolic risk, e.g. dyslipdaemia. They only take account of congestive heart failure, age, diabetes mellitus, gender, history of stroke or vascular disease. For instance, obstructive sleep apnoea (OSA) is strongly associated with hypercoagulation, and clinical ischaemic events. Unsurprisingly, patients with OSA have higher CHADS2 and CHA2DS2-VASc scores, and they rise with severity of OSA. Since we know there was clinical heterogeneity between the various DOAC trials in AF, we duly envisage differing outcomes. Nice accordingly recognises patients in ROCKET-AF had a higher baseline risk of stroke or	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted

					systemic embolism (i.e. baseline CHADS2 of 3.6 for ROCKET-AF, 2.1 for ARISTOTLE, 2.1 for RE-LY) and also that the mean percentage time in therapeutic range was lower in ROCKET-AF (55%) than in ARISTOTLE (62%) and RE-LY (64%). It is understood that the inter-study differences between the populations being evaluated and in the study design of phase III DOAC stroke prevention studies in patients with non-valvular atrial fibrillation (e.g. ROCKET AF, ARISTOTLE, RE-LY, and ENGAGE AF), will yield differences in potential impact on outcomes, and that this also occurs in real-world data, e.g. XANTUS. For example, the definitions that are used to record bleeding events is substantially different between these studies. It is also understood that known risk factors for bleeding are largely the same as for stroke. Hence cohorts with higher CHADS2 and CHA2DS2-VASc scores are also more likely to bleed. It is therefore not entirely unexpected that ROCKET-AF had greater rates of non-major bleeding. Nice acknowledges there is no head-to-head data for apixaban compared with dabigatran or rivaroxaban. Yet, Nice appears to accept the proposition there are materially significant differences between the DOACs in AF by relying on 2 meta-analyses based on a stimulation fixed-effect model. This neither provides NICE sufficient nor robust scientific or clinical evidence to presently justify expressing a recommendation for any DOAC to be the generally preferred medication in patients with AF. Moreover, various learned societies have meanwhile actively refrained from presently recommending any specific DOAC(s) after having pored over the extensive available data. Furthermore, in the absence of sufficient proven differences in clinical effectiveness and side-effects between the various DOACs, important publications that outline variations in drug profiles and their interactions (e.g. North Central London Joint Formulary Committee) underscore the importance of enabling clinicians to retain choice over a spectrum of DOACs for what best suits the patient. NICE is correct to not overtly rank or favour DOACs for treatment of venous thromboembolic disorders. Endeavours to treat chronic conditions are undermined worldwide by a strikingly low adherence to therapies. Failure by patients on long-term treatment to adhere to their medication regime seems to account for ~50% of the shortfall in drugs delivering the therapeutic goals. Such patients are largely asymptomatic and do not immediately recognise	for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. Recommendation 1.6.2 refers to shared decision making and this should include a discussion of personal preference, clinical risk factors and factors likely to affect adherence. It may be argued that broader sources of data can help determine the “real-world” effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making.

					the benefits of extended duration of treatment. Most cardiovascular conditions are chronic and problems with adherence are prevalent, such as in hypertension. In the meantime, international and national guidelines from learned societies rightly promote patient choice during individualised planning of anticoagulation treatment according to the patient's personal, clinical and demographic profile, and specific thromboembolic risk, whilst these societies refrain from recommending any particular DOAC ahead of others in the presence of data that shows effectiveness of all the DOACs. Key to joint decision making in the care of patients with AF are patient choice and concordance with treatment. It is reported that > 80% of patients express a preference to take anticoagulation medication once daily compared with only about 8% that preferred a twice daily regimen. Notwithstanding the large body of data from hypertension studies overwhelmingly showing better concordance with patients actually taking their medication when prescribed once daily as opposed to further dosing such as b.d., recent meta-analyses supported reduced dosage frequency from multiple dosing to OD helping improve adherence to therapies among patients, across acute and chronic disease states Data shows that taking medication once daily for chronic cardiovascular disease decreases the risk of non-adherence to treatment by approximately 50%. Only this year, data from 17,462 patients with atrial fibrillation raised caution that patients on significant polypharmacy (as many AF patients are) may be at higher risk of stroke and mortality on apixaban (b.d) compared with warfarin and rivaroxaban (o.d). Patients with AF are not only at higher risk of stroke they are x3-4 more likely to suffer severe strokes and greater functional impairment compared with patients with normal sinus rhythm.Earlier this year, a retrospective cohort study of 20,473 patients with CHA_2DS_2-VASc score ≥2 treated with either rivaroxaban or warfarin reported for the first time with any DOAC that patients receiving rivaroxaban derived significantly greater risk reduction for stroke, especially severe stroke, and all-cause mortality after a stroke. This study may help inform anticoagulant choice. Also, for secondary prevention in AF patients after their first stroke, treatment with rivaroxaban was found to lead to significantly fewer recurrent strokes and TIAs, composite cardiovascular end-points, bleeding events, and hemorrhagic transformations of cerebral infarcts. The benefits were generally greater if rivaroxaban was started ≤14 days of the index stroke onset. Such data does not yet appear to be reported with other DOACs.	

					Nevertheless, until there is unequivocal clinical data to support superiority or specific supremacy of a particular DOAC(s), it is inappropriate for NICE to recommend a broadly preferred DOAC or to encourage switching to a preferred DOAC. As we do not presently have such data for superiority amongst DOACs, such NICE guidance goes against best medical practice and good clinical governance. It also fails to maintain NICE's independence and the full choice of DAOC therapy, whereby NICE hinders clinicians from tailoring patient care to the specific needs of the patient and from retaining the patient choice encouraged by guidelines arising from learned societies. Meanwhile, NICE's draft guidelines for AF, by singling out any specific DOAC, are unjustified and over-simplify clinical practice and wrongly sign post clinicians, especially non-specialists and colleagues in primary care. Contrary to the NICE draft guidance on AF patients that recommend apixaban as the preferred DOAC and/ or to switch patients to apixaban, the basis for caution to presently resist making the suggestion a specific DOAC has superiority over others is evident in some reported trials. For instance, the real world data from the REVISIT-US Study in non-valvular AF patients found that rivaroxaban was associated with a significant reduction of the combined endpoint of ischemic stroke or intracranial haemorrhage (ICH) and also a non-significant reduction in ischemic stroke compared to warfarin (n=22,822 matched patients); meanwhile apixaban was found to non-significantly reduce the combined endpoint of ischemic stroke or ICH versus warfarin, yet ischemic stroke risk was non-significantly increased with apixaban (n=8166 matched patients). Quite correctly, this would not be grounds to suggest rivaroxaban has superiority over apixiban or should become the preferred DOAC. Also, the effectiveness of DOACs seems to differ substantially between AF patients with and without a history of stroke or TIA; specifically, apixaban appears less effective in patients with a history of stroke or TIA. Furthermore, with improved adherence to medications also delivering improved outcomes, the resultant decreases in health care costs (for instance from an avoided stroke or severe stroke) must be fully accounted for in any analysis of cost-effectiveness. The importance of real-world data in financial considerations is evident. It is paramount that any economic evaluation of patient management retains 'cost-effectiveness' at its core, and fully accounts for the entire economic burden of AF, stroke management (mental and physical), severe strokes versus milder impairments, wider economic impact through family, friends and carers, amongst others. For treatment with DOACs this has to account for concordance with treatments and outcomes, offset against the costs of non-major bleeding.	

					The heterogeneity amongst patients included in DOAC studies and in the study designs necessitates caution during indirect comparisons across studies and subsequent representation of the published data, whilst resisting over-interpretation and unjustified recommendations, including data on cost effectiveness. For instance, the subject and methodological differences in the DOAC trials requires meta-analyses of phase III studies to be as robust as possible, whilst maintaining caution in translating purportedly 'direct' comparisons, especially where the outcomes of the comparator 'warfarin-treated' arms differ significantly, for both phase III and real-world data sets. Notwithstanding, limitations of indirect comparisons, such indirect comparisons should be used to generate hypotheses that require testing in dedicated randomised trials comparing the drugs directly, and should not be over-interpreted or relied upon to make any therapeutic recommendations in national guidelines. It is right that few countries presently make statements recommending one DOAC over another. Dong J, et al Atherosclerosis 2013 229:489–495 Yaggi H, et al N Engl J Med 2005 353:2034–2041 Hrynkiewicz-Szymanska A, et al Sleep Breath 2011 15:607–609 Szymanski F et al Sleep Breath (2015) 19:531–537 DOI 10.1007/s11325-014-1042-5 Nice [TA275] 27.02.13 Camm AJ et al, Europace. 2018;20(1):1-11 Mantha S et al, Thromb Haemost. 2012;108(3):476-484 Camm AJ et al, Eur Heart J. 2016 7;37(14):1145-53 Hirschl M et al, Vasa. 2019 48(2):134-147 Jansson M et al, Thromb Res. 2020 185:135-141 Xiaoxi Y et al AJC 2017 120; 9, 1549-1556 doi.org/10.1016/j.amjcard.2017.07.051 Nice [TA275] 27.02.13 Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fifibrillation	

					North Central London Joint Formulary Committee: Direct Oral Anticoagulant (DOAC) Interactions Aug 2018 NICE ng158: Venous thromboembolic diseases: diagnosis, management and thrombophilia testing NICE QS29: Venous thromboembolism in adults: diagnosis and management Dunbar-Jacob J, et al Annu Rev Nurs Res 2000; 18:48–90. Jackevicius CA, et al JAMA. 2002;288(4):462–467. Stuart B, et al Med Care Res Rev 2002; 59(2):123–145. World Health Organization. News. www.who.int/mediacentre/news/releases/2003/pr54/en. Song X, etc [abstract]. Value Health. 2010; 13:A170. Srivastava K, et al, Patient Preference and Adherence 2013:7 419–434 http://dx.doi.org/10.2147/PPA.S44646 Coleman C et al, Curr Med Res Opin. 2012;28(5):669-680 Bakhai et al BMC Cardiovascular Disorders 2013, 13:108 Caldeira D, et al, Rev Port Cardiol. 2014;33(7-8):431-437 Mentias A et al, Stroke. 2020; 51:2076–2086 Andrew N et al, Neuroepidemiology: 2013; 40:227–239. Ali A et al, J Atr Fibrillation: 2016; 8:1279. Alberts M et al, Stroke. 2020;51:549–555 Yasaka M et al, 2019: PLoS ONE 14(2): e0212354.	

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					Coleman et al, The REVISIT-US study, Current Medical Research and Opinion, 32:12, 2047-2053 Yang L et al, Am J Cardiol 2020; 126:29− 36 Bowrin K et al, J Mark Access Health Policy 2020 25;8(1):1782164 Camm AJ et al, Europace. 2018;20(1):1-11 Mantha S et al, Thromb Haemost. 2012;108(3):476-484 Lip G et al, J Am Coll Cardiol. 2012;60(8):738-746 Lopes R et al, Int J Cardiol. 2020;319:85-93	
SH	Leeds Teaching Hospitals NHS Trust	Guideline	009	017-022	Specific guidance would be helpful particularly for men and CHA_2DS_2-VASc score of 1 with AF and when anticoagulation should be considered i.e. does it matter what the score of 1 is for, is the risk the same for all i.e. age > 65 but no hypertension or diabetes.	Thank you for your comment. Recommendation 1.6.9 states that stroke prevention should not be offered to people under the age of 65 yrs with no risk factors other than sex
SH	Leeds Teaching Hospitals NHS Trust	Guideline	009	General	The VTE document contains details for patients with renal dysfunction, extremes of body weight, cancer etc, these specific groups and choice of agent would be helpful in this document. The recommendation of apixaban and dabigatran for all is not appropriate for certain groups.	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2). Which anticoagulant should be offered should be discussed in the context of shared decision making (recommendation 1.6.2) and this would include consideration of patient factors and clinical indications.
SH	Leeds Teaching Hospitals NHS Trust	Guideline	009	General	Patient choice is extremely important. This guideline lacks consideration of patient choice and therefore there are likely to be issues with adherence as there is no once daily anticoagulation option.	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2). Which anticoagulant should be offered should be discussed in the context of shared decision making (recommendation 1.6.2) and this would include consideration of patient factors and clinical indications.
SH	Leeds Teaching Hospitals NHS Trust	Guideline	009	General	Dabigatran is not widely used yet has been out the longest. I and other clinicians would find it difficult to change prescribing practices completely to use dabigatran. Many patients with this condition have poor renal function or require medication in compliance aids, both of these preclude dabigatran use	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2). Which anticoagulant should be offered should be

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						discussed in the context of shared decision making (recommendation 1.6.2) and this would include consideration of patient factors and clinical indications.
SH	Leeds Teaching Hospitals NHS Trust	Guideline	009-010	General	Many clinicians spend a long time with patients choosing the most appropriate anticoagulant for them. This is not considered in the statement regarding switching those not on apixaban and dabigatran to these drugs. The cost and resources of actively switching patients stabilised on either rivaroxaban or edoxaban with no consideration of patient choice is large and no consideration is given. The loss of confidence in the healthcare professional who initiated the anticoagulant has implications There is a potential for medication supply disruption and/or procurement issues with only two DOACs recommended	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. Recommendation 1.6.5 recommends a vitamin K antagonist if DOACs are contraindicated, not tolerated or not suitable.
SH	Leeds Teaching Hospitals NHS Trust	Guideline	022	011-016	When is AF classed as AF likely to recur i.e. patients with one episode of AF triggered by an event e.g. sepsis, alcohol, thyrotoxicosis, cardiac surgery, when should they be considered as having permanent/persistent or paroxysmal AF. Some guidance on this would be extremely helpful	Thank you for your comment. We did not perform an evidence review as part of this guideline update that would be able to inform recommendations on this area. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	Liverpool Health Partners	Guideline	009	011 – 028	*"Offer anticoagulation with either apixaban or dabigatran to people with atrial fibrillation and a CHA_2DS_2-VASc score of 2 or above, taking into account the risk of bleeding."* *"If apixaban and dabigatran are not tolerated in people with atrial fibrillation, offer anticoagulation with either edoxaban or rivaroxaban."* There has not been a head-to-head comparison of NOACs. Basing the recommendation on evidence from network meta-analyses relies on assumptions and has significant limitations. In general, the NOACs are effective and safe. There are some minor differences that may make a particular choice more appealing in certain situations. Therefore, it does not seem appropriate to 339eneralize these NOACs into 1st and 2nd line treatment options.	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. Recommendation 1.6.3 and 1.6.4 now recommend any licensed DOAC.
SH	Liverpool Health Partners	Guideline	016	023	*" Consider RF point-by-point ablation or laser ablation…."*	Thank you for your comment.

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					Few centres in the UK are actually able to offer laser ablation. The draft NICE guidelines do not discuss cryoablation, which is one of the most commonly used techniques in the UK (and worldwide). In the evidence review section, it is clearly acknowledged that laser ablation has limited evidence and the costings do not take into account the fact that new equipment will be needed to perform this procedure in the majority of hospitals. Furthermore, each technique (cryo, RF and laser) has its own set of advantages and disadvantages. A generalised statement based on costing benefits does not seem appropriate and also ignores patient choice in the matter. For example, some patients may be unable to tolerate general anaesthesia and therefore cryoablation may be more suitable for them. Decisions on ablation technique need to be individualised and a blanket statement that laser and RF is better than the other options do not seem helpful	The evidence based on all relevant studies showed that radiofrequency point by point ablation was more cost effective over a lifetime than antiarrhythmic drug treatment and other ablation strategies in people for whom 1 or more antiarrhythmic drug has failed. Our de novo model demonstrated that the greater costs of cryoballoon made it less cost-effective in our model. Nevertheless, recommendations 1.7.19 and 1.7.20 have been amended to reflect the fact that RF point by point may not always be possible. 1.7.20 now recommends cryoballoon or laser ablation in people who are assessed as unsuitable for radio frequency point-by-point ablation.
SH	Liverpool Health Partners	Guideline	027	024	It is important to distinguish between statistical and clinical significance in this setting. Given the current pressures on the NHS, it does not seem appropriate to compromise ease of use for a marginal gain in statistics that has little clinical relevance and yet imposes more demands on current physicians.	Thank you for your comments. While the differences in discriminative measures were small, we found consistent and important benefits for ORBIT in calibration at all levels of risk. This will provide a more accurate measure of absolute risk to allow a more accurate and informed discussion about risk factor modification between clinician and patient. Whilst we accept that some risk factors for modification are not part of ORBIT, these can be obtained through other means as part of normal clinical practice.
SH	Liverpool Health Partners	Guideline	028	003	*"ORBIT is the best tool….."* This is debatable as much of the evidence is derived from highly selected non-UK cohorts. Furthermore, these do not account for the dynamic nature of risk factors[1]. Moreover, bleeding risk tools should be used first-and-foremost to identify modifiable risk factors that can then be addressed accordingly with appropriate follow-up intervals. Overall, all bleeding risk scores have modest predictive capabilities with c-statistics in the range of 0.6 - 0.7.	Thank you for your comment. The decision that ORBIT was the best tool was made on a combination of calibration and discrimination evidence, which were based on a non-selective literature search of all the relevant literature. Calibration evidence was given priority because of the importance of accurate prediction of absolute risk in the context of using the tools as an aid to the discussion between patient and clinician about the need for risk-modification, rather than as a decision

						tool about risk modification. In other words, it is envisaged that all patients will be encouraged to risk modify, but that an accurate risk prediction will be helpful in encouraging compliance, particularly in people at higher risk. We have clarified this point in the discussion. Although ORBIT may not involve all of the modifiable risk factors within its set of criteria, these risk factor measurements may be derived from elsewhere. The primary role of the bleeding risk tool is to make an accurate prediction, and although it is helpful if there is an overlap between the tool's criteria and the risk factors to be discussed with the patient, this is not essential. It is true that the evidence does not account for the dynamic nature of risk factors (how the risk factor profile at baseline may differ from the risk factor profile some years later at the point that bleeding occurs) but this is true across all tools and both discrimination and calibration methods. The evidence was not restricted to the UK as it was not believed at the time of protocol development that geographical location or ethnicity would have a major impact on accuracy of risk tools. Had the committee felt that ethnicity would affect accuracy then ethnicity would have been designated as a sub-grouping variable.
SH	Liverpool Health Partners	Guideline	028	006	*"The committee emphasised the importance of using a bleeding risk tool to inform plans to reduce reversible causes of bleeding"* In comparison to the HAS-BLED score, the ORBIT score has some glaring *omissions* such as labile INR, uncontrolled blood pressure, harmful alcohol excess and liver disease. These are indisputably major risk factors for bleeding and yet is 'missed' within the ORBIT score.	Thank you for your comment. Whilst it is true that ORBIT does not involve measurement of some of the important modifiable risk factors, such as labile INR, such modifiable risk factors can be measured in other ways, and may already be available on the patient's data. Furthermore, whether ORBIT or HAS-BLED are used does not actually change the amount of modifiable risk factor investigations that need to be carried out by the investigating clinician.

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						For example, measurement of haemoglobin, labile INR, blood pressure, liver function tests and renal function tests will need to be carried out in both cases to evaluate whether current bleeding, increased blood pressure or treatable liver or renal disorders are present, each of which can be treated if needed to reduce bleeding risk. The only difference is that the results of labile INR, blood pressure, liver function tests and renal function tests will feed into informing the HAS-BLED score whereas haemoglobin and renal function results (GFR) will feed into the ORBIT score. This does not make ORBIT any more costly in terms of clinician time and resources, as other variables in ORBIT do not require invasive investigations. In addition, the notion that if the modifiable risk factors are not part of the tool then clinicians will not be prompted to discuss their modification is not a real disadvantage. This is because assessment of the modifiable risk factors of bleeding forms part of routine care. We would therefore argue that the real benefits of the greater absolute risk prediction accuracy from ORBIT outweigh the disadvantages of ORBIT not incorporating some of the modifiable risk factors, because the advantages are very real but the disadvantages are surmountable.. The committee agreed that the tool that most accurately predicts risk should be recommended rather than one that gives you more information on risk factors.
SH	Liverpool Health Partners	Guideline	028	006	The ORBIT score is limited by retrospective data. In contrast, the HAS-BLED score is supported by the prospective mAFA-II cluster randomised trial which showed that implementation of this score to highlight modifiable bleeding risk factors was associated with a reduction in bleeding events and increased OAC uptake, compared to 'standard care'[2].	The sub-optimal derivation methodology of a tool is not crucial if it is still able, despite this setback, to achieve better predictive capacity than other tools. The committee agreed that the calibration data demonstrated that ORBIT was best placed to predict absolute bleeding risk in relevant patient populations.

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SH	Liverpool Health Partners	Guideline	General	General	**What's lacking** There is a missed opportunity to propose integrated care management pathways. This has been shown to be associated with improved outcomes and reduce hospitalisations[16, 19], and has been tested in a cluster RCT (mAFA II trial) which clearly shows improved clinical outcomes (composite of 'ischaemic stroke/systemic thromboembolism, death, and rehospitalization') compared to 'usual care'[20, 21]. Integrated care is delivered based on the ABC pathway (A, Avoid stroke; B, Better symptom management with patient centred and symptom directed rate or rhythm control; C, Cardiovascular risk and comorbidity optimisation), supported by numerous observational cohorts[22-25], and one prospective RCT (mAFA II trial)[20, 21]. The ABC pathway is part of the West Midlands AHSN Primary Care Clinical Pathway for AF Detection and Management (https://bit.ly/2FhrwXQ) **All this evidence for integrated care and the value of ABC pathway for improved AF care is ignored by the NICE guidelines.** Opportunistic screening is briefly mentioned, and the NICE recommendation is unchanged from old guidelines. However, there is no point screening without AF patients entering a structured awareness and detection programme, followed by integrated care management[26].	Thank you for your comment. Integrated care management pathways were outside of the scope of the guideline. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date. Opportunistic screening is outside of the remit of NICE guidelines.
SH	Liverpool Heart and Chest Hospital NHS Foundation Trust	Guideline	009	024	A new recommendation is to relegate edoxaban and rivaroxaban to the second option in terms of DOAC agents behind apixaban and dabigatran. The rationale focuses on (Page 71) Network meta-analysis (NMA) from Lopez-Lopez 2017 and Sterne 2017. Whilst the NMA method is good for making comparisons across interventions never been directly contrasted, it relies upon assumptions, most importantly *transitivity* in indirect comparisons. The analytic strategy to estimate the difference in the trials between warfarin and comparator (apixaban or dabigatran) were different for the assessment of the bleeding outcomes (ITT or modified PP).Additionally, there were major differences in inclusion criteria and therefore in patient characteristics, which will no doubt affect the absolute risk of outcomes in the included populations. This was clearly outlined in Ruff et al. 2014 (Lancet) showing that proportions with a CHADS2 score of 3-6 was 87% in the ROCKET-AF trial and 53-54% in the ENGAGE AF-TIMI 48 trial; in both the RE-LY trial and ARISTOTLE trial these proportions were 33% and 30%, respectively. This is bound to impact the NMA outputs. We believe there is very little to choose between the different DOAC agents in terms of effectiveness outcomes. The convenience of once a day dosing with edoxaban and rivaroxaban is preferred by many patients, and has been shown to lead to increased compliance	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and we now recommend any licensed DOAC. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. The recommendation on switching to edoxaban or rivaroxaban has been deleted as it is no longer applicable. When deciding on what DOACs to offer the health professional and person should decide in the context of shared decision making taking into consideration dose frequency (recommendation 1.6.2).

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SH	Liverpool Heart and Chest Hospital NHS Foundation Trust	Guideline	013	007	**1.7 Rate and rhythm control** We are concerned that this recommendation does not include referral for pacemaker and AV node ablation to facilitate rate control. This treatment is particularly beneficial to patients who cannot achieve satisfactory rate control on medical therapy (or only do so with significant side effects from medication) and in patients with LBBB and LV impairment who would benefit from cardiac resynchronisation therapy.	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	Liverpool Heart and Chest Hospital NHS Foundation Trust	Guideline	016	022 - 023	**Left atrial ablation** We are concerned that guideline implies that the choice of ablation technology to achieve pulmonary vein isolation should be restricted and not include cryoballoon ablation. ***'consider radiofrequency point-by-point ablation or laser ablation'*** This recommendation has several areas of concern. First, it is recognised that the key aspect of successful AF / left atrial ablation is effective and durable pulmonary vein isolation (PVI). The 2020 ESC AF guidelines emphasise the importance of this technical result as below. P45 of ESC 2020 AF Guidance **Techniques and technologies:** Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures. References: 235_237,239,606,608_610,613,614,678,679,681,683,684,686,713,731,759,780 Level of Evidence I A It is recognised by those performing ablation that there are several energy modalities (RF, cryo, laser) that can achieve effective PVI. The most widely used techniques in Europe are point by point RF and the cryoballoon. These have been compared for clinical effectiveness in a head to head trial – FIRE and ICE – published in the New England Journal of Medicine in 2016 (N Engl J Med. 2016;374:2235–2245). This study showed point-by-point RF and the cryoballoon to be equally effective for the primary endpoint of AF recurrence. An economic analysis of the initial procedure and subsequent follow-up in the study was published in 2017. (J Am Heart Assoc. 2017;6:e006043.DOI: 10.1161) This showed the cryoballoon technique to be more cost effective with an average saving of £364 per case for the UK health system.	Thank you for your comment. Recommendations 1.7.19 and 1.7.20 have been amended. 1.7.20 now recommends cryoballoon or laser ablation in people who are assessed as unsuitable for radio frequency point-by-point ablation. The evidence based on all relevant studies showed that radiofrequency point by point ablation was more cost effective over a lifetime than antiarrhythmic drug treatment and other ablation strategies in people for whom 1 or more antiarrhythmic drug has failed. FIRE and ICE was included in the evidence review and the results in that paper mirror our overall NMA results – that the clinical efficacy in terms of recurrence of RF point by point and cryoballoon is similar. Please note the health economic analysis of FIRE and ICE was also included in the evidence review. It was assessed as partially applicable with potentially serious limitations. Our de novo model demonstrated that the greater costs of cryoballoon made it less cost-effective in our model. A threshold analysis was conducted where we explored the costs of cryoballoon. The threshold analysis for cryoballoon, indicated a reduction of £2,913 in the procedure costs is required for it to become cost effective. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge, this equated to £1,289 in savings which is not

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						enough for cryoballoon to become more cost effective than RFPP.
SH	Liverpool Heart and Chest Hospital NHS Foundation Trust	Guideline	031	014 - 015	**Left atrial ablation** Recommendations 1.7.19 to 1.7.20 – see comments below	Thank you for your comment.
SH	Medtronic	Guideline	016	023-025	We reverentially ask the Committee to consider including a specific indication for catheter ablation for patients with atrial fibrillation (AF) and heart failure in light of recent clinical evidence demonstrating the benefits of catheter ablation for this patient group. The NICE guidelines document for AF management is an important reference tool that helps to guide general practitioners and cardiologists in their AF therapy referral decisions. The lack of specific guidance related to AF treatment for patients with both AF and heart failure may result in the benefits of ablation for this indication being overlooked. This can be particularly problematic since AF is a progressive disease that often coexists with heart failure (Hindricks et al., 2020). Together, AF and heart failure can lead to atrial structure and electrical remodelling, perpetuating a cycle of impaired left ventricular (LV) filling, contractility, and cardiac output (Hohendanner et al., 2018). Two major randomized controlled trials evaluated AF ablation in heart failure patients with reduced ejection fraction, that resulted in improved quality of life and reduction in hospitalizations and all-cause mortality compared to rate or rhythm control drug therapy (Di Biase et al., 2016 and Marrouche et al., 2018). The CASTLE-AF trial demonstrated that after a median follow-up period of 37.8 months, the ablation arm experienced fewer deaths (13.4% vs. 25.0%) and fewer hospitalisations for worsening heart failure (20.7% vs. 35.9%) compared to the rate or rhythm control arm. Studies have also shown that AF catheter ablation can reverse LV dysfunction in AF patients with tachycardia-induced cardiomyopathy (Prabhu et al., 2017, Dagres et al., 2011 and Prabhu et al., 2018). Several published meta-analyses pooled these studies and have confirmed the benefit of catheter ablation rhythm control compared to medical therapy in this population of patients (Malik et al., 2018 and Chen et al., 2020): • a lower all-cause mortality (OR= 0.51, p=0.0003) • a reduced re-hospitalization rate (OR=0.44, p=0.003)	Thank you for your comment. The committee made the pre-hoc decision when formulating the review protocol that the existence of HF would be a sub-grouping criterion. This meant that if there was any statistical heterogeneity in any meta-analysis, the studies within the meta-analysis would be sub-grouped into those where the majority of participants had HF, and those where the majority did not have HF. The plan was that if this sub-grouping resolved heterogeneity (by reducing the heterogeneity to acceptable levels within each sub-group) then results would be presented for each separate sub-group. Unfortunately, the sub-grouping variable of HF did not succeed in resolving heterogeneity in any of the meta-analyses. This meant that we did not have any results data that would imply separate indications for those with HF and those without. Because our sub-grouping analyses suggested that the presence of HF did not affect the variability in outcome, the committee agreed that this evidence showed that people with HF and people without HF would both respond to the ablation treatments in a similar way, and would therefore be eligible for the same recommendations.

					• a greater improvement in left ventricular ejection fraction (weighted mean difference (WMD)=6.8%, p=0.0004) • a lower arrhythmia recurrence (29.6% vs. 80.1% respectively, OR=0.04, p<0.00001) • a greater improvement in quality of life (Minnesota Living with Heart Failure Questionnaire score) (WMD=9.1, p=0.007) We recall that multiple stakeholders requested guidance on ablation in patients with AF and heart failure during Scoping. We note the following specific mentions on this topic from the consultation comments and responses document: • The British Heart Rhythm Society (BHRS) requested "Guidance on the role of AF ablation in heart failure patients." NICE responded, "*This population will be included*". • The University of Birmingham commented "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)". NICE responded, "*People with heart failure may be identified as a separate group requiring consideration when devising the review protocol for this question*." • The AF Association requested guidance on "Atrial Fibrillation in the setting of heart failure" within a list of topics. NICE did not specifically comment on this point. • Medtronic commented "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. 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." NICE responded "*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*." The responses provided by NICE during Scoping stated and/or implied that the evidence for ablation for patients with AF and heart failure would be assessed and guidance provided. The final Scope stated that key areas that will be covered in this update included "Rate and rhythm control" and under the description of what NICE plans to do, it was stated "Review evidence: update existing recommendations as needed". However, it appears that a single, narrower	

					question was specified to the exclusion of the broader issues, which was "What is the clinical and cost effectiveness of different ablative and non-ablative therapies in people with atrial fibrillation?". We are concerned that the omission of specific recommendations regarding ablation for patients with AF and heart failure will lead to sub-optimal treatment of this patient group. Both diseases are relatively common and the combination of the two is known to adversely affect the patients' prognosis and cause a substantial burden on the healthcare system. There is a clear need for guidelines to raise awareness and adoption of therapies for this patient population which have been proven to be safe and effective and are likely to be highly cost-effective. References: • Chen S et al (2020) Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. Eur Heart J (2020): 7;41(30):2863-2873 • Dagres N, Varounis C, Gaspar T, Piorkowski C, Eitel C, Iliodromitis EK, Lekakis JP, Flevari P, Simeonidou E, Rallid is LS, Tsougos E, Hindricks G, Sommer P, Anastasiou-Nana M. Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. J Card Fail 2011;17:964_970. • Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation 2016;133:16371644. • Hindricks, G., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2020. 00, 1-126 • Hohendanner F, Messroghli D, Bode D, et al. Atrial remodelling in heart failure: recent developments and relevance for heart failure with preserved ejection fraction. ESC Heart Fail. 2018;5(2):211-221. doi:10.1002/ehf2.12260 • Malik AH et al (2018) Comparative Therapeutic Assessment of Atrial Fibrillation in Heart Failure With Reduced Ejection Fraction—A Network Meta-Analysis. Am J Ther. 2020 May/Jun;27(3):e286-e296 • Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H,	

					Vogt J, Bansch D; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417427. • Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. J Am Coll Cardiol 2017;70:1949_1961. • Prabhu S, Costello BT, Taylor AJ, Gutman SJ, Voskoboinik A, McLellan AJA, Peck KY, Sugumar H, Iles L, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Lee G, Mariani J, Kaye DM, Ling LH, Kalman JM, Kistler PM. Regression of diffuse ventricular fibrosis following restoration of sinus rhythm with catheter ablation in patients with atrial fibrillation and systolic dysfunction: a substudy of the CAMERA MRI trial. JACC Clin Electrophysiol 2018;4:999_1007.	
SH	Medtronic	Guideline	016	023-025	We think the guideline as they are written overlook the importance of minimally invasive surgical ablation. For many patients with de novo persistent symptomatic atrial fibrillation, catheter ablation and medical management are ineffective treatments. We would like NICE to consider the use of minimally invasive surgical ablation in this cohort of patients, a procedure which has been used successfully to restore sinus rhythm. Recently, the Society of Thoracic Surgeons (STS) and Heart Rhythm Society (HRS) have provided Class IIb recommendations for standalone minimally invasive surgical ablation (radiofrequency or cryo) for treatment of persistent atrial fibrillation. Appreciating NICE should be guided by the evidence in this area, we have highlighted some studies below. This is by no means exhaustive, but serves to emphasise that this technique should be a considered option if deemed clinically appropriate. • STS Guidelines. Badhwar, V., Rankin, J., Damiano, R., Gillinov, A., Bakaeen, F., Edgerton, J., Philpott, J., McCarthy, P., Bolling, S., Roberts, H., Thourani, V., Suri, R., Shemin, R., Firestone, S. and Ad, N., 2017. The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial Fibrillation. The Annals of Thoracic Surgery, 103(1), pp.329-341. • HRS Guidelines: Calkins, H., Hindricks, G., Cappato, R., Kim, Y., Saad, E., Aguinaga, L., Akar, J., Badhwar, V., Brugada, J., Camm, J., Chen, P., Chen, S., Chung, M., Cosedis Nielsen, J., Curtis, A., Davies, D., Day, J., d'Avila, A., (Natasja) de Groot, N., Di Biase, L., Duytschaever, M., Edgerton, J., Ellenbogen, K., Ellinor, P., Ernst, S., Fenelon, G., Gerstenfeld, E., Haines, D., Haissaguerre, M., Helm, R., Hylek, E.,	Thank you for your comment. The committee decided pre-hoc, during the formulation of the review protocol, that the types of ablation treatment that should be compared were surgical, hybrid, thoracoscopy, RF point by point, RF multielectrode, cryoballoon and laser. We would have included any RCT studies covering minimally invasive surgical ablation within the surgical ablation category, but no eligible RCTs were found.

					Jackman, W., Jalife, J., Kalman, J., Kautzner, J., Kottkamp, H., Kuck, K., Kumagai, K., Lee, R., Lewalter, T., Lindsay, B., Macle, L., Mansour, M., Marchlinski, F., Michaud, G., Nakagawa, H., Natale, A., Nattel, S., Okumura, K., Packer, D., Pokushalov, E., Reynolds, M., Sanders, P., Scanavacca, M., Schilling, R., Tondo, C., Tsao, H., Verma, A., Wilber, D., Yamane, T., Blomström-Lundqvist, C., De Paola, A., Kistler, P., Lip, G., Peters, N., Pisani, C., Raviele, A., Saad, E., Satomi, K., Stiles, M. and Willems, S., 2017. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. EP Europace, 20(1), pp.e1-e160.	
SH	Medtronic	Guideline	016	023-025	In line with the consensus from the clinical societies, surgical treatment for de novo persistent Atrial Fibrillation (AF) using a minimally invasive hybrid approach has recently received a Class IIb treatment recommendation from the Heart Rhythm Society (HRS) and European Society of Cardiology (ESC). The hybrid procedure requires a multi-disciplinary approach combining the expertise of a surgeon and electrophysiologist. Several studies have assessed this approach to treating de novo persistent AF and have demonstrated a return to normal sinus rhythm. • HRS Guidelines: Calkins, H., Hindricks, G., Cappato, R., Kim, Y., Saad, E., Aguinaga, L., Akar, J., Badhwar, V., Brugada, J., Camm, J., Chen, P., Chen, S., Chung, M., Cosedis Nielsen, J., Curtis, A., Davies, D., Day, J., d'Avila, A., (Natasja) de Groot, N., Di Biase, L., Duytschaever, M., Edgerton, J., Ellenbogen, K., Ellinor, P., Ernst, S., Fenelon, G., Gerstenfeld, E., Haines, D., Haissaguerre, M., Helm, R., Hylek, E., Jackman, W., Jalife, J., Kalman, J., Kautzner, J., Kottkamp, H., Kuck, K., Kumagai, K., Lee, R., Lewalter, T., Lindsay, B., Macle, L., Mansour, M., Marchlinski, F., Michaud, G., Nakagawa, H., Natale, A., Nattel, S., Okumura, K., Packer, D., Pokushalov, E., Reynolds, M., Sanders, P., Scanavacca, M., Schilling, R., Tondo, C., Tsao, H., Verma, A., Wilber, D., Yamane, T., Blomström-Lundqvist, C., De Paola, A., Kistler, P., Lip, G., Peters, N., Pisani, C., Raviele, A., Saad, E., Satomi, K., Stiles, M. and Willems, S., 2017. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. EP Europace, 20(1), pp.e1-e160. • ESC Guidelines: Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J., Blomström-Lundqvist, C., Boriani, G., Castella, M., Dan, G., Dilaveris, P., Fauchier, L., Filippatos, G., Kalman, J., La Meir, M., Lane, D., Lebeau, J., Lettino, M., Lip, G., Pinto, F., Thomas, G., Valgimigli, M., Van Gelder, I., Van Putte, B., Watkins, C., Kirchhof, P., Kühne, M., Aboyans, V., Ahlsson, A., Balsam, P., Bauersachs, J., Benussi, S., Brandes, A., Braunschweig, F., Camm, A., Capodanno, D., Casadei, B., Conen, D., Crijns, H., Delgado, V., Dobrev, D., Drexel, H., Eckardt, L., Fitzsimons, D.,	Thank you for your comment. Our reviews included analysis of the hybrid ablation procedure (J1 and J2). However, the committee did not make a recommendation for the hybrid procedure because although it showed very low rates of recurrence, the rates of serious adverse effects were far higher than the catheter ablation approaches.

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					Folliguet, T., Gale, C., Gorenek, B., Haeusler, K., Heidbuchel, H., Iung, B., Katus, H., Kotecha, D., Landmesser, U., Leclercq, C., Lewis, B., Mascherbauer, J., Merino, J., Merkely, B., Mont, L., Mueller, C., Nagy, K., Oldgren, J., Pavlović, N., Pedretti, R., Petersen, S., Piccini, J., Popescu, B., Pürerfellner, H., Richter, D., Roffi, M., Rubboli, A., Scherr, D., Schnabel, R., Simpson, I., Shlyakhto, E., Sinner, M., Steffel, J., Sousa-Uva, M., Suwalski, P., Svetlosak, M., Touyz, R., Dagres, N., Arbelo, E., Bax, J., Blomström-Lundqvist, C., Boriani, G., Castella, M., Dan, G., Dilaveris, P., Fauchier, L., Filippatos, G., Kalman, J., La Meir, M., Lane, D., Lebeau, J., Lettino, M., Lip, G., Pinto, F., Neil Thomas, G., Valgimigli, M., Van Gelder, I. and Watkins, C., 2020. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal,. • Haywood, G., Varini, R., Osmancik, P., Cireddu, M., Caldwell, J., Chaudhry, M., Loubani, M., Della Bella, P., Lapenna, E., Budera, P. and Dalrymple-Hay, M., 2020. European multicentre experience of staged hybrid atrial fibrillation ablation for the treatment of persistent and longstanding persistent atrial fibrillation. IJC Heart & Vasculature, 26, p.100459. • Tonks, R., Lantz, G., Mahlow, J., Hirsh, J. and Lee, L., 2020. Short and Intermediate Term Outcomes of the Convergent Procedure: Initial Experience in a Tertiary Referral Center. Annals of Thoracic and Cardiovascular Surgery, 26(1), pp.13-21.	
SH	Medtronic	Guideline	General	General	We would like to highlight “NICE DG41 – Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke” and request it is added to the list of related NICE publications	Thank you for your comment. The section on related NICE guidance is in the scope document, which we are unable to edit.
SH	NHS Derby and Derbyshire CCG	Guideline	010	General	We believe that the recommendations in this draft guideline will have a substantial resource impact which will introduce a cost pressure into the health and social care system. The draft guideline makes mention of the fact that there are ongoing procurement discussions and that the results may have an impact on this guidance. As NICE will be aware there are already rebates in place from some of the manufacturers of NOACs and these are already having an impact on preferred formulary choices across England. Switching prescribing to apixaban and dabigatran would result in a loss to Derby and Derbyshire CCG of several million pounds over the next few years. This is a considerable opportunity cost which will undoubtedly have a knock on effect when considering the commissioning of other services. It is possible that this could have a negative effect on health services across the STP and lead to health inequalities.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently

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						available. Following completion of the procurement NICE will consider an update of the guideline.
SH	NHS England and NHS Improvement	Guideline	004	018 - 020	This should also cover asymptomatic episodes; should include patients with cryptogenic stroke and the use of insertable cardiac monitors, plus AF detection on CIEDs. (NL)	Thank you for your comment. The use of insertable cardiac monitors and AF detection on CIEDs was outside of the scope of this update.
SH	NHS England and NHS Improvement	Guideline	005	013-015	The vast majority of published guidelines, including the 2020 European Society of Cardiology recommend the use of the HAS-BLED score. Recommending a different scoring system that is not in widespread use is not helpful and is likely to be ignored by many. (NL)	Thank you for your comment. The committee agreed that the ORBIT score was the most appropriate bleeding risk tool. The evidence showed that it was the most accurate tool to predict absolute risk of major bleeding, both for people using vitamin K antagonists and those using direct-acting oral anticoagulants. The committee were aware that some discrimination evidence showed that ORBIT places more patients in the low-risk category than HAS-BLED, thus potentially under-predicting their major bleeding risk. However, calibration data, which was viewed as the best way to evaluate absolute risk prediction, showed that ORBIT did not under-predict more than other tools, and that it was generally more accurate at all levels of risk than the other tools. Overall the committee agreed that the data supported the use of ORBIT.
SH	NHS England and NHS Improvement	Guideline	009	011 et seq	I have had many comments fed back to me expressing concerns over this section and I would add my own worries. Recommending the use of apixaban and dabigatran will not only create massive logistical issues, it is also a flawed recommendation. Dabigatran currently has a market share of 1 – 2 % as doctors do not wish to prescribe this agent due to complexity over dosing, increased incidence of side effects and increased under-dosing of patients. Furthermore, to recommend two twice daily agents rather than a once daily and a twice daily dosing is illogical. It is likely that these recommendations will be largely ignored. I have a major concern that there is a recommendation that patients already established on edoxaban or rivaroxaban should be switched to an alternative, twice daily medication. This will create a significant burden on the health service and create confusion and concern with patients. This should be strongly avoided. These recommendations will not be supported by most clinicians nor their professional societies. (NL)	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Recommendation 1.6.2 refers to following the principles on shared decision making and supporting adherence to the NICE guidelines on medicines adherence, medicines optimisation and patient experience in adult NHS services which would include taking into account personal preferences such as dose frequency.

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SH	NHS England and NHS Improvement	Guideline	007	021	This section of the guideline has not been updated, however, it is out of date. There is no recommendation on lifestyle modification, particularly looking at weight loss and exercise. This is very important in management of patients with AF and I would recommend that this section is revised. (NL)	Thank you for your response. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	NHS England and NHS Improvement	Guideline	016	023	The preferencing of point by point or laser ablation is flawed. The costings model assumes national uniform pricing without associated efficiency savings. Laser ablation is undertaken in very few centres and the most commonly performed procedure, cryoablation not considered, despite it being at least as effective as laser ablation, without the significant start up costs of laser ablation. The concern is that this is another recommendation that is likely to be ignored. (NL)	Thank you for your comment. Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.
SH	NHS England and NHS Improvement	Guideline	General	General	I have a concern that this guideline has specifically looked at certain sections of the previous 2006 guidelines that we reviewed, again in part, in 2014. This has resulted in a somewhat disjointed document where some sections have not been updated with more recent evidence. I would recommend that there is a good case for considering a full review and potential re-write of the guideline, taking into account the concerns raised above. (NL)	Thank you for your response. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	NHS England and NHS Improvement	Guideline	006	014	It would be useful to include advice regarding use of medications and their indications. (MJ)	Thank you for your comment. NICE guidelines assume that medications will be used in accordance with the guidance in the BNF.
SH	NHS England and NHS Improvement	Guideline	009	019 - 021	It would be helpful to add hyperlink to the reference (like lines 13-15) (MJ)	Thank you for your comment. The recommendation has been written to make it clear that combinations of any two of the following can be considered: beta-blockers, diltiazem and digoxin. We are unable to suggest an edit that will make it clearer.
SH	NHS England and NHS	Guideline	014	009	Recommendation needs further clarification to make sure there is no confusion regarding combination of medicines to use (MJ)	Thank you for your comment. We have reviewed the recommendation and agree that the recommendation cannot be made any more

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	Improvement					specific as it is clear that combinations of any two of the following can be considered: beta-blockers, diltiazem and digoxin.
SH	NHS England and NHS Improvement	Guideline	014	015	The recommendation to use Diltiazem as an off-label medicine to prescribe is not provided in the BNF (MJ)	Thank you for your comment. We have deleted this.
SH	NHS England and NHS Improvement	Guideline	016	022	It is best to use a separate heading to clarify recommended treatment is for secondary care services only (MJ)	Thank you for your comment. As ablation is only available in secondary care we have not edited the heading.
SH	NHS England and NHS Improvement	Guideline	027	029	HAS-BLED is very widely used and understood risk stratification tool, recommending change at this stage risks causing confusion and challenges of implementing risk assessment strategies. (MJ)	The committee agreed that the ORBIT score was the most appropriate bleeding risk tool. The evidence showed that it was the most accurate tool to predict absolute risk of major bleeding, both for people using vitamin K antagonists and those using direct-acting oral anticoagulants. The committee agreed that the benefits of a more accurate tool outweigh the difficulties in implementation.
SH	NHS England and NHS Improvement	Guideline	029	008	It would be relevant to highlight risks of concomitant use of DOACs with liver enzyme inducing drugs such as anti-epileptic medicines (MJ)	Thank you for your comment. We have noted this in the committee's discussion of the evidence in evidence review G1.
SH	NHS England and NHS Improvement	Guideline	035	015	In the light of content of paragraph the heading could be clarified further by changing the term to post cardiac surgery atrial fibrillation (MJ)	Thank you for your comment. We have made the change as suggested.
SH	NHS England and NHS Improvement	Guideline	007 008	022 - 030 001-006	This area could more explicitly describe a 'personalised package of care' aligned with national policy in England and evidence of effectiveness of personalised care. It is recommended to add details around understanding the things that matter to the person and what is important to them and how best they can be supported ("what matters to me"). Risk of this is confusing	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team

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					clash with national policy and evidence and missing opportunity for impact of benefits of personalised care. (AR)	which monitors guidelines to ensure that they are up to date.
SH	NHS England and NHS Improvement	Guideline	007	022-023	The personalised package of care, and accompanying documentation and information needs to be functional and health literate, meaning it is relevant to their everyday life and that they can understand and act on it. (AR)	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	NHS England and NHS Improvement	Guideline	007	023	Documentation of the personalised package of care should explicitly include the development of a personalised care and support plan, agreed with the person, which reflects what matters to them, and pays attention to not just their clinical needs but their wider health and wellbeing. (AR)	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	NHS England and NHS Improvement	Guideline	007	024-030	Include within the bullets – "options for supported self-management to help the person in managing their own health and wellbeing" (AR)	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	NHS England and NHS Improvement	Guideline	008	011-013	Good to see cross referencing to NICE guidelines on medicines adherence and medicines optimisation, where shared decision making is sighted throughout. It would enhance clarity further to state shared decision making within this section. (AR)	Thank you for your comment. We now highlight shared decision making in recommendation 1.6.2.
SH	NHS England and NHS Improvement	Guideline	008	022 - 024	Would be helpful to include within this that principles of shared decision making should be central to this conversation. For example rephrasing to include: "*When discussing the benefits and risks of anticoagulation use clinical risk profiles and personal preferences to guide treatment choices. Discuss with the person that: …."* (AR)	Thank you for your comment. We have edited the recommendation in accordance with your suggestion.
SH	NHS England and NHS Improvement	Guideline	017	005 - 023	It will be important to cite GMC consent guidance within this in relation to interventional procedures. (AR)	Thank you for your comment. We can only signpost to related NICE guidance in this section.
SH	NHS England and	Guideline	029	012 - 015	This is a very reductionist/didactic view of shared decision making which is all about "information and education" and doesn't align with the definition provided either by the SDM	Thank you for your comment. We have edited this section in line with the NICE description of shared

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	NHS Improvement				Collaborative hosted by NICE or as set out *Universal Personalised Care: Implementing the comprehensive model January 2019.* Shared decision making ensures that individuals are supported to make decisions that are right for them. Either of the following definitions would be more appropriate: "People are supported to a) understand the care, treatment and support options available and the risks, benefits and consequences of those options, and b) make a decision about a preferred course of action, based on evidence-based, good quality information and their personal preferences." *Universal Personalised Care: Implementing the comprehensive model January 2019* "Shared Decision Making is where individuals and clinicians work together to understand and decide what tests, treatments, management or support packages are most suitable bearing in mind the persons individual circumstances. It brings together the individual's expertise about themselves and what is important to them together with the clinician's knowledge about what is known about the benefits and risks of the available options." *NICE SDM Collaborative 2015* It would be good to see the spirit of these definitions more clearly reflected in this section. Additionally, this would also be an opportunity to reference the forthcoming NICE guidelines on SDM. Additionally, SDM is important to consider in the context of all treatment options, not just in relation to Stroke Prevention. It may be more appropriate to include a section on SDM under 1.4 on 'Personalised package of care and information' (AR)	decision making. We now refer to shared decision making in the section on a personal package of care (1.4.2).
SH	NHS Kent and Medway Clinical Commissioning Group	Guideline	General	General	We are concerned that adopting the draft guideline in its current form (with Apixaban/Dabigatran) as first choice) is likely to profoundly challenge clinical practice and local capacity. Clinicians and patients are likely to question the validity of previous decisions to prescribe/receive alternative DOAC treatments. There may be a scramble to switch patients from other DOACs. This will have a profoundly negative effect on primary care capacity; already pressured GP practices can ill afford to cope with an increased influx of patients especially during the current pandemic.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Switching is therefore only relevant for people taking a vitamin K antagonist and should be discussed at the next routine appointment (1.6.6).
SH	NHS Kent and Medway Clinical Commissioning Group	Guideline	General	General	Current clinical practice is largely based on the premise that all direct oral anticoagulants (DOACs) with a UK marketing authorisation are appropriate for use by clinicians. NICE Technology appraisals recommend all the different medicines in the class without preference for one over the other.There are no genuine head to head phase 3 clinical trials available which conclude that one DOAC is superior to another. Available network meta-analyses are inconclusive about superiority of one DOAC over another due to heterogeneity of studies used	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of

					in analyses. Many clinicians are likely to defer to other guidelines e.g. European (Escardio) or American guidelines which recognise and uphold this fact	the NMA estimates (see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals were wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore were no longer confident to recommend a specific DOAC or DOACs.
SH	NHS Kent and Medway Clinical Commissioning Group	Guideline	General	General	Kent and Medway CCG like many CCGs in England has taken advantage of the flexibility in choice of DOAC to enter into commercial arrangements with some of the DOAC manufacturers to drive down procurement cost of DOACs(which have a significant financial impact on the NHS). The ability to procure DOACs at significantly less cost than the list price has led to significant savings to the NHS drugs budget. We think that the draft guidance may diminish the opportunity to drive down DOAC prescribing costs	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.
SH	NHS Kent and Medway Clinical Commissioning Group	Guideline	General	General	A common challenge for clinicians in everyday practice (particularly in primary care) is how to manage AF patients at extremes of weight. The guidelines do not include recommendations on stroke prevention in patients at extremes of weight. We feel that including such recommendations can have a significant impact on the safe management of this patient cohort.	Thank you for your comment. Weight was not specified by the committee as a sub-group in the presence of heterogeneity in the meta-analysis. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	NHS Southend CCG	Guideline	009	017	We are concerned that this recommendation may conflict with future advice from NHS England if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis,	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC.

					apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices". If the procurement prices change the cost-effectiveness, then this may change and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices being established with NHSE. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 1: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and NHSE. CCGs could be in the impossible position of being asked to implement two sets of guidelines from two different NHS bodies. It is imperative that they are aligned to be credible and implementable.	The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.
SH	NHS Southend CCG	Guideline	009	023	We are concerned that this recommendation may conflict with future advice from NHS England if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices". If the procurement prices change the cost-effectiveness, then this may change and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance".	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently

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					It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices being established with NHSE. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 1: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and NHSE. CCGs could be in the impossible position of being asked to implement two sets of guidelines from two different NHS bodies. It is imperative that they are aligned to be credible and implementable.	available. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.
SH	NHS Southend CCG	Guideline	009	029	Question 2: The draft recommendations may have significant cost implications if warfarin is only offered when DOACs are contraindicated, not tolerated or not suitable. Although there has been a significant move away from warfarin, and towards DOACs, over the last 6 years, this recommendation will see a further reduction in the use of warfarin. Whilst it is recognised that the cost of warfarin needs to include the cost of INR monitoring, it may not be straightforward for CCGs to extract these costs, depending on the local commissioning arrangements of their anticoagulant monitoring service. This has the potential to increase drug costs (due to increased DOAC costs) without reducing warfarin monitoring costs, as adequate arrangements for warfarin monitoring will still need to be maintained and paid for in each STP/ICS locality.	Thank you for your comment. The results of the evidence review demonstrated that DOACs are more clinically and cost effective than warfarin across all outcomes critical to decision making. A separate resource impact assessment will accompany the guideline and it is expected that there will be a financial impact as a result of increased DOAC prescribing. Although there will not be any cash savings it is expected there will be a non-cash releasing saving for providers, such as community, primary and secondary care which is driven by a reduction in anticoagulation clinics for the management of INR levels in people receiving treatment with warfarin.
SH	NHS Southend CCG	Guideline	010	001	We are very concerned about the recommendation, “For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist and are stable, discuss the option of switching treatment at their next routine appointment”. Switching anticoagulants, on the basis of cost-effectiveness only (and given that the cost-effectiveness may be flawed and may change depending on procurement prices) seems to be an unnecessary risk to patient safety as there is clearly potential for patients to inadvertently end up taking two anticoagulants.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend (1.6.6) that the opportunity to switch to a DOAC should be discussed with a person who is on a

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					Risks around switching from warfarin to DOACs during the COVID-19 pandemic have already been recognised and the NHS BSA and the Medicines Safety Improvement Programme, have developed a data set to help pick up whether unintentional co-prescribing potentially happened. The switch from warfarin to DOAC in this case was at least for the valid reason of reducing face to face attendance at anticoagulant clinics. Switching from one DOAC to another as suggested here, appears unnecessary and potentially unsafe. There has been discussion locally on the matter of switching between DOACs previously, and there was no appetite amongst clinicians to do so on grounds of safety. A secondary factor is that such switches are also likely to lead to medicines waste as patients discard their remaining supply of their existing DOAC. Question 1: This recommendation will be a challenging change in practice because of the safety issues mentioned and also because of the workload/capacity issues in general practice. Would GPs be prepared to switch AF patients between DOACs? Is there enough evidence of safety? Would they want to refer to haematology for DOAC switches? Question 4: Any switches would be likely to happen via remote consultation, due to COVID-19, and this may increase patient safety concerns due to potential confusion/lack of patient understanding. It will also take up healthcare professional consultation time, which we know is already extremely stretched. It will require extra care and vigilance for residents in care homes and their staff responsible for medicines ordering and administration.	vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.
SH	NHS Wakefield CCG	Guideline	009	017	As a CCG we are concerned that this recommendation may conflict with future advice from NHS England if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the “results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices”. If the procurement prices change the cost-effectiveness, then this may change and the guideline would need revision.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently

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					This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices being established with NHSE. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 2: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and NHSE. We as a CCG could be in the impossible position of being asked to implement two sets of guidelines from two different NHS bodies. It is imperative that they are aligned to be credible and implementable.	available. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.
SH	NHS Wakefield CCG	Guideline	009	023	As a CCG we are concerned that this recommendation may conflict with future advice from NHS England if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices". If the procurement prices change the cost-effectiveness, then this may change and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices being established with NHSE.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are

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					Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 2: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and NHSE. We as a CCG could be in the impossible position of being asked to implement two sets of guidelines from two different NHS bodies. It is imperative that they are aligned to be credible and implementable.	identified, and the impact on the guideline recommendations is assessed.
SH	NHS Wakefield CCG	Guideline	009	029	Question 3: The draft recommendations may have significant cost implications if warfarin is only offered when DOACs are contraindicated, not tolerated or not suitable. Although there has been a significant move away from warfarin, and towards DOACs, over the last 6 years, this recommendation will see a further reduction in the use of warfarin. Whilst it is recognised that the cost of warfarin needs to include the cost of INR monitoring, it may not be straightforward for us as a CCG to extract these costs, depending on the local commissioning arrangements of the anticoagulant monitoring service. This has the potential to increase drug costs (due to increased DOAC costs) without reducing warfarin monitoring costs, as adequate arrangements for warfarin monitoring will still need to be maintained and paid for in across the locality.	Thank you for your comment. The results of the evidence review demonstrated that DOACs are more clinically and cost effective than warfarin across all outcomes critical to decision making. A separate resource impact assessment will accompany the guideline and it is expected that there will be a financial impact as a result of increased DOAC prescribing. Although there will not be any cash savings it is expected there will be a non-cash releasing saving for providers, such as community, primary and secondary care which is driven by a reduction in anticoagulation clinics for the management of INR levels in people receiving treatment with warfarin.
SH	NHS Wakefield CCG	Guideline	010	001	We are very concerned about the recommendation, “For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist and are stable, discuss the option of switching treatment at their next routine appointment”. Switching anticoagulants, on the basis of cost-effectiveness only (and given that the cost-effectiveness may be flawed and may change depending on procurement prices) seems to be an unnecessary risk to patient safety as there is clearly potential for patients to inadvertently end up taking two anticoagulants. Risks around switching from warfarin to DOACs during the COVID-19 pandemic have already been recognised and the NHS BSA and the Medicines Safety Improvement Programme, have developed a data set to help pick up whether unintentional co-prescribing potentially	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. We therefore no longer recommend switching people on edoxaban or rivaroxaban.

					happened. The switch from warfarin to DOAC in this case was at least for the valid reason of reducing face to face attendance at anticoagulant clinics. Switching from one DOAC to another as suggested here, appears unnecessary and potentially unsafe. A secondary factor is that such switches are also likely to lead to medicines waste as patients discard their remaining supply of their existing DOAC. Question 4: This recommendation will be a challenging change in practice because of the safety issues mentioned and also because of the workload/capacity issues in general practice. Would GPs be prepared to switch AF patients between DOACs? Is there enough evidence of safety? Would they want to refer to haematology for DOAC switches? Question 5: Any switches would be likely to happen via remote consultation, due to COVID-19, and this may increase patient safety concerns due to potential confusion/lack of patient understanding. It will also take up healthcare professional consultation time, which we know is already extremely stretched. It will require extra care and vigilance for residents in care homes and their staff responsible for medicines ordering and administration.	
SH	NHS West Essex CCG	Guideline	009	011-016	We are concerned that this recommendation is prioritising apixaban and dabiatran over other anticoagulants when the national guidelines for anticoagulation which states the most appropriate anticoagulant should be used; this could be a DOAC **or** VKA. In addition if the pricing structure of DOACs change apixaban and dabigatran may not be the most cost effective use of NHS resources.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and we now refer to any licensed DOAC.
SH	NHS West Essex CCG	Guideline	009	017 - 028	We are concerned that this recommendation is prioritising apixaban and dabiatran over other anticoagulants when the national guidelines for anticoagulation which states the most appropriate anticoagulant should be used; this could be a DOAC **or** VKA. In addition if the pricing structure of DOACs change apixaban and dabigatran may not be the most cost effective use of NHS resources.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. Following completion of the procurement NICE will consider an update of the guideline.
SH	NHS West Essex CCG	Guideline	009	029-031	We are concerned that this recommendation is prioritising DOACs above VKA. VKA should be an equal option as per national guidance.	Thank you for your comment. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes that were prioritised by the committee as most important for decision making.
SH	NHS West Essex CCG	Guideline	010	001-004	We are extremely concerned that this recommendation is advising switching stable patients. Whatever the treatment if a patient is stable and safe, guidance is always to maintain treatment until clinically appropriate to switch	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between

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					• What is the evidence base for this recommendation? • Has the capacity of primary care been evaluated to safely switch patients given that a large percentage of consultations are remote? • Has there been a real world evaluation of the safety and effectiveness of DOAC outside of trials as data from primary care shows an increase in mortality of DOACs compared to VKA • Real world data also shows many patients are on inappropriate doses of DOACs • Real world data also shows many patients on DOACs are not being monitored appropriately. DOACs are being promoted as not requiring monitoring therefore weight, U&Es and CrCl are not being routinely monitored leading to significant patient safety issues. • What is the cost implication of this switch and have primary care prescribing budgets been uplifted to take increased costs into account? • What measures have been put in place to ensure the pricing structure is assured and stable This recommendation will be a challenging change in practice because it will require significant resources to undertake the switch and follow up safely	DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making (see evidence review G1). We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation (1.6.6) and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration. The DOACs should be prescribed in accordance with the guidance in the BNF (1.6.2).
SH	NHS West Leicestershire CCG on behalf of LLR CCGs	Guideline	009	011 - 031	This rationale states … • Offer anticoagulation with either apixaban or dabigatran to people with atrial fibrillation and a CHA2DS2-VASc score of 2 or above • Consider anticoagulation with either apixaban or dabigatran for men with atrial fibrillation and a CHA2DS2-VASc score of 1, taking into account the risk of bleeding. • If apixaban and dabigatran are not tolerated in people with atrial fibrillation, offer anticoagulation with either edoxaban or rivaroxaban • If direct-acting oral anticoagulants are contraindicated, not tolerated or not suitable in people with atrial fibrillation, offer a vitamin K antagonist. [2020] We are concerned about the first ,second and third line options because: 1. Our local outcome data (using Eclipse) suggests that patients on DOACs have more A&E attendances compared with those on warfarin. Range of average A&E admissions per patient per year for LLR CCGs for DOACs are (0.45-0.6) compared with (0.27-0.42) for warfarin.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. A and E attendances were not specified in the review protocol for this question but adverse events that could have led to them were captured (see appendix A evidence review G1). The DOACs were demonstrated to be more clinically and cost effective compared to warfarin across all outcomes critical for decision making. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise.

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					2. There is only one clinical trial comparing 2 of the DOACs. All of the major clinical trials compare the DOAC with warfarin with major differences in the methodology and therefore a direct comparison not flawed e.g. inclusion criteria, TTR, average age, CHADsVAsc2 score, use of aspirin etc. 3. Restricted patient choice: Having a blanket recommendation of apixaban or dabigatran also removes patient choice especially between a DOAC and Warfarin but also within the DOACs to avoid pill burden with twice daily dosing, frequency of monitoring and attendance at the GP surgery. 4. The complexities around dosing and the burden of monitoring on primary care also needs to be taken into account in the economic analyses with respect especially in those with renal impairment, frail and elderly and the renal clearance of the DOAC.	Warfarin remains an option for people in whom a DOAC is contraindicated, not tolerated or not suitable (recommendation 1.6.5). The choice of DOAC should take place in the context of shared decision making and includes consideration of factors such as dosing frequency, frequency of monitoring and attendance at the GP surgery. Although the health economic model did not quantitively account for the complexities of dosing or monitoring, these were discussed by the committee and the recommendations reflect this, with warfarin remaining an option for people in whom a DOAC is contraindicated, not tolerated or not suitable (recommendation 1.6.5).
SH	NHS West Leicestershire CCG on behalf of LLR CCGs	Guideline	012	022 - 025	• For people who are taking an anticoagulant, review the need for anticoagulation and the quality of anticoagulation at least annually, or 23 more frequently if clinically relevant events occur affecting anticoagulation 24 or bleeding risk. We are concerned that this recommendation lacks clarity regarding high risk groups and underestimates the level of monitoring required with DOACs. • Extremes of bodyweight BMI <18kg/m2 and >40kg/m2) taking into consideration whether the increase weight is due to fat or muscle. • Patients with BMI 30-40kg/m2 near a dosing boundary. • All patients with CrCl 15-30ml/min irrespective of BMI • Patients on dialysis • Heart failure patients with fluid overload- use dry weight/ euvolaemic estimate. • Patients with extensive amputations, or neurological diseases (eg spina bifida, multiple sclerosis) and myopathy that may result in profound muscle loss. • Patients with gastric bands/ gastrectomies. • Patients at risk of AKI Also of concern is the absence of any recommendation around determination of CrCl as numerous embedded calculators and apps in both primary and secondary care. Local audits	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

					have shown that the difference can be quite large at extremes of body weight depending on the calculator use and a national consensus would be very welcome. The issues are outlined in the RMOC statement on DOAC dosing issues. https://www.sps.nhs.uk/articles/direct-acting-oral-anticoagulants-doacs-in-renal-impairment-practice-guide-to-dosing-issues/	
SH	North Central London Joint Formulary Committee	Guideline	009	029	Real word data suggests there is relatively little difference between DOACs and warfarin. Further, warfarin is more expensive than branded DOACs (even when monitoring costs are considered). Given the uncertain benefit and certain increase in cost with branded DOACs, can NICE justify the recommendation that warfarin should **only** be considered where a DOAC is contraindicated or not tolerated.	Thank you for your comment. DOACs were more clinically and cost effective than DOAC across all outcomes critical to decision making. The evidence for DOACs over warfarin was based on direct estimates, which are not dependent on model coherence for their validity.
SH	North Central London Joint Formulary Committee	Guideline	010	001	Real word data suggests that there is relatively little difference between DOACs and warfarin. Further, warfarin is more expensive than branded DOACs (even when monitoring costs are considered). Given the uncertain benefit and certain increase in cost with branded DOACs, can NICE justify the recommendation that stable patients prescribed warfarin, edoxaban or rivaroxaban should be **switched** to apixaban or dabigatran? There are additional risks associated with switching which are not modelled; recently there was concern about patients co-prescribed DOACs and warfarin following the initiative to switch people from warfarin to a DOAC. This proposal was justified at the time to reduce face-to-face contacts at anticoagulation clinics during COVID-19 pandemic.	Thank you for your comment. It may be argued that broader sources of data can help determine the “real-world” effectiveness of interventions (i.e., bridge the efficacy/effectiveness gap) and therefore may be useful in making between-intervention comparisons for sub-groups of interest. However, it should be emphasised that randomised efficacy data remain the optimal design for assessing the comparative effectiveness of interventions. The committee judged that there was sufficient RCT evidence on the effectiveness of anticoagulants to support decision-making. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.

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SH	Powys Teaching Health Board	Guideline	009	017	We are concerned that this recommendation may conflict with future national advice if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices". If the procurement prices change this may then change the cost-effectiveness and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 1: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and national . Health Boards could be in the impossible position of being asked to implement guidance where the cost-effectiveness estimates have been arrived at based on prices negotiated for English prescribers. It is imperative that they are aligned to be credible and implementable.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been edited and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.
SH	Powys Teaching Health Board	Guideline	009	023	We are concerned that this recommendation may conflict with future national advice if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices".	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical

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					If the procurement prices change this may then change the cost-effectiveness and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 1: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and national . Health Boards could be in the impossible position of being asked to implement guidance where the cost-effectiveness estimates have been arrived at based on prices negotiated for English prescribers. It is imperative that they are aligned to be credible and implementable.	devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.
SH	Powys Teaching Health Board	Guideline	009	029	Question 2: The draft recommendations may have significant cost implications if warfarin is only offered when DOACs are contraindicated, not tolerated or not suitable. Although there has been a significant move away from warfarin, and towards DOACs, over the last 6 years, this recommendation will see a further reduction in the use of warfarin. Whilst it is recognised that the cost of warfarin needs to include the cost of INR monitoring, it may not be straightforward for Health Boards to extract these costs, depending on the local commissioning arrangements of their anticoagulant monitoring service. This has the potential to increase drug costs (due to increased DOAC costs) without reducing warfarin monitoring costs, as adequate arrangements for warfarin monitoring will still need to be maintained and paid for in each Health Board.	Thank you for your comment. The results of the evidence review demonstrated that DOACs are more clinically and cost effective than warfarin across all outcomes critical to decision making. A separate resource impact assessment will accompany the guideline and it is expected that there will be a financial impact as a result of increased DOAC prescribing. Although there will not be any cash savings it is expected there will be a non-cash releasing saving for providers, such as community, primary and secondary care which is driven by a reduction in anticoagulation clinics for the management of INR levels in people receiving treatment with warfarin.
SH	Powys Teaching	Guideline	010	001	We are very concerned about the recommendation, "For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching

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	Health Board				vitamin K antagonist and are stable, discuss the option of switching treatment at their next routine appointment". Switching anticoagulants, on the basis of cost-effectiveness only (and given that the cost-effectiveness may be flawed and may change depending on procurement prices negotiated in each country) seems to be an unnecessary risk to patient safety as there is clearly potential for patients to inadvertently end up taking two anticoagulants. Risks around switching from warfarin to DOACs during the COVID-19 pandemic have already been recognised. The switch from warfarin to DOAC in this case was at least for the valid reason of reducing face to face attendance at anticoagulant clinics. Switching from one DOAC to another as suggested here, appears unnecessary and potentially unsafe. A secondary factor is that such switches are also likely to lead to medicines waste as patients discard their remaining supply of their existing DOAC. Question 1: This recommendation will be a challenging change in practice because of the safety issues mentioned and also because of the workload/capacity issues in general practice. Would GPs be prepared to switch AF patients between DOACs? Is there enough evidence of safety? Would they want to refer to haematology for DOAC switches? Question 2: Any switches would be likely to happen via remote consultation, due to COVID-19, and this may increase patient safety concerns due to potential confusion/lack of patient understanding. It will also take up healthcare professional consultation time, which we know is already extremely stretched. It will require extra care and vigilance for residents in care homes and their staff responsible for medicines ordering and administration. Question 3: This recommendation could be interpreted to read that organisations should engage in broad switch programs for these patients which on the basis of cost-effectiveness which may then change as the effective price (list price-rebate) is renegotiated multiple times across the lifetime of the guideline.	between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.
SH	Powys Teaching Health Board	Guideline	General	General	The Costing report which accompanied the 2014 guideline estimated that the guideline would result in approximately 10,000 fewer strokes per year in people with AF. https://www.nice.org.uk/guidance/cg180/resources/costing-report-pdf-243730909 (page 7). However, data from the Sentinel Stroke National Audit Program https://www.strokeaudit.org/Home.aspxreports 15,610 AF related strokes in 2013/14 and 16,761 in 2018/19, despite increasing rates of anticoagulation over that time.	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned. Monitoring was outside of the scope of this guideline. Recommendation 1.6.2 directs people to the BNF which contains information on dosing.

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					Even taking into account increased prevalence, there does not appear to have been anything approaching the estimated reduction in AF related strokes. We believe that NICE should investigate the causes of this apparent lack of expected benefit despite increased anticoagulation with DOACs and publish an updated costing report. We consider that the guideline should include practical recommendations for monitoring, appropriate dosing based on renal function, patient information and adherence to help ensure that patients achieve the expected benefits, for example: • There is a table in a Drug Safety Update bulletin published in June 2020 which helpfully sets out the differences between the medicines including adjustment of therapy for patients with renal impairment and availability of reversal agents. https://www.gov.uk/drug-safety-update/direct-acting-oral-anticoagulants-doacs-reminder-of-bleeding-risk-including-availability-of-reversal-agents • An article in the June 2020 issue of the Journal of the American Heart Association gives a practical guide to dealing with common challenges around DOAC use and has a comprehensive section on renal impairment - https://www.ahajournals.org/doi/epub/10.1161/JAHA.120.017559 • It should be noted that dabigatran cannot be dispensed in Monitored Dosage Systems whereas the other DOACs can. • PPI cover to mitigate bleeding risk is also not discussed.	Information and support were outside of the scope of this guideline; however, recommendation 1.6.1 refers to discussing the risks and benefits of anticoagulation. Recommendation 1.4.3 signposts to the NICE guidelines on adherence and medicines optimisation which contain recommendations on information. Anticoagulant treatment should be discussed in the context of shared decision making (recommendation 1.6.2) as this would include a discussion of whether monitored dosage systems are being used. The use of PPIs with anticoagulants was outside of the scope of this guidance.
SH	PrescQIPP	Guideline	009	017	We are concerned that this recommendation may conflict with future advice from NHS England if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices". If the procurement prices change the cost-effectiveness, then this may change and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance".	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been edited and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline.

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					It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices being established with NHSE. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 1: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and NHSE. CCGs could be in the impossible position of being asked to implement two sets of guidelines from two different NHS bodies. It is imperative that they are aligned to be credible and implementable.	NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.
SH	PrescQIPP	Guideline	009	023	We are concerned that this recommendation may conflict with future advice from NHS England if a national procurement process changes the cost-effectiveness of each DOAC. We understand that the "results from the indirect comparisons based on the clinical evidence showed that the direct-acting oral anticoagulants performed differently depending on the outcome. When all these outcomes were combined in the cost-effectiveness analysis, apixaban was the clinically most effective option, followed by rivaroxaban and dabigatran. When costs were also considered, apixaban and dabigatran emerged as the most cost-effective options, based on their list prices". If the procurement prices change the cost-effectiveness, then this may change and the guideline would need revision. This position is acknowledged in the guideline: "The economic modelling for these recommendations was based on UK drug tariff prices at the time of consultation. NICE is aware that procurement of direct acting anticoagulants for use in the NHS is ongoing and that the results of this may have an impact on this guidance". It is difficult to understand therefore, how the NICE guideline can be planned for publication in February without a joined-up position on prices being established with NHSE. Also, our understanding is that the patents on dabigatran and rivaroxaban expire in 2023 while that for apixaban is 2027. Therefore by time of publication post appeals it would suggest rivaroxaban would be more cost effective in the medium term than apixaban. Question 1: This recommendation will be a challenging change in practice because of the potential conflict between recommendations from NICE and NHSE.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.

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					CCGs could be in the impossible position of being asked to implement two sets of guidelines from two different NHS bodies. It is imperative that they are aligned to be credible and implementable.	
SH	PrescQIPP	Guideline	009	029	Question 2: The draft recommendations may have significant cost implications if warfarin is only offered when DOACs are contraindicated, not tolerated or not suitable. Although there has been a significant move away from warfarin, and towards DOACs, over the last 6 years, this recommendation will see a further reduction in the use of warfarin. Whilst it is recognised that the cost of warfarin needs to include the cost of INR monitoring, it may not be straightforward for CCGs to extract these costs, depending on the local commissioning arrangements of their anticoagulant monitoring service. This has the potential to increase drug costs (due to increased DOAC costs) without reducing warfarin monitoring costs.	Thank you for your comment. The results of the evidence review demonstrated that DOACs are more clinically and cost effective than warfarin across all outcomes critical to decision making. A separate resource impact assessment will accompany the guideline and it is expected that there will be a financial impact as a result of increased DOAC prescribing. Although there will not be any cash savings it is expected there will be a non-cash releasing saving for providers, such as community, primary and secondary care which is driven by a reduction in anticoagulation clinics for the management of INR levels in people receiving treatment with warfarin.
SH	PrescQIPP	Guideline	010	001	We are very concerned about the recommendation, “For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist and are stable, discuss the option of switching treatment at their next routine appointment”. Switching anticoagulants, on the basis of cost-effectiveness only (and given that the cost-effectiveness may be flawed and may change depending on procurement prices) seems to be an unnecessary risk to patient safety as there is clearly potential for patients to inadvertently end up taking two anticoagulants. Risks around switching from warfarin to DOACs during the COVID-19 pandemic have already been recognised and the NHS BSA and the Medicines Safety Improvement Programme, have developed a data set to help pick up whether unintentional co-prescribing potentially happened. The switch from warfarin to DOAC in this case was at least for the valid reason of reducing face to face attendance at anticoagulant clinics. Switching from one DOAC to another as suggested here, appears unnecessary and potentially unsafe. A secondary factor is that such switches are also likely to lead to medicines waste as patients discard their remaining supply of their existing DOAC.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.

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					Question 1: This recommendation will be a challenging change in practice because of the safety issues mentioned and also because of the workload/capacity issues in general practice. Question 4: Any switches would be likely to happen via remote consultation, due to COVID-19, and this may increase patient safety concerns due to potential confusion/lack of patient understanding. It will also take up healthcare professional consultation time, which we know is already extremely stretched. It will require extra care and vigilance for residents in care homes and their staff responsible for medicines ordering and administration.	
SH	Primary Care Cardiovascular Society	Guideline	010	001	We are concerned that there is a recommendation that patients already established on edoxaban or rivaroxaban should be switched to apixaban or dabigatran. This will increase the workload for healthcare professionals, who are already under significant pressure because of COVID-19. The work and burden associated with this change will be greater in some areas than others, depending on which DOAC has been used first-line locally. For example, there are areas of the country in which 90% of patients are prescribed rivaroxaban - it will create a significant challenge within these areas to review and switch so many patients. The patient perspective is also important - patients may have been perfectly stable on their medication for many years and the guidelines may mean they will need to be switched to a different medication. In addition, many patients will have switched from warfarin to a DOAC because of COVID19 – to switch them again will add to their anxiety, stress and mental health burden. We are also concerned that imminent patent expiries for the DOACs could mean that patients will be switched again in the near future – possibly to the DOAC that they were on originally and, as a result of this guidance, may have been told it is not as effective! Patent expiry has not been taken into consideration in the budget impact model. Patients will need to switch from well-established once daily dosing to twice daily dosing which increases the risk of under-dosing if the patient misunderstands the new dosing instructions. This would be avoided by implementing the revised recommendations on drug choice for patients newly initiated on therapy and not for those already established on therapy.	Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. We therefore no longer recommend switching people on edoxaban or rivaroxaban.
SH	Primary Care Cardiovascular Society	Guideline	General	General	PCCS will not support the implementation of this guidance without revision of the anticoagulation prescribing recommendations.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.
SH	Public Health England	Guideline	009	011 - 016	We agree and support NICE's action to provide clear CHADSVasc thresholds on the prescribing of anticoagulants. The phrasing of 1.6.3 could be strengthened to make explicit that this applies to women only. Otherwise it seems to contradict paragraph 1.6.4 which states men with CHADSVasc of 1 should be anticoagulated.	Thank you for your comment. 1.6.4 is aimed at men and women whereas 1.6.3 is for men.

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SH	Public Health England	Guideline	010	005 - 008	This sentence could be confusing and needs to be made clearer.	Thank you for your comment. This recommendation has been edited.
SH	Public Health England	Guideline	015	005 - 007	Acknowledging that the current recommendations are restrictive for ablation, PHE suggests changes to the recommendations included in the guidance to reflect this.	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	Public Health England	Guideline	4	1.1 Detecti on	There should be focus on detection and taking a pulse, especially across different age groups, because the simplest way to detect AF is to feel a pulse. If some devices were accurate for diagnosis, they should be recommended.	Thank you for your comment. No devices were sufficiently accurate to replace palpation as the first test. Although some devices showed sensitivity values above that of palpation, these were either based on very limited evidence, or insufficiently different (in terms of the overlap of confidence intervals of the pooled effects) to offer the committee sufficient assurance of any real difference.
SH	Roche Diagnostics	Guideline	010	001	As detailed in Evidence review G1 (Page 72, Line 13-17): "The committee discussed the situation for people already on warfarin, or on DOACs other than apixaban or dabigatran. The committee considered these people could reasonably continue on their current regimen provided they did not wish to change to apixaban/dabigatran, and that they were not experiencing serious problems from their existing prescription." We believe that guideline 1.6.7 is unclear and could be interpreted as recommending a switch of treatment even in patients who are stable (high time in therapeutic range, TTR) on warfarin. We suggest the following amendments to the guideline: **"Adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist and are stable, may continue with their current treatment but should have the opportunity to discuss the option of switching treatment at their next routine appointment"**	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend (1.6.6) that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration
Stake holder	Royal College of General Practitioners	Guideline	010	001	Can the committee consider adding the rationale for changing to apixaban or dagigatran within the guidance to enable clinicians to effectively discuss this with their patients. e.g. instead of 4 bleeds per 100 patients with edoxaban, there are only 2 bleeds per 100 patients with apixaban.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted.

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					Alternatively, a simple decision aid could be included/developed to clearly explain this.	
Stake holder	Royal College of General Practitioners	Guideline	014	004	There is a typo in recommendation 1.7.4 'monotherapy for as initial' (don't need both 'for' and 'as')	Thank you for your comment, this has been corrected
SH	Royal College of Physicians of Edinburgh	Guideline	016	023 - 025	Not many centres are actually able to offer laser ablation. The draft guideline does not discuss cryoablation and radiofrequency ablation, which are the most commonly used techniques in the UK (and worldwide). There is currently limited evidence on laser ablation for AF and this strategy is only offered in a few centres across the UK. As acknowledged in the evidence review, the benefits and cost of this strategy remains uncertain, especially as new equipment would need to be purchased for many centres to begin performing this procedure. The cost of training and learning curve with laser ablation should also not be discounted. Yet, the recommendations do not reflect the reality of the situation and appears to be motivated strongly by an imperfect assessment of cost-analysis. The draft NICE guidelines does not incorporate evidence on the benefits of catheter ablation in AF-induced cardiomyopathy. CASTLE-AF showed benefits on mortality and hospitalisation in selected AF patients with heart failure[21]. Early rhythm control may be associated with improved outcomes (EAST trial) in selected populations with structured follow-up and care[22]	Thank you for your comment. Recommendations 1.7.19 and 1.7.20 have been amended. 1.7.20 recommends cryoballoon or laser ablation in people who are assessed as unsuitable. The evidence showed that radiofrequency point by point ablation was more cost effective over a lifetime than antiarrhythmic drug treatment and other ablation strategies in people for whom 1 or more antiarrhythmic drug has failed. The committee made the pre-hoc decision when formulating the review protocol that the existence of HF would be a sub-grouping criterion. This meant that if there was any statistical heterogeneity in any meta-analysis, the studies within the meta-analysis would be sub-grouped into those where the majority of participants had HF, and those where the majority did not have HF. The plan was that if this sub-grouping resolved heterogeneity (by reducing the heterogeneity to acceptable levels within each sub-group) then results would be presented for each separate sub-group. Unfortunately, the sub-grouping variable of HF did not succeed in resolving heterogeneity in any of the meta-analyses. This meant that we did not have any results data that would imply separate indications for those with HF and those without. Because our sub-grouping analyses suggested that the presence of HF did not affect the variability in outcome, the committee agreed that this evidence showed that people with HF and people without HF would both respond to the ablation

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						treatments in a similar way, and would therefore be eligible for the same recommendations.
SH	Royal College of Physicians of Edinburgh	Guideline	General	General	The College feels that this guideline misses an opportunity to propose integrated care management pathways. They have been shown to be associated with improved outcomes and reduce hospitalisations[18, 23]. This has been tested in a cluster RCT (mAFA II trial) which clearly shows improved clinical outcomes ('ischaemic stroke/systemic thromboembolism, death, and rehospitalization') compared to 'usual care'[24, 25]. Integrated care is delivered based on the ABC pathway (A, Avoid stroke; B, Better symptom management with patient centred and symptom directed rate or rhythm control; C, Cardiovascular risk and comorbidity optimisation), supported by numerous observational cohorts[26-29], and one prospective RCT (mAFA II trial)[24, 25]. The ABC pathway is part of the West Midlands AHSN Primary Care Clinical Pathway for AF Detection and Management (https://bit.ly/2FhrwXQ) This considerable evidence supporting integrated care and the value of ABC pathway for improved AF care has been left out from the NICE guidelines. Opportunistic screening is briefly mentioned, and the NICE recommendation is unchanged from old guidelines. However, there is no point screening without AF patients entering a structured awareness and detection programme, followed by integrated care management, as evidenced by the mAFA programme[30]. Finally, guidelines should try to harmonise with other guidelines were possible unless there is new evidence to support new recommendations or other guidelines are incorrect. Having vastly differing guidelines causes confusion and uncertainty and disparate practice and inequitable patient care.	Thank you for your comment. Integrated care management pathways were outside of the scope of the guideline. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date. Opportunistic screening is outside of the remit of NICE guidelines. The recommendations in this update have been checked with other NICE guidelines for consistency, where appropriate.
SH	Royal College of Physicians of Edinburgh	Guideline	General	General	ORBIT score vs HAS-BLED score The use of the ORBIT score is a new addition to the guideline and the College has serious reservations about the move away from HAS-BLED. College Fellows do not support the use of ORBIT over HAS-BLED, and therefore cannot support this recommendation. This proposed change will require a huge piece of education for junior and senior doctors, physician assistants and nurses to avoid confusion. Therefore any proposal to change practice and be effective should bear this in mind.	Thank you for your comment. The committee were confident that the benefits of ORBIT will outweigh any disadvantages from the need for some degree of initial adaptation on the part of new users. Whilst it is true that ORBIT does not involve measurement of some of the important modifiable risk factors, such as labile INR, such modifiable risk factors can be measured in other ways, and

					The College acknowledges that there is no perfect risk score for bleeding (or indeed stroke). All clinical risk scores are designed to aid practical management. All the published bleeding risk scores have broadly similar performance – meaning that simplicity and ease of practical application is vital. <u>Comparing components of ORBIT vs HAS-BLED</u> The ORBIT bleeding risk score[1] is comprised of Older age (1 point), Reduced Hb/HCT/anaemia (2 points), Bleeding history (2 points), Insufficient renal function (1 point), and Treatment with antiplatelets (1 point); logically therefore this score would perhaps be better abbreviated as OR_2B_2IT. The ORBIT score also notes many similarities to the HAS-BLED score components, including elderly age, bleeding tendency, or predisposition [this encompasses reduced haemoglobin (Hb) or anaemia; given 1 point in HAS-BLED but can sum up to a maximum of 4 points in ORBIT, with 2 points from Reduced Hb/HCT/anaemia and 2 points from Bleeding history], abnormal renal function, and concomitant antiplatelets[2]. Significant differences between the ORBIT score and HAS-BLED score include the different weighing for bleeding tendency or predisposition, and no consideration of uncontrolled hypertension, abnormal liver function, prior stroke, chronic use of NSAIDs, and labile INRs in the ORBIT score. Reduced Hb/HCT/anaemia is already within the HAS-BLED score under the B criterion ie. Bleeding history or predisposition. The ORBIT score does not consider important bleeding risk such as uncontrolled hypertension (esp. for intracranial bleeds) and prior stroke. An AF patient with a haemorrhagic stroke would have zero points on the ORBIT score (so 'low risk') whilst would score a minimum of 2 points on the HAS-BLED score. Although the guidelines do suggest monitoring in these groups they do not form part of the scoring system. As another example[2], a 50-year-old man with uncontrolled hypertension (e.g. blood pressure >180/110 mmHg), prior stroke, (very) labile INRs on warfarin (e.g. TTR 40%), concomitant use of NSAIDs (e.g. Cox-2 inhibitors), abnormal liver function, and excess alcohol intake would have an ORBIT score of 0 (i.e. low risk), but would have a HAS-BLED score of 5 (high risk). The responsible physician would certainly 'flag up' this patient with a high HAS-BLED score, and, in accordance with good clinical practice, would strive to control blood pressure, optimize the TTR (or swap to an NOAC), and reduce NSAID use and alcohol intake. Crucially, the ORBIT score would not flag up such a patient or draw attention to the reversible bleeding risk factors	may already be available on the patient's data. Furthermore, whether ORBIT or HAS-BLED are used does not actually change the amount of modifiable risk factor investigations that need to be carried out by the investigating clinician. For example, measurement of haemoglobin, labile INR, blood pressure, liver function tests and renal function tests will need to be carried out in both cases to evaluate whether current bleeding, increased blood pressure or treatable liver or renal disorders are present, each of which can be treated if needed to reduce bleeding risk. The only difference is that the results of labile INR, blood pressure, liver function tests and renal function tests will feed into informing the HAS-BLED score whereas haemoglobin and renal function results (GFR) will feed into the ORBIT score. This does not make ORBIT any more costly in terms of clinician time and resources, as other variables in ORBIT do not require invasive investigations. In addition, the notion that if the modifiable risk factors are not part of the tool then clinicians will not be prompted to discuss their modification is not a real disadvantage. This is because assessment of the modifiable risk factors of bleeding forms part of a routine assessment. We would therefore argue that the real benefits of the greater absolute risk prediction accuracy from ORBIT outweigh the disadvantages of ORBIT not incorporating some of the modifiable risk factors, because the advantages are very real but the disadvantages are surmountable. Calibration data was prioritised because the purpose of predicting risk was not as a decision aid, but as an aid to the patient/clinician discussion about modifying risk. Thus, accurate prediction of risk was seen as more important than accuracy of binary decision thresholds. Our committee agreed that the calibration evidence showed that ORBIT

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					Bleeding risk assessment should be undertaken not only when taking oral anticoagulant (OAC), but also when first diagnosed (ie. on no antithrombotic therapy), on aspirin (perhaps when the AF patient with vascular disease is first diagnosed) and whilst on OAC. Thus, the bleeding risk assessment tool needs to be applicable at all steps of the patient pathway. The average general practitioner and non-specialist will not be concerned about calibration or complex statistics. It is important to recognize that statistical significance is not the same as clinical significance. The recommendation on bleeding risk assessment (and the score) also needs to consider clinical and practical merits, far beyond the inappropriate focus on marginal statistical differences in predicting the occurrence of bleeding events. In the NICE evidence appraisal, much attention is focused on calibration curves some of which were reported from highly selected non-UK cohorts. In terms of risk prediction, all bleeding risk scores based on clinical factors have modest predictive value (c-indexes of approx. 0.6), typical of clinical scores. Indeed, all prediction scores based on clinical factors (whether $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED, ATRIA, ORBIT, etc.) have broadly similar c-statistics, 0.6 – 0.7. Again we stress that statistical significance is not the same as clinical significance and the two should not be confused. The calibration focus also assumes bleeding risk is 'static' and is consistently the same in different populations, clinical settings etc**.** This is not the case, given the dynamic nature of bleeding (and stroke) risks[3].Bleeding risk scores should be used appropriately to draw attention to the modifiable bleeding risk factors, and then to 'flag up' the high bleeding risk patients for early review and followup[4]. Calibration is of more interest when prognosis is of interest. The point is that the focus on calibration is appreciable since they highlight that absolute risk of events when using a prediction model is of highest clinical interest. On the other hand, the outlines from the discussion states (p82 line 1-4) that "*The committee reiterated the importance of using a bleeding risk tool to inform plans to reduce reversible causes of bleeding and to maintain appropriate levels of vigilance, rather than as a threshold based tool to determine if anticoagulation should take place*". Hence, they infer that it is most important to have accurate risk predictions (good calibration) and less important to have good discrimination. Nevertheless, the draft NICE guidelines does not recommend to actually use the accurate risk predictions to make any clinical decisions based on these risk predictions. It also makes the points about modifiable bleeding risk factors, but many (eg uncontrolled BP) are not in the ORBIT score. In terms of discrimination, this is often of most interest when looking for accurate diagnostic testing, i.e., does a patient have the disease at X level of predicted risk / above prespecified cut-points on a score. Good discrimination gives the opportunity to identify certain characteristics of	was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk. Our review question was focussed on the most accurate bleeding risk tools for people who were on, or about to be on, anticoagulants, as this was agreed to be the most relevant population in terms of bleeding risk. Therefore we have only looked at evidence that evaluated tools in the anticoagulated population. The committee also appreciated that bleeding risk is not static, but that the evidence may assume stasis by mapping baseline characteristics to later bleeding events. Whilst the committee accept this limitation of the evidence, it is common across discrimination and calibration evidence, and across all tools. Thus, they did not think it invalidated their conclusions. When stating the lack of comparative studies in section 1.5 we were specifically referring to the lack of any randomised trials comparing outcomes of the use of different tools. In part E we initially looked for randomised prediction tool studies [where people are randomised to one tool or another and the groups are prospectively compared for patient-centred health-related outcomes such as quality of life] as they are considered the best evidence for the efficacy and cost effectiveness of prediction tools, though none were found. These are not studies primarily designed to evaluate accuracy directly, which were looked at in our prediction section F instead. In our prediction section F we have included many studies (including Lip 2018 and Guo 2018, which you have mentioned) where the different tools were

					the model parameters (i.e. risk factors) that can accurately discriminate. Indeed, the discussion in the document emphasises that the tools for bleeding risk scoring that are of most interest to identify certain characteristics, which may be identified as modifiable risk factors. The performance of a prediction model cannot be measured solely on either calibration or discrimination. Various validation studies have examined HAS-BLED in predicting bleeding risk in AF whilst on OAC (both VKA and non-VKA anticoagulants), aspirin, or without any antithrombotic therapy[4, 5]; hence, applicable at all stages of the patient journey. HAS-BLED is also the only score shown to be predictive of intracranial haemorrhage (ICH), the most serious form of bleeding[6]. The HAS-BLED score has also been validated in non-AF populations, including those with venous thrombo-embolism,acute coronary syndrome, or percutaneous coronary interventions,or those undergoing bridging therapy, as well as in venous thromboembolism (VTE)[4, 7, 8]. The 2020 NICE VTE guideline (https://www.nice.org.uk/guidance/ng158) recommends the use of HAS-BLED score, where a score of >4 indicates high risk and the decision for long term anticoagulation use should be reviewed. This is not the case for the ORBIT score which essentially has been studied in anticoagulated AF patients only (not VTE). This widespread use adds to the argument to keep things simple to avoid confusion rather than the proliferation of scoring systems. Otherwise the ORBIT score components are already within the HAS-BLED score. The latter also offers simplicity, and can be used in patients on DOAC as well as warfarin (and many patients continue on warfarin, despite the increasing use of DOACs) where the L criteria ('labile INR') draws attention to the quality of anticoagulation control, which is a powerful determinant of bleeding risk if time in therapeutic range is low. Bleeding risk (like stroke risk) is dynamic and is influenced by age and mitigation of modifiable bleeding risk factors[3]. When used practically, the HAS-BLED score is supported in the prospective mAFA-II cluster randomised trial, where the mAFA intervention (which used HAS-BLED score to draw attention to modifiable bleeding risk factors and schedule high risk patients for review) was associated with lower bleeding events and an increase in OAC use, compared to 'usual care'[9]. In the latter patients, there was actually a decline in OAC use and higher bleeding event rates. The ORBIT score has not been tested in such a prospective manner. Evidence for ORBIT vs HAS-BLED It appears to the College that the use of ORBIT in the draft guidance is not evidence-based and the colleges is somewhat surprised by this given the reliance on NICE to use the most robust	compared for prediction accuracy. Chao, 2018 was considered but excluded because it had a non-anticoagulated cohort (see exclusion list). Thank you for your literature review. For full details of our systematic review including the search strategy and inclusion/exclusion lists see evidence review E and F.

evidence in making recommendations which will impact patient care. We wonder if NICE has missed examination of some important studies. The evidence tables state that no relevant comparative clinical studies comparing bleeding risk tools with HAS-BLED were identified, which is not correct.

Using the large nationwide Danish registries[10], the HAS-BLED, ATRIA, and ORBIT bleeding scores were compared in AF Patients Using DOACs. At one year, the c-indexed were approximately 0.59, with only minor differences between scores. Both ATRIA and ORBIT categorized more patients as "low risk" (both >83%, when compared with HAS-BLED, only 53%), and qualitatively, the receiver operating characteristic curves revealed higher sensitivity (62.8%) for HAS-BLED compared with ATRIA (29.7%) and ORBIT (37.1%). HAS-BLED classified least patients at low risk and achieving the highest benefit if applying a major bleeding intervention threshold of approximately 2%, whereas benefit from using either ATRIA score or ORBIT score was only evident using higher intervention thresholds.

Table 1 Predictive Ability of Different Bleeding Risk Scores in 4824 Chinese Patients with Atrial Fibrillation

Bleeding Event	C-index	95% CI	*P* Value
Major bleeding event (n = 55)			
HAS-BLED	0.72	0.65-0.79	<.001
HEMORR$_2$HAGES	0.69	0.62-0.77	<.001
ATRIA	0.66	0.58-0.74	<.001
ORBIT	0.64	0.56-0.73	<.001
European score	0.63	0.56-0.69	.001
Intracranial hemorrhage (n = 25)			
HAS-BLED	0.83	0.75-0.91	<.001
HEMORR$_2$HAGES	0.73	0.61-0.85	<.001
European score	0.72	0.65-0.79	<.001
ORBIT	0.67	0.54-0.79	<.001
ATRIA	0.66	0.54-0.76	<.001
Extracranial bleeding (n = 28)			
ATRIA	0.69	0.58-0.80	<.001
HEMORR$_2$HAGES	0.69	0.68-0.71	.014
HAS-BLED	0.67	0.66-0.68	.002
ORBIT	0.65	0.64-0.66	.006
European score	0.55	0.54-0.56	.361

Guo et al[11] compared bleeding risk prediction only focused on modifiable bleeding risk factors (as recommended in the 2016 European guidelines, ie. 'European score') versus other published bleeding risk scores that have been derived and validated in AF subjects (HEMORR $_2$HAGES, HAS-BLED, ATRIA, and ORBIT) in a large hospital-based cohort of Chinese inpatients with atrial fibrillation. The HAS-BLED score was superior to predict bleeding events compared with the European score, with the differences between c-indexes of 0.10-0.12 (Delong test, all $P < .05$), NRI values of 13.0%-34.5% (all $P < .05$), and IDI values of 0.7%- 1.4% (all $P < .05$) [Table 1]. The European score had predictive ability similar to other bleeding risk schemes (HEMORR2HAGES, ATRIA, and ORBIT) for major bleeding and ICH, as reflected by nonsignificant differences in c-indexes, NRI, and IDI (all $P > .05$). Decision curve analysis

					showed that HAS- BLED had better net benefit of predicting major bleeding compared with the European score. Other comparisons of HAS-BLED versus ORBIT have been published, but this evidence has not been taken into account by the NICE guideline development group. Chao et al[12]compared a risk assessment strategy for major bleeding and intracranial haemorrhage (ICH) based on modifiable bleeding risk factors against established bleeding risk stratification scores ($HEMORR_2HAGES$, HAS-BLED, ATRIA, ORBIT). All contemporary bleeding risk scores had modest predictive value for predicting major bleeding but the best predictive value and NRI was found for the HAS-BLED score. One systematic review and metaanalysis[13] comparing the ORBIT and HAS-BLED scores in anticoagulated AF patients included seven selected studies, where the pooled C- statistic of continuous variables for major bleeding was 0.65 (0.60,0.69) for ORBIT and 0.63 (0.60,0.66) for HAS-BLED. Compared with HAS-BLED, more anticoagulated AF patients (88.45% versus 32.59%) and major bleeding events (75.57% versus 25.57%) were categorized as low risk. The ORBIT score had a 1.21, 1.73 and 1.44-fold elevated risk of major bleeding in the low, intermediate and high risk strata respectively. Calibration analysis demonstrated that the ORBIT score under-predicted major bleeding in the low, intermediate, and high-risk stratifications, where a odds ratio of 0.64 (0.37-1.10), 0.63 (0.38-1.05) and 0.64 (0.38-1.06), respectively. Thus, when compared with HAS-BLED, the ORBIT score does not perform better in predicting major bleeding events in anticoagulated AF patients. More anticoagulated AF patients and major bleeding events were categorized as low risk when using ORBIT. An independent Patient-Centred Outcomes Research Institute (PCORI) systematic review and evidence appraisal concluded that the HAS-BLED score had the best evidence for predicting bleeding risk (moderate strength of evidence)[14, 15]. This review only compared the HAS-BLED score, HEMORR2HAGES score, ATRIA score, Bleeding Risk Index (BRI) and ABC bleeding risk score, although they state they were aware of other tools, such as ORBIT score, but their scope was focused on the scores used most frequently in clinical settings and prioritized through the stakeholder panel and topic refinement process with PCORI. An European Heart Rhythm Association survey found that HAS-BLED was the most commonly used bleeding score (>75%) amongst European cardiology centres[16]. The PCORI review also concluded that *"Clinical risk scores must take into account the balance between simplicity and practicality versus accurate prediction, especially in a high-capacity clinical environment. While clinical risk scores are necessarily reductionist and cannot feasibly*	

					consider all patient parameters, our results here show moderate predictive ability of risk scores that can be calculated relatively easily from patient history and demographics." Other international guidelines also recommend use of the HAS-BLED score, for example the 2018 CHEST expert panel guidelines from the American College of Chest Physicians[17], which was based on systematic review and GRADE methodology. Also, the 2020 ESC AF guidelines on AF management[18]. It would seem surprising that the UK was not consistent with International guidelines based on the same evidence. <u>Other considerations</u> There are several methodological limitations with the ORBIT score which should be highlighted[1]. The ORBIT score was derived from an observational registry (ORBIT-AF) and validated using the ROCKET-AF trial[19]. The latter was a highly selected clinical trial patient cohort that only included high risk patients with AF (i.e. $CHADS_2$score of ≥2, with those with $CHADS_2$ score 2 being capped at 10%) and excluded patients with significant renal impairment (creatinine clearance <30 mL/min). Also, the warfarin-treated patients in ROCKET-AF had a poor TTR (55%), and the warfarin-treated patients in ORBIT-AF used as the derivation cohort were only those who remained on warfarin. In the paper by O'Brien et al[1], a 'low risk' category ORBIT score has a bleeding risk of 2.4 bleeds per 100 patient-years, whilst a 'medium risk' patient has a bleeding risk of 4.7 per 100 patient-years. Corresponding rates in the initial derivation cohort for HAS-BLED were ,1.13 and 1.88 per 100 patient-years, respectively.Thus, a patient categorized as having a 'low risk' of bleeding by HAS-BLED has a (low) bleeding rate of ~1 per 100 patient-years, but even a supposedly 'low risk' patient using the ORBIT score has a bleeding rate of 2.4 per 100 patient-years. Indeed, even an ORBIT score of 1 has a bleeding rate of >2 per 100 patient-years. In summary, bleeding risk assessment is not a static phenomenon, and many common clinical factors that increase bleeding risk are potentially reversible. Undue oversimplification of bleeding risk scores with focus on statistical significances for c-statistics and recalibration completely neglects the clinical utility of applying the score in everyday clinical practice**.** A useful prediction model may inform public health (e.g. screening) or patient care (prognosis or decision support). Discrimination may have higher research interests relative to calibration, but it really comes down to how a score is applied. Calibration is very important if a score is used to inform patients or if used in making clinical decisions; however, this is apparently not the case, since in the assessment of ORBIT vs HAS-BLED the Guideline Development Group mentions that it should not be used for decision making.	

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SH	Royal Free Hospital NHS Foundation Trust	Guideline	010	003	Discussing switching is a very difficult concept for patients to understand without head to head RCTs and retrospective real world data. Please reconsider this comment and withdraw. Stable patients for no significant NHS budget impact should not be switch without head to head data prompted re-evaluation. Many practitioners may not have an adequate conversation and will switch patients and lose faith in the system to communicate with them and see this as a cost cutting exercise and reduce compliance and confidence in medications. Even short interruptions in OAC can lead to strokes so undermining this with switching without careful discussion will almost be sanctioned by this section needlessly in stable patients. In summary NICE guidance could become a mechanism of commercial advantage not useful to any company, all of whom have invested heavily in atrial fibrillation and stroke prevention space. Thank you however for tackling a difficult area where there is less head to head RCT data but please be humble to trial differences and the needs of patients.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.
SH	Royal Surrey County Hospital	Guideline	010	001	The authors state that the rankograms provided are for doses of licensed products examined in prevention of stroke in patients with atrial fibrillation. However, the rankograms do not include dabigatran 110mg, which is both licenced for this indication & extensively evaluated in the RELY trial. There are a number of other errors in the Lopez-Lopez paper, with some examples being listed below: 1. "….gastrointestinal bleeding was lower with apixaban 5 mg twice daily than with other doses of DOACS" a. Suggest this relates to the low risk population in ARISTOTLE, absence of dual anti-platelet therapy, low incidence of patients taking aspirin, higher percentage of patients taking PPI. Do not see that any correction for these factors is applied and therefore cannot see how this conclusion can be made. 2. "There was strong evidence that the risk of intracranial bleeding was lower with apixaban 5 mg twice daily" a. This is not correct as per the data supplied in the paper. In table 3 the comparison of NOACs all cross the point of no difference and none is shown to be superior (or inferior) to another in this regard. It is not acceptable to make a statement of superiority when the numbers demonstrate that it is absolutely not the case.	Thank you for your comments. We have amended the incorrect statement that apixaban was ranked first for stroke and systemic embolism. A correct summary of the rankograms has now been added. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration. .

					3. "Figure 4 shows that apixaban 5 mg twice daily was ranked as being the most effective intervention for several of the outcomes evaluated including stroke or systemic embolism, myocardial infarction, and all-cause mortality." a. Except that this is not correct as per the illustrations in figure 4 which do not show as the authors claim. Rather dabigatran 150mg bd is shown to be the most effective intervention for stroke / systemic embolism, and rivaroxban to be the most effective for myocardial infarction and all cause mortality. 4. "Warfarin and edoxaban 60 mg twice daily are unlikely to be cost effective." a. I agree that this may well be true. But that is because edoxaban is a once a day drug and so using it as Lopez-Lopez state would be to give double to licenced dose and so would very likely be harmful and cause a large number of adverse events. On the basis that the twice daily is an error and the intention was to describe the licenced once daily use, then the statement still seems odd since table 4 gives edoxaban a positive incremental net benefit for edoxaban at both the £20 and £30K thresholds which would suggest it is cost effective. Although the CIs cross the zero point they also do for other agents but these are not dismissed as being non-cost effective. 1.6.7 For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist and are stable, discuss the option of switching treatment at their next routine appointment. This would appear to be requested on the basis of cost-effectiveness. However, there are problems with the cost-effectiveness calculations that appear to be flawed on several levels (incorrect drug prices as one example, and an artificial expectation that apixaban is superior to other agents based on the flawed Lopez-Lopez paper as another). There is also the issue that many CCGs have signed up to a rebate scheme with edoxaban and hence switching from the drug with the lowest acquisition cost to one with the highest will cost an enormous amount of money. There are additionally risks involved with switching drugs, including from agents taken once daily to those intended to be taken twice daily. Switching from one NOAC to another as suggested here, appears unnecessary and potentially unsafe. These switches may also lead to medicines waste as patients discard their remaining supply of their existing NOAC. These switches are likely to be labour intensive and involve clinical risk to patients. Neither the clinical superiority, nor the cost effectiveness benefits, of apixaban / dabigatran over edoxaban / rivaroxaban have been adequately demonstrated, and hence it is hard to understand why stable patients should be switched.	With regards to patent expiry, NICE monitors guidelines to ensure that they are up to date. As part of this surveillance process changes that may mean modifications are needed, such as changes in licencing arrangements, are identified, and the impact on the guideline recommendations is assessed.

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					It is unclear whether NICE have considered the patent expiry dates when making the recommendation to switch stable patients to different agents. Given the current UK market share of apixaban & dabigatran any such instruction is likely to result in large numbers of patients being switched to the most expensive of the four agents, which also has the highest time remaining on its patent. Evidently this will increase costs substantially. Some of the NICE documentation is ambiguous about switching and this causes unnecessary confusion.	
SH	South London Cardiovascular Medicines Working Group	Guideline	010	003	If patients are suited to a particular anticoagulant and have been adherent and stable on therapy, there are concerns that switching patients to a twice daily regime that may not suit their lifestyle and/or may not be as well tolerated may cause treatment failures and patient safety risks. The emphasis should be to ensure that anticoagulation to prevent stroke risk is effective and safe- but if the patient is not taking it as directed or is experiencing ill effects then this benefit is lost. In the cost saving analysis, a once daily preparation should also be considered as a preferred agent option. Many areas within the UK have already established patients on a preferred DOAC agent as a cost-saving exercise considering the use of an agent with a low acquisition cost when there is no head-to-head data demonstrating effectiveness or safety benefit for a DOAC of choice. Given current pressures within primary and secondary care due to COVID-19, the work resource involved in switching patients seems counter-productive, especially if the patient's therapy is well tolerated. The patent expiries for DOAC agents are also approaching and should be considered in a budget impact assessment. There are also significant number of patients who have recently switched to a DOAC from warfarin to reduce the need for blood testing during COVID-19. We worry that these patients may lose confidence in their HCP or their chosen DOAC therapy if they are switched so soon after starting a regime.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted.
SH	South London Cardiovascular Medicines Working Group	Guideline	010	009	We agree that anticoagulation should not be withheld solely because of age or falls risk. Is it also best to recommend a DOAC over warfarin if renal function allows here to reduce ICB risk? And a consideration of other medications that may contribute to bleeding risk?	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF including consideration of renal function and other medications (1.6.2).
SH	South London Cardiovascular Medicines	Guideline	021	006	Post cardiothoracic surgery: amiodarone prescribing- in local centres this is prescribed for 6 weeks and then stopped- could you add to the guidance that this is short term use and/or will be reviewed at follow up as we do not want primary care to continue amiodarone prescribing indefinitely?	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team

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	Working Group					which monitors guidelines to ensure that they are up to date.
SH	South London Cardiovascular Medicines Working Group	Guideline	022	016	When basing decisions to stop anticoagulation on risk:assessments and a discussion of patient preference- please also consider patient tolerability, preference and lifestyle in a decision around the choice of anticoagulation and alternative options	Thank you for your comment. Patient tolerability, preference and lifestyle would be discussed as part of patient preferences.
SH	The Stroke Association	Guideline	009	029	The guideline should make it clearer that patient and clinician choice still plays a role in anticoagulation options. Currently, key details outlined in the evidence review are missing from the draft guideline: • 'The recommendation wording allowed for any of the four currently licensed DOACs to be used if necessary. The committee discussed the situation for people already on warfarin, or on DOACs other than apixaban or dabigatran. The committee considered these people could reasonably continue on their current regimen provided they did not wish to change to apixaban/dabigatran, and that they were not experiencing serious problems from their existing prescription.' • 'The committee were aware that there were circumstances where the other DOACs might be the only ones available, or where patients might express a wish not to use apixaban or dabigatran'. • 'The committee discussed the patient experience of using apixaban and dabigatran, and described how dabigatran may lead to more upper GI side effects, and also possibly less compliance because of the greater number of doses per day (…) A decision on the best drug to use should be based on shared decision making between the clinician and patient, taking into account all risk factors and preferences'. We suggest making it clearer in the guideline that any of the licensed DOACs can be used if necessary, and that the 'decision on the best drug to use should be based on shared decision making between the clinician and patient, taking into account all risk factors and preferences'. As well as this, it should be made clearer that people on stable prescriptions of DOACs other than apixaban or dabigatran can 'reasonably continue on their current regimen provided they did not wish to change to apixaban/dabigatran, and that they were not experiencing serious problems from their existing prescription'.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOACs. In recommendation 1.6.2 on choosing an anticoagulant we refer to the guidance on shared decision making in the NICE guideline on patient experience in adult NHS services. The recommendation on switching between DOACs has been deleted as it is no longer relevant given the edits above. Recommendation 1.6.6 refers to switching from a vitamin K antagonist to a DOAC and that time in therapeutic range should be taken into consideration.

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SH	The Stroke Association	Guideline	023	014	NICE guidelines should address the need for more research on patient and public perspectives on acceptability and feasibility of treatments and support for management of atrial AF, including any relevant findings identified in the James Lind Alliance Stroke Priority Setting Partnerships (to be published May 2021).	Thank you for your comment. The research recommendations were based on the evidence reviews conducted as part of this update including the outcomes or carried over from previous versions of the guideline. However, when this research is conducted researchers may include outcomes on acceptability and feasibility.
SH	The Stroke Association	Guideline	General	General	The Stroke Association welcomes this consultation by the National Institute for Health and Care Excellence (NICE) and the opportunity to provide comment on the draft proposal. The improvement of the detection and management of AF in England needs to be prioritised given the scale of the burden of stroke. The growing number of strokes and the cost of stroke to society means that preventing strokes, including through effective AF management, is critical and there are still huge gains to be made by managing AF properly. As AF detection and management is cost effective, prevents strokes and improves quality of life, health and care systems need to do more. The Stroke Association understands that COVID-19 has created huge difficulties but we think this is a time to be ambitious and not complacent. In the past two years a number of national level initiatives have committed to better detection, treatment and management of AF. NHS England and Improvement's Long Term Plan commits to preventing 150,000 strokes, heart attacks and dementia cases over the next 10 years and highlights the importance of managing AF, recognising that the 'early detection and treatment of CVD can help patients live longer, healthier lives'.[32] The National Stroke Programme, which underpins the delivery of the Long Term Plan's stroke-related goals, is working closely with the CVD & Respiratory Conditions Programme Board to look at ways to improve detection and management of AF. Public Health England (PHE) has also outlined ten-year cardiovascular ambitions for England, including the goal that 90% of patients with known atrial fibrillation should be appropriately anticoagulated by 2029.[33] We welcome the update to the AF management guideline to help contribute to these ambitions. Emerging and established Integrated Care Systems (ICSs) in England provide a unique opportunity to deliver true integrated health and care through joint-budgets. Progress on AF management has previously been hampered by the commissioner/provider divide within the NHS when the commissioner frequently bore the cost, but the wider NHS and social care	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned.

[32] NHS England and Improvement, NHS Long Term Plan, (January, 2019) Available: https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf, p.62
[33] NHS Health Check e-Bulletin, World Heart Day (2020) Available: https://www.nhshealthcheck.nhs.uk/nhs-health-check-e-bulletin-world-heart-day/front-page/nhs-heath-check-e-bulletin-world-heart-day

					system received the financial benefits. Consequently, patient benefits have been slow to materialise. The new ICSs provide an opportunity to demonstrate better outcomes. ICSs, as well as systems like Integrated Stroke Delivery Networks (ISDNs), should have a key responsibility to deliver on the CVD prevention elements of the Long Term Plan and associated programmes. We look forward to working with NHS England and Improvement to ensure there are clear deliverables for local systems. The Stroke Association wants to see improvement to the detection, management and treatment of AF in the UK, to help prevent more strokes. AF increases your risk of stroke by around 4 to 5 times, affects around 1.2 million people in the UK, and is a contributing factor in around 1 in 5 strokes. AF-related strokes are more severe and more likely to result in institutional care. However, AF is undetected in 30% of those it affects and over half of those who are diagnosed are not appropriately medicated. Once AF is detected, the risk of stroke can be reduced by two-thirds with anticoagulation medication. However, in 2018/19 27.8% of patients with known AF admitted to hospital because of a stroke were not on anticoagulants, highlighting the gains still to be made in managing AF properly.[34] Achieving optimal treatment in people who are already diagnosed with atrial fibrillation in England has the potential to prevent up to 14,220 strokes, saving £241m over 3 years. In 2018-19, 94% of those with a diagnosis of AF had undergone a stroke risk estimation. Of those estimated to have a high stroke risk, 86% were receiving treatment with an anticoagulant.[35] However, AF remains chronically underdiagnosed with estimates of around 500,000 people in the UK unaware they have the condition.[36] The problem is only going to get worse, with research indicating that the number of people aged 55 and over living with AF will more than double by the year 2060.[37]	
SH	The Stroke Association	Guideline	General	General	The Stroke Association has responded to previous consultations on this issue with similar recommendations and this submission is consistent with those. See for reference, our responses to: • Department of Health and Social Care's 'Advancing our health in the 2020s' prevention Green Paper in July 2019 where we recommended that pharmacists	Thank you for your comment.

[34] NHS Digital, Quality and Outcomes Framework (QOF) 2018-2019 results. Available: https://qof.digital.nhs.uk/
[35] Ibid.
[36] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7032580/
[37] Lang A, Edwards F, Norton D, Semple L, Williams H. Using mobile ECG devices to increase detection of atrial fibrillation across a range of settings in south London. *Future Healthc J*. 2020;7(1):86-89. doi:10.7861/fhj.2019-0033

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					and other health professionals are supported to check for AF and AF is included in the scope of the NHS Health Check review; • UK National Screening Committee Screening for Atrial Fibrillation in June 2019 where we recommended opportunistic pulse checking to help increase diagnosis and make every contact count, highlighted the growing range of new technologies which can detect possible AF and recommend that pharmacists and other health professionals also check for AF; • NICE 'Stroke TIA' consultation in May 2019; and • NICE 'Hypertension in adults: diagnosis and management' consultation in August 2019, where we again advocated for opportunistic pulse testing for atrial fibrillation. Outside of these consultation responses, we have made several recommendations for the management of atrial fibrillation in other parts of the UK, including: o The recent report *The future of stroke care in Wales* on the inquiry into the implementation of the Welsh Government's Stroke Delivery Plan by the Cross Party Group on Stroke, which called for Health boards in Wales to fully implement the new AF pathway and referenced AF as a key area to target for stroke prevention; and In our response to *Reshaping stroke care in Northern Ireland*, whereby we called for more information from the Department of Health on their plans to improve stroke prevention and, in particular, efforts to improve the detection and management of hypertension and AF.	
SH	The Stroke Association	Guideline	General	General	There are areas within the current draft guideline that are both unclear and open to interpretation, and need to be clarified in order to ensure the safe use of the guideline. We have highlighted a few examples below: a. Page 8, line 20 – we suggest directly placing this section alongside those it is relevant to, and briefly outlining what is meant by 'off-label use'. b. 1.6.7 (page 10, line 1) - the wording of the line 'for adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist and are stable discuss the option of switching treatment at their next routine appointment' is unclear. Those reading this might be uncertain as to whether a vitamin K antagonist is to be switched or not, if they did not have former knowledge. The guidelines should be clear to members of the public and not just those with detailed medical knowledge. Please	Thank you for your comment. a. This recommendation is relevant to a number of areas of the guideline and we have therefore placed it in a separate section rather than repeating it. b. The recommendation has been edited to make it clearer whether a person on a vitamin K antagonist should be switched. c. The recommendations have been ordered so that they cover who should be offered anticoagulants first and then who does not require anticoagulation. This should make the recommendations easier to follow. d. Recommendation 1.2.4 covers what to do with the bleeding risk score results.

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					also briefly include why the clinician should consider switching within the guideline and the evidence behind this, for clarity. c. Sections 1.6.4 and 1.6.8 (page 9, line 17) - we suggest putting these sections alongside each other in the guideline, as well as making them clearer as to when anticoagulation is appropriate. d. 1.2.2 (page 5, line 13) - we are supportive of an approved bleeding risk score. However, we suggest making it clearer within the guideline of what to do with the score once completed. Doctors need to be supported in making decisions based on the risk. General Practitioners may refresh their memory of guidelines during the patient's consultation. These traditionally last ten minutes, and therefore every paragraph must give the right message when read in isolation or potentially be unsafe.	We work with the editorial team at NICE to ensure the recommendations can be read in isolation. The recommendations hyperlink to the relevant rationale and impact sections. These explain why the recommendation was made by the committee and the impact of the recommendation on practice.
SH	Thrombosis UK	Guideline	009	011-017	We are concerned that recommendations in 1.6.3 and 1.6.4 are Not in keeping with current NICE guidance TA256 and TA355	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and we now refer to any licensed DOAC.
SH	Thrombosis UK	Guideline	009	011-017	We are extremely concerned that patient choice has been excluded in decision making on anticoagulation therapy. The draft guideline seems to have ignored significant issues, including: lessons from current practice, key population characteristics such as frailty/renal impairment/obesity, dangers of indirect comparisons, and crucially medication adherence. Such action is likely to cause potential harm, especially in some groups: (i) Patients who are better suited to a once per day treatment option due to their medical / life-style / work needs. (ii) Patients who would be medically better suited to rivaroxaban or edoxaban. (iii) Medical conditions that would make some of the DOAC options unsuitable including renal impairment / obesity. (iv) Patients who may be frail or reliant on carers to administer medication where once per day option would be much easier to administer. (v) Individuals who may struggle with compliance. It is recognised that multiple-doses can impact on compliance, not least in vulnerable patients with memory / mental health / life-style instability or multiple therapy regimes Such a restriction may increase burden on carers, for example of Dementia / Alzheimer patients, where administering medication can be challenging and being able to consider a once per day option can offer significant benefits.	Thank you for your comment. Recommendations 1.6.3. and 1.6.4 have been amended and we now refer to any licensed DOAC. In recommendation 1.6.2 we refer to the guidance in the BNF on prescribing. In recommendation 1.6.2 we cross refer to the guidance in the NICE guideline on patient experience in adult services on shared decision making and this would include discussion of factors such as dose frequency. In the committee's discussion of the evidence in evidence review G1 and in the rationale and impact we refer to the importance of considering adherence when making decisions.
SH	Thrombosis UK	Guideline	009	011-017	We are unclear as to why NICE seems to have carried out an unofficial meta-analysis on four anticoagulation therapy options without remit or peer review.	Thank you for your comment.

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						The Lopez-Lopez network meta analysis was peer-reviewed as part of the publication process for the Journal and the health economic model was peer reviewed by the British Medical Journal group.
SH	Thrombosis UK	Guideline	009	011-017	The draft guideline seems to have placed all reasoning for implementing an unofficial meta-analysis upon one paper - Lopez-Lopez, which was a network meta-analysis and received very mixed reviews when published, including • Inappropriate comparison between trials with different patient populations and underlying stroke and bleeding risk, resulting in flawed conclusions regarding relative effectiveness. We are not aware of any other approved UK-wide/ NHS England / NICE meta-analysis review that has been officially endorsed and published and so feel there is no evidence base for NICE to introduce guidelines restricting access to therapies that are currently all approved and with equal standing. An individual's healthcare professional's review of their medical needs and what is medically best suited/safe for them, along with discussion to understand the patient's needs, considerations and preferred choice, should be the only recommended, safe and appropriate line of selection for an anticoagulant therapy treatment in any patient.	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates **(**see the committee's discussion of the evidence in evidence review G1). The health economic model has been revised to account for an error in the coding for the annual cost of stroke and an error in the probabilistic sensitivity analysis sampling. As a consequence of these revisions the credible intervals are now wider and the results more uncertain regarding which DOAC(s) are the most clinically and cost effective. The committee therefore are no longer confident to recommend a specific DOAC or DOACs. The committee acknowledged that there was heterogeneity amongst the study populations and that this may not have been adequately accounted for by the meta regression, resulting in effect estimates that may not have been valid and confidence intervals that were too precise. In recommendation 1.6.2 on choosing anticoagulant treatment we cross refer to the guidance in the NICE guideline on patients experience in adult services on shared decision making. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC.

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SH	Thrombosis UK	Guideline	009	011-017	In April 2020 NHS England issued '***Clinical guide for the management of anticoagulant services during the coronavirus pandemic***' (publication approval ref no: 001559) Website link: https://thrombosisuk.org/downloads/C0077-Specialty-guide_Anticoagulant-services-and-coronavirus-v1-31-March.pdf Guidance in this publication recommended patients who were suitable to 'switch' from a VKA were moved to a DOAC after discussion and agreement. The purpose of this was to reduce potential harm at a time when appointments and safe management of patients were under pressure from the corna virus pandemic. All NICE approved DOAC anticoagulation therapies were recommended in this guidance, with a caveat: - (page 2), "*In line with NICE guidance, where more than one product is available for the indication, the product with the lowest acquisition cost should be used."* All DOAC therapies were recommended equally, in line with NICE TA guidance (TA256, TA355, TA275, TA249), and judgment was left to enable clinical review, patient-HCP discussion and then decision making based on what was safest and most appropriate for the individual. We are concerned that even though the pandemic continues, NICE draft guidance in this AF Management Update document has acted against the NHS England April 2020 publication.	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. We now only refer to switching people from a vitamin k antagonist to a DOAC in recommendation 1.6.6
SH	Thrombosis UK	Guideline	009	011-017	The draft guideline shows a lack of consideration of issues which affect patient safety: • renal dose adjustment • drug interactions age and bodyweight dose adjustment.	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2). Clinical risk profiles should be used to guide treatment choices (recommendation 1.6.1).
SH	Thrombosis UK	Guideline	009	011-017	The draft guideline is recommending only apixaban or dabigatran as first line DOAC options. • Yet real life data has shown that there is significant underdosing with apixaban resulting in patient harm.	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2).

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					In current practice – despite being first to market, dabigatran has failed to secure usage which indicates than clinicians are not willing to prescribe it.	
SH	Thrombosis UK	Guideline	009	017	1.6.4 Re-iterates, *"Consider anticoagulation with either apixaban or dabigatran"* Despite NICE Guidance TA256, TA355, TA249, TA275 all being equally approved and weighted for options in treatment for stroke prevention in patients identified as at risk and diagnosed with non-valvular AF. • There is a complete lack of consideration of patient preference, not least, as there is no once daily option If the draft AF guidelines are recommending *only* offering two dose a-day options re: apixaban or dabigatran, we find this extremely concerning.	Thank you for your comment. We now recommend any licensed DOAC (see recommendations 1.6.3 and 1.6.4) enabling dosing regimen to be taken into consideration in the context of shared decision making (see recommendation 1.6.2).
SH	Thrombosis UK	Guideline	010	001	1.6.7 We are extremely alarmed to read that this guideline is advocating 'switching' stable anticoagulated patients on the basis that if they are currently prescribed rivaroxaban or edoxaban, they should be considered to swap to an alternative DOAC. *"For adults with atrial fibrillation who are already taking a direct-acting oral anticoagulant other than apixaban and dabigatran or a vitamin K antagonist and are stable, discuss the option of switching treatment at their next routine appointment."* We can find no scientific, economic or patient centred reason for this recommendation. If patients are stable and doing well on a DOAC, why is there reason to engage them to swap to an alternative? There is no possible benefit to the patient, but there is potential to do significant harm. All therapies have side-effects, switching also brings some risk factors, even when well managed. Furthermore, NICE are proposing patients who have been complaint and well managed change from a once a day therapy to twice per day option, where compliance may reduce, even if accidental. Why is NICE advocating this action? - It is not in a patient's interest. - It is not within any NHS / NICE guidelines. - It is not supported by science. In a time of a pandemic when the NHS is under considerable pressure and where there is continued cost challenges across the NHS, why is NICE advocating switching stable and well	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted. The evidence review and health economic model showed that DOACs were more clinically and cost effective than warfarin across all outcomes critical to decision making. We therefore recommend that the opportunity to switch to a DOAC should be discussed with a person who is on a vitamin K antagonist. We have edited the recommendation and now recommend that the person should continue on their current medication until the next routine appointment and that time in therapeutic range should be taken into consideration.

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					controlled anticoagulated patients to an alternative DOAC which can only increase risk, cost and workload?	
SH	UK Clinical Pharmacy Association	Guideline	009	011 - 022	Some manufacturers offer rebate schemes – was this considered in the cost analysis by the guideline group? Were any conflicts of interest declared that has potentially led to only two DOAC agents being recommended?	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 have been amended and now recommend any licensed DOAC. The NICE methods manual https://www.nice.org.uk/process/pmg20/chapter/introduction states that public list prices for technologies (for example, medicines or medical devices) should be used in the reference-case analysis. Only national reductions can be included in the reference case analysis. In the case of DOACs we have used the NHS tariff/BNF list price as no nationally available reductions are currently available. Following completion of the procurement NICE will consider an update of the guideline. Conflicts of interests are recording in the register and dealt with in accordance with NICE policy https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/declaration-of-interests-policy.pdf. The register for the guideline is available on the website.
SH	UK Clinical Pharmacy Association	Guideline	009	017 - 022	Specific guidance would be helpful particularly for men and CHA_2DS_2-VASc score of 1 with AF and when anticoagulation should be considered due to varying practice dependent of risk factors – in practice, if male sex is the only risk factor then anticoagulation not offered. This would support decision-making in when anticoagulation should be offered.	Thank you for your comment. Recommendation 1.6.9 states that stroke prevention should not be offered to people under the age of 65 yrs with no risk factors other than sex.
SH	UK Clinical Pharmacy Association	Guideline	009	General	There are no head to head studies to compare DOACs and the comparison between trials with different patient populations (and underlying stroke and bleeding risk) resulting in flawed conclusions regarding relative effectiveness	Thank you for your comment. On further discussion, the committee accepted that there were possible limitations of the analysis by Lopez-Lopez/Sterne that made it difficult to be confident of the validity or precision of the NMA estimates (see the committee's discussion of the evidence in

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						evidence review G1). Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC.
SH	UK Clinical Pharmacy Association	Guideline	009	General	Lack of consideration of issues which affect patient safety – renal dose adjustment, drug interactions, age and bodyweight dose adjustment. It is recognised that there is significant underdosing with apixaban resulting in patient harm.	Thank you for your comment. Recommendation 1.6.1 refers to clinical risk profiles when discussing the risks and benefits of anticoagulation treatment. The DOACS should be prescribed in accordance with guidance in the BNF (see recommendation 1.6.2).
SH	UK Clinical Pharmacy Association	Guideline	009	General	Lack of consideration of patient choice and medicines adherence as there is no anticoagulation agent with once daily option/dosing	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2). Recommendation 1.6.1. refers to personal preferences when discussing the risks and benefits of anticoagulant treatment. Which anticoagulant should be offered should be discussed in the context of shared decision making (recommendation 1.6.2) and this would include consideration of patient factors and clinical indications.
SH	UK Clinical Pharmacy Association	Guideline	009	General	Current practice – despite being first to market dabigatran has failed to secure usage which indicates than clinicians are not willing to prescribe it	Recommendations 1.6.3 and 1.6.4 have been edited and now recommend any licensed DOAC. Which anticoagulant should be offered should be discussed in the context of shared decision making (recommendation 1.6.2).
SH	UK Clinical Pharmacy Association	Guideline	009	General	Inclusion of rivaroxaban with once daily dosing as clinically effective and cost-effective option compared to edoxaban due to reduced efficacy with high creatinine clearance	Thank you for your comment. The DOACs should be prescribed in accordance with the guidance in the BNF (see recommendation 1.6.2). Which anticoagulant should be offered should be discussed in the context of shared decision making (recommendation 1.6.2) and this would include consideration of patient factors and clinical indications.
SH	UK Clinical Pharmacy Association	Guideline	009 - 010	General	Lack of consideration of the practicalities, cost and resources of actively switching patients stabilised on either rivaroxaban or edoxaban with no consideration of patient choice with significant burden of switch across all healthcare settings	Thank you for your comment. Recommendations 1.6.3 and 1.6.4 now recommend any licensed DOAC. The recommendation on switching between DOACs has therefore been deleted.

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					Potential medication supply disruption and/or procurement issues with only two DOACs recommended – likely to lead to poor uptake of NICE guideline with local deviations in practice	
SH	UK Clinical Pharmacy Association	Guideline	012	005 - 009	Detailed and specific guidance on antiplatelet section would be welcomed	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	UK Clinical Pharmacy Association	Guideline	012	022 - 025	'Quality of anticoagulation' is too vague with no mention of follow-up blood tests and frequency of when blood tests should be performed and checked – detailed recommendations would be helpful	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	UK Clinical Pharmacy Association	Guideline	012	General	Consider including specific guidance on assessment of adherence at annual reviews	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	UK Clinical Pharmacy Association	Guideline	022	011 - 016	Further detailed information required for stopping anticoagulation – limited evidence/uncertainty noted but specific recommendations would be welcomed to support decision-making i.e. consensus-based specific recommendations	Thank you for your comment. The evidence was too uncertain and practice variable and the committee were therefore unable to make further consensus recommendations.
SH	UK Clinical Pharmacy Association	Guideline	022	011 - 016	Unclear if the recommendations apply to people post DC cardioversion and ablation – further clarity would be welcomed	Thank you for your comment. These recommendations do apply to people post-DC cardioversion and ablation. The recommendations state that discussions about whether to stop anticoagulation should be based on stroke and bleeding risk scores and not whether or not AF is no longer detectable. We have edited the discussion in the rationale and impact section to make this clearer.
SH	UK Clinical Pharmacy Association	Guideline	022	011 - 016	Specific recommendations would be welcomed in the main guideline for one episode of AF triggered by an event e.g. sepsis	Thank you for your comment. The evidence was too uncertain and practice variable and the committee were therefore unable to make further consensus recommendations.

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SH	University College Hospitals NHS Foundation Trust	Guideline	009	017	We are concerned that this recommendation may imply that there is no once daily option for anticoagulation which some patients may prefer. Why is edoxaban not recommended? Dabigatran is also not suitable for people unable to swallow whole and those that use a medication compliance aid.	Thank you for your comment. We now recommend any licensed DOAC (see recommendations 1.6.3 and 1.6.4) enabling dosing regimen and clinical indications to be taken into consideration in the context of shared decision making (see recommendation 1.6.2).
SH	University College Hospitals NHS Foundation Trust	Guideline	020	004	Suggests using heparin. Most acute trusts do not use unfractionated heparin anymore. Is this referring to low molecular weight heparin?	Thank you for your comment. These recommendations were not reviewed as part of this update and therefore cannot be edited. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
SH	University Hospitals Birmingham	Guideline	010	005	The guidelines state do not offer “stroke prevention” therapy to people aged under 65 years with atrial fibrillation and no risk factors”. This is an incorrect and dangerous statement what I think you mean is “do not offer stroke prevention therapy with anticoagulation”. There are many other treatments that reduce stroke risk that might be offered including alcohol cessation advice, weight loss advice, exercise advice which are equally appropriate in patients with no risk factors and also reduce stroke.	Thank you for your comment. We have made the edit as suggested.
SH	University Hospitals Birmingham	Guideline	013	022	This guidance is incorrect. There are no randomised controlled trials showing any advantage of beta-blockers or calcium channel blockers over digoxin in atrial fibrillation. (Indeed there is new data to suggest quite the opposite although I appreciate NICE cannot have reviewed this when producing the guideline). Indeed the only randomised blinded trial suggested that calcium channel blockers were superior to beta blockers in the rate control of atrial fibrillation. All the data we have may show that it is easier to achieve a lower rate with beta blockers than digoxin but we also have clear trial evidence from the RACE 2 study that aggressive rate control is not important. Ref Am J Cardiol. 2013 Jan 15;111(2):225-30, N Engl J Med 2010; 362:1363-1373	Thank you for your comment. The committee were aware that digoxin is sometimes used for rate control. The recommendation in the previous version of the guideline was updated to also cover those where other rate control drugs are ruled out due to comorbidities or the person’s preferences. However, as digoxin is not used as often compared to beta-blockers or calcium channel blockers in current practice, and the evidence comparing digoxin with other rate control drugs was limited, its use could not be expanded to further groups of people without further comparative evidence.
SH	University Hospitals Birmingham	Guideline	014 030	001 018	There is absolutely no basis for signposting these guidelines. There is very clear evidence from the trials that beta-blockers do not offer any benefit in heart failure when associated with atrial fibrillation	Thank you for your comment. It is standard practice for NICE guidelines to signpost to other NICE guidelines that cover areas overlapping with this guideline and where recommendations have already been made. The committee sought to highlight the discussion on beta blockers in the guideline where no recommendations were made

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						on its use in people with heart failure and atrial fibrillation.
SH	University Hospitals Birmingham	Guideline	014	017	Occasionally a specialist electrophysiologist may use amiodarone as part of a rate control strategy in rare patients although this is rare I would suggest that the guidance should be changed to allow this by specialists	Thank you for your comment. The recommendation does not prevent amiodarone being used by specialists but makes it clear that it should not be used long-term due to concerns about adverse effects of long-term use.
SH	University Hospitals Birmingham	Guideline	015 030	004 013	There is absolutely no trial evidence to make digoxin a second line therapy. There are no randomised studies showing a benefit of beta blockers or calcium channel blockers over digoxin in terms of hard endpoints. There is data from the DIG trial which showed no increased mortality with digoxin but reduced hospitalisation in patients with heart failure and sinus rhythm. There is clear evidence from the RACE 2 study that aggressive rate control was of no benefit. Refs N Engl J Med 2010; 362:1363-1373 Oliver J Ziff et al. BMJ 2015;351 The committee use current practice as a justification for these guidelines but the 2020 ESC guidelines a marked of best practice recommend the use of any of digoxin, beta-blockers or calcium channel blockers as first line therapy. Increasing electrophysiologists are using digoxin as a first line agent.	Thank you for your comment. The committee were aware that digoxin is sometimes used for rate control. The recommendation in the previous version of the guideline was updated to also cover those where other rate control drugs are ruled out due to comorbidities or the person's preferences, rather than limiting to those who do very little or no exercise. However, the evidence comparing digoxin with other rate control drugs was too limited to be able to expand its use to further groups of people.
SH	University Hospitals Birmingham	Guideline	019	002	This should be removed there is no evidence for any mortality benefit of beta blockers in patients with heart failure. There is clear meta-analysis data to show this : ref Lancet Volume 384, ISSUE 9961, P2235-2243, December 20, 2014	Thank you for your comment. This recommendation was added as the committee was concerned about the potential use of beta-blockers in those with atrial fibrillation and acute heart failure and wanted to emphasise that specialist input should be sought on this. The committee wanted to highlight the discussion on beta blockers in heart failure by signposting to the guideline on chronic heart failure without implying that there is any mortality benefit.
SH	University Hospitals Coventry and Warwickshire NHS Trust	Guideline	016	023 - 025	**Re: Guidance Page 17 Section 1.7.19 Comment General** We are writing regarding the recent draft document regarding the proposed NICE guidance on atrial fibrillation (AF) and specifically limit our comments on AF ablation. There are a number of areas which the guidance is somewhat surprising and some areas where more could be considered.	Thank you for your comment. Recommendations 1.7.19 and 1.7.20 have been amended. 1.7.20 recommends cryoballoon or laser ablation in people who are assessed as unsuitable. The evidence showed that radiofrequency point by point ablation was more cost effective over a lifetime than antiarrhythmic drug treatment and other ablation strategies in people for whom 1 or more antiarrhythmic drug has failed.

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					1) The use of the Cryoballoon technology is not even considered. The two technologies which are considered cost effective within the guidance are point-by-point radiofrequency (RF) ablation and laser ablation. We would not disagree with the use of point by point RF ablation, but the proposal that laser AF ablation is the other cost effective technique is surprising. Laser ablation is used by relatively few operators in this country and in Europe and has limited data surrounding its efficacy and cost-effectiveness. Cryoballoon has been a technology which has been shown to be as effective as point-by-point ablation and is widely adopted in the UK. The ease of doing cryo-ablation for AF means that many more patients can be put through in a limited amount of catheter laboratory time. The number of procedures required in order to get an operator competent at doing cryo-ablation is also much lower than the other ablation techniques. We would challenge the true cost of laser ablation used in the cost effectiveness analysis within the guidance, in particular with comparison to other established technologies such as point by point RF and cryoballoon ablation. Additionally, no capital equipment costs were incorporated into the costing side of the economic model. The omission of such cost misses the true cost of implementing an ablation technology such as Laser ablation in the NHS healthcare setting. This results in the costs calculated within the health economic analysis to be significantly understated with only the consumables and procedure cost included in the economic model . We therefore strongly feel that use of cryoballoon should be included in the guidance and encouraged. The current draft will disenfranchise the cryoballoon technique which has efficacy equivalent to point-by-point RF ablation and the ease of practice makes it of great utility. **2) The numbers of left atrial ablation procedures has been limited to two ablations (including the mapping and ablation of atrial tachycardias).** However, there are a number of patients who present with more than one type of atrial tachycardia at different intervals following an AF ablation. Here a third or more procedure with high density mapping and ablation of the atrial tachycardia can restore sinus rhythm and improve the symptomatic status. The recommendation that procedures should be limited to 2 will greatly disadvantage these patients and make it difficult to fund the extra procedure. More leniency to allow third or more ablations to occur, particularly in those patients with recurrent atrial tachycardias would be very helpful. **3) The role of hybrid ablation, though discussed, is limited in large part to the use of the transthoracic Maze operation**.	Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. This included a threshold analysis where we explored the costs of cryoballoon. The threshold analysis for cryoballoon indicated a reduction of £2,913 in the procedure costs is required for it to become cost effective. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge this equated to £1,289 in savings which is not enough for cryoballoon to become more cost effective than RFPP. Capital equipment was not included in the costing as the committee stated that in most cases this is provided free of charge by manufacturers as part of a contractual agreement in exchange for the purchase of a minimum volume of equipment. The recommendation does not state a limit on the number of ablations, however for the purpose of the health economic model it was assumed on average people would have up to 2 ablations. Thank you for your comments about the convergent hybrid procedure. We have checked through the list of references you gave. Although pertinent, most are non-randomised and so would not be eligible for our review. We did identify 3 randomised trials amongst them, however. Jan has been included in our pairwise and NMA analyses. Marrouche 2018 was considered but not included because it did not differentiate between catheter

					The area of hybrid techniques for ablation of persistent AF, in particular the Convergent procedure has not been considered. There is emerging and substantial evidence that patients with symptomatic long-standing persistent atrial fibrillation treated with the Convergent hybrid procedure have a better long-term outcome then repeated trans-catheter ablation. Hybrid ablation strategies have been developed to leverage epicardial surgical ablation complemented by endocardial catheter ablation to complete and ensure posterior wall and pulmonary vein isolation. In the hybrid convergent approach, pericardial access to the left atrial posterior wall is gained through a small subxiphoid incision, allowing the procedure to be performed closed chest on the beating heart. A surgeon performs the epicardial ablation focused on posterior wall homogenization enhanced by endoscopic visualization of the lesions. Following the surgical procedure, an electrophysiologist performs mapping and endocardial ablation. The epicardial-endocardial approach was first developed in 2009 and has evolved significantly(1). Improvements to the convergent procedure have further reduced serious complications while maintaining high effectiveness of the procedure. Several published studies as well as the randomized controlled clinical trial CONVERGE have shown safety and effectiveness of the Convergent procedure. A recently reported meta-analysis of 12 published studies with 740 patients, 91% with non-paroxysmal AF, showed freedom from AF/atrial arrhythmias with or without AADs to be 77.1% (95% CI 66.0%-88.2%) at 1 year or later and 68.6% (95% CI 58.7%-78.5%, off of AADs at 1 year or later(2). The overall pooled complication rate was 8.5% (95% CI: 6.5%-10.5%). Importantly, most studies that evaluated repeat procedures following Convergent procedures reported low repeat ablation rates. Two published propensity-score matched studies showed significantly improved effectiveness of hybrid Convergent ablation compared to endocardial ablation alone(3,4). There was both statistically and clinically significant improvement in patient reported symptoms and their quality of life. Favourable success rates have been shown irrespective of whether Convergent ablation was a first ablation procedure, as in CONVERGE, or if it was performed after failed catheter ablation, in patients with persistent and longstanding persistent AF (6). In persistent and longstanding AF, minimizing residual AF burden is a clinically meaningful endpoint for patients and may be a more realistic one in the context of longer duration disease contributing to the increased risk of stroke, heart failure and dementia (7-10). Low residual AF burden in patients with continuous monitoring after the Convergent procedure has been reported in two studies, with one reporting 94% of patients had ≤5% AF burden at 12 months (11) and another study reporting 88% of patients had ≤5% AF burden after mean 19 months follow-up (12).	treatments (i.e. surgeons were allowed to use their preferred catheter ablation method). The CONVERGE RCT was reported in a pre-print paper that we managed to source, and because it is eligible we have now added it to the review. It had to be placed in the mixed stratum because there was a mixture of patients with persistent < 1 year and persistent > 1 year. The results concurred with our findings for the paroxysmal stratum – that while the hybrid procedure does lead to lower recurrence rates, it also carries a larger burden of adverse events and stroke.

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					Owing to these outcomes, the hybrid Convergent procedure has resulted in cost effectiveness over time, when compared to medical management or catheter ablation.(13) Since this technique is likely to give a better long-term results then standard transcatheter methods we will be there for grateful if this could be considered for inclusion in the NICE recommendations. Kind regards Yours sincerely **Professor Faizel Osman MD FRCP FESC** **Consultant Cardiologist / Electrophysiologist** **Honorary Professor of Cardiology (Warwick Medical School)** **Lead for Cardiac Rhythm Management** **Dr Sandeep Panikker** **Consultant Cardiologist / Electrophysiologist** **Dr Tarv Dhanjal** **Consultant Cardiologist / Electrophysiologist** **Dr Shamil Yusuf** **Consultant Cardiologist / Electrophysiologist** **Dr Ahmed Merghani** **Locum Consultant Cardiologist / Electrophysiologist** **Dr Will Foster** **Visiting Consultant Cardiologist / Electrophysiologist (Worcester Royal Hospital)** **Dr Bashar Aldhoon** **Visiting Consultant Cardiologist / Electrophysiologist (Worcester Royal Hospital)** **University Hospital Coventry** **Clifford Bridge Road** **Coventry CV2 2DX UK** **Tel: +44 (0) 2476 965668** **E-mail: Faizel.osman@uhcw.nhs.uk**	

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SH	University Hospitals Leicester NHS Trust	Guideline	005 027	013 022 - 029	The rationale for change to the ORBIT score for bleeding requires further clarification. On page 27, it is stated that this score underestimates the bleeding risk. There is significant concern that anticoagulation is used in older age groups than studied in RCTs, who have higher bleeding risk. Thus underestimating bleeding risk carries a significant risk of exposing elderly patients to a higher risk of bleeding on treatment, coupled with the suggestion on P26 15-18 of CHADSVASC overestimating individual stroke risk is a cause for significant concern & overall suggests a bias for anticoagulation.	Although the discrimination data suggested that ORBIT may underestimate risk, this was not observed in the calibration data, where we placed most emphasis. Calibration was given priority because of the importance of accurate prediction of absolute risk in the context of using the tools as an aid to the discussion between patient and clinician about the need for risk-modification, rather than as a decision tool about risk modification. In other words, it is envisaged that all patients will be encouraged to risk modify, but that an accurate risk prediction will be helpful in encouraging compliance, particularly in people at higher risk. We have clarified this point in the discussion. Our committee agreed that ORBIT was the best-calibrated tool, and therefore the most accurate tool to predict absolute levels of bleeding risk, including high levels of risk. With regard to the suggestion that CHADSVASC overestimates individual stroke risk, the committee were acceptable of this because the harms of underestimating stroke risk far exceed the harms of over-estimating it. No other stroke tool offers the minimum level of acceptable sensitivity of detecting stroke risk with a high enough specificity to improve upon CHADSVASC in this respect.
SH	University Hospitals	Guideline	013	029	Presumably, the statement should say 2014 rather than 2020?	Thank you for your comment. As this statement is not a recommendation no date is assigned to it.

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	Leicester NHS Trust					
SH	University Hospitals Leicester NHS Trust	Guideline	014	015	Same as above	Thank you for your comment. As this statement is not a recommendation no date is assigned to it.
SH	University Hospitals Leicester NHS Trust	Guideline	016	022	Does NICE propose to monitor complication rates following ablation, to ensure clinical effectiveness in routine clinical practice? There is potential for intervention options to be overused as a panacea, with an underestimation of complication rates.	Thank you for your comment. It is not within the remit of NICE to monitor complication rates. Recommendation 1.7.19 states when ablation should be considered.
SH	University Hospitals Leicester NHS Trust	Guideline	016	023	The use of the Cryo balloon is considered non cost-effective and the 2 technologies which are considered cost effective are point-by-point ablation and also laser ablation. We would not disagree with the use of point by point ablation, but the proposal that laser ablation is the other cost effective technique is surprising. Laser ablation is used by relatively few operators in this country and in Europe. Conversely, cryoballoon has been a technology which has been shown to be as effective as point-by-point ablation and is widely adopted in the UK. The ease of doing cryoablation for paroxysmal atrial fibrillation means that many more patients can be put through in a limited amount of catheter laboratory time. The number of procedures required in order to get a trainee competent at doing cryoablation is much lower than the other techniques. Consequently, we suggest that the status of cryoablation should be reconsidered owing to its utility, due to lower procedure time and ease of training.	Thank you for your comment. Please note further to stakeholder comments and discussion with the committee, the equipment costs for laser have been edited to increase a 30% uplift to account for local negotiations, omissions to some of the catheter ablation kit have been corrected and additional sensitivity analyses have been conducted. The sensitivity analyses included a threshold analysis where we explored the costs of cryoballon. The threshold analysis for cryoballoon indicated a reduction of £2,913 in the procedure costs is required for it to become cost effective. When estimating what the total savings may be if all people with cryoballoon ablation had sedation, shorter procedure time and same day discharge, this equated to £1,289 in savings which is not enough to for cryoballoon to become more cost effective than RFPP. Overall, the new results indicate RFPP is the most cost effective option. The recommendations 1.7.19 and 1.7.20 have been changed to reflect this. The committee made a further 'consider' recommendation for either cryoballoon and laser ablation for people who are unsuitable for RFPP.
SH	University Hospitals Leicester NHS Trust	Guideline	General	General	The numbers of ablation procedures should be limited to two ablations (including the mapping and ablation of atrial tachycardias). However, there are a number of patients who present with more than one type of atrial tachycardia at different intervals following an atrial fibrillation ablation. Here a third procedure with high density mapping and ablation of the atrial tachycardia	Thank you for your comment. The guidance does not contain recommendations on the number of ablations that should be performed as this was not specified in the scope/review question.

					can restore sinus rhythm and improve the symptomatic status. The recommendation that procedures should be limited to 2 will disadvantage these patients and make it difficult to fund the extra procedure. More leniency to allow third ablations to occur particularly in those patients with recurrent atrial tachycardias would be helpful.	For the purposes of modelling over a lifetime horizon it was assumed that up to two ablations would be provided. This was based on the proportion of people having a repeat ablation and the mean number of repeat ablations reported in the studies which informed the clinical effectiveness data and on clinical expert advice.

*None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.

Registered stakeholders