NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 27 November 2019

THEME: Detection of atrial fibrillation by BioMonitor 2-AF

Comment number	Name and organisation	Section number	Comment	NICE response
1	Biotronik	1.2	We submitted new evidence during this consultation round. The new evidence compares the atrial fibrillation (AF) detection performance of BioMonitor 2-AF to Reveal LINQ and shows equivalence in terms of AF detection. So it removes the uncertainty of whether the data about Reveal devices can be used to model the performance of the BioMonitor 2-AF to detect AF. Considering these study findings and given the results of EAG's cost-effectiveness analyses showing BioMonitor 2-AF dominates the other two comparators, we suggest the following revision to this section: 1. BioMonitor 2-AF is recommended as the implantable cardiac monitor of choice for detecting atrial fibrillation after cryptogenic stroke.	Thank you for your comment which the committee considered. The committee considered the unpublished study which compared the BioMonitor 2-AF with the Reveal LINQ. This had been critiqued by the External Assessment Group (EAG) who highlighted the following points: - the analysis comprises a non-clinical comparison of the BioMonitor 2 and Reveal LINQ and so the devices may perform differently when implanted in patients - the analysis uses a 6-minute threshold for detection of atrial fibrillation and so the performance and comparability of the devices may be different if a shorter threshold is used such as a 30-second threshold that is used in CRYSTAL-AF - the population that the data was selected from is not a cryptogenic stroke population and it comprises patients with known paroxysmal atrial fibrillation (70%) and persistent atrial

				fibrillation (30%) so the devices may perform differently in patients with cryptogenic stroke who do not have known atrial fibrillation. The committee noted the EAG's concerns and further discussed the study. It noted that the study had a small population size and had not been published or peer reviewed. Clinical experts commented that electrode positioning is different for Holter monitors and implantable cardiac monitors; therefore, the ECG output from a Holter monitor would not be equivalent to the signal that an implantable cardiac monitor would receive. The results could therefore be considered to be artificial and not reflect clinical reality. The committee considered that this study did not demonstrate that the Reveal LINQ and BioMonitor devices were comparable in detecting atrial fibrillation in a cryptogenic stroke population. Section 4.6 of the diagnostics consultation document has been changed to reflect these committee considerations. The committee considered that it is not appropriate to use data from CRYSTAL-AF to model the performance of

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				BioMonitor 2 AF or Confirm Rx and that it was not appropriate to consider the cost effectiveness estimates for BioMonitor 2 AF or Confirm Rx (see section 4.7 of the diagnostics consultation document).
2	Biotronik	1. Why the committee made these recommendations	We recommend revising the last paragraph of this section regarding whether the evidence about Reveal devices can be used to make decisions about BioMonitor 2-AF. The new submitted evidence demonstrates that the performances of the two devices are clinically equivalent in terms of detecting AF. Hence, the evidence removes the uncertainty around whether the data about Reveal devices can be used to model the performance of the BioMonitor 2-AF to detect AF.	Thank you for your comment which the committee considered. The committee concluded that the provided unpublished study did not demonstrate that the Reveal LINQ and BioMonitor devices were comparable in detecting atrial fibrillation in a cryptogenic stroke population (see section 4.6 of the diagnostics consultation document). Therefore, no change to the recommendation for the BioMonitor has been made.
3	Biotronik	3.44	One of the studies previously marked as academic in confidence (Piorkowskit et al, 2019) is published. The study reports the sensitivity of BioMonitor 2-AF (100% for detecting AF). Reference: Piorkowski, Christopher, et al. "Clinical evaluation of a small implantable cardiac monitor with a long sensing vector." Pacing and Clinical Electrophysiology (2019).	Thank you for your comment which the committee considered.

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4	Biotronik	3.44	Given the newly submitted data, we recommend adding the following sentence to this section for clarification: "Another head-to-head study comparing the atrial fibrillation detection performance of BioMonitor 2-AF and LINQ was provided by BIOTRONIK. In this first head-to-head comparison of AF detection algorithms, BIOMONITOR and LINQ devices performed with clinical equivalence. Patient-averaged episode sensitivity for BIOMONITOR and LINQ were 78.0% and 79.0%, respectively. Patient-averaged PPV was also within 1% with a 98.7% and 99.7% result for BIOMONITOR and LINQ, respectively. Further, the total duration of classified true AF rhythm compared to total Holter duration was nearly equivalent with BIOMONITOR classifying 79.2% of AF correctly and LINQ classifying 74.9% of AF correctly. This study demonstrated that when the two devices analyse the same clinical data, with a single adjudicated data set, performance between the devices is consistent at a technical level and completely equivalent at the level of the clinical user."	Thank you for your comment which the committee considered. Detail on the provided data has been added to the diagnostics consultation document (see section 3.21). The committee concluded that the provided unpublished study did not demonstrate that the Reveal LINQ and BioMonitor devices were comparable in detecting atrial fibrillation in a cryptogenic stroke population (see section 4.6 of the diagnostics consultation document).
5	Biotronik	3.59	We recommend revising this statement: "No equivalent data were identified for BioMonitor 2-AF or Confirm Rx (or the current Reveal LINQ version)." We suggest the following addition in this section for more clarity, given the new evidence: "There is data comparing the atrial fibrillation detection performance of BioMonitor 2-AF and LINQ (see 3.44), and the data obtained from CRYSTAL-AF is therefore	Thank you for your comment which the committee considered. Detail on the provided data has been added to the diagnostics consultation document (see section 3.21). The statement referred to (now in section 3.60 of the updated diagnostics consultation document) refers to

			generalisable to BioMonitor 2-AF. No equivalent data were identified for comparing the performance of BioMonitor 2-AF to Confirm Rx or Confirm RX to Reveal devices."	there being no diagnostic yield data (similar to data from CRYSTAL-AF) for the use of the BioMonitor 2 AF or Confirm Rx (or the current Reveal LINQ version). No change to the diagnostics consultation document has been made.
6	Biotronik	3.66	Given the new data, we recommend revising the description of the assumption concerning BioMonitor 2-AF – "BioMonitor 2-AF and Confirm Rx were equivalent to Reveal XT or Reveal LINQ for detecting atrial fibrillation"— for more clarity: • BioMonitor 2-AF was at least as good as Reveal LINQ for detecting atrial fibrillation.	Thank you for your comment which the committee considered. The committee concluded that the provided unpublished study did not demonstrate that the Reveal LINQ and BioMonitor devices were comparable in detecting atrial fibrillation in a cryptogenic stroke population (see section 4.6 of the diagnostics consultation document). Therefore, no change to the diagnostics consultation document has been made.
7	Biotronik	3.69	Given the new evidence, we recommend removing BioMonitor 2-AF from the following sentence of this section, which should read:	Thank you for your comment which the committee considered.

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			"The EAG advised that Confirm Rx results should be viewed with caution because it is based on a strong assumption of equivalence with Reveal LINQ."	
8	Biotronik	4.6	1. We suggest revising the title of this section by removing "but not BioMonitor 2-AF" and would like to ask the committee to review the new data and revise this section. 2. The new evidence demonstrates that BioMonitor 2-AF and LINQ are clinically equivalent in terms of detecting atrial fibrillation so it can be concluded that these devices will show similar performance in detecting atrial fibrillation when used in people who have had a cryptogenic stroke. Thus, the data obtained from CRYSTAL-AF is generalisable to BioMonitor 2-AF.	Thank you for your comment which the committee considered. The committee considered the evidence provided at consultation. It concluded that the provided unpublished study did not demonstrate that the Reveal LINQ and BioMonitor devices were comparable in detecting atrial fibrillation in a cryptogenic stroke population (see section 4.6 of the diagnostics consultation document). Therefore, no change to the diagnostics consultation document has been made.
9	Biotronik	4.7	1. We suggest revising the title of this section by removing "but not BioMonitor 2-AF" and would like to ask the committee to review the new data and revise this section. 2. The new evidence demonstrates that BioMonitor 2-AF and LINQ are clinically equivalent in terms of detecting atrial fibrillation so it can be concluded that these devices will show similar performance in detecting atrial fibrillation when used in people who have had a cryptogenic stroke. Thus, it is appropriate to use the	Thank you for your comment which the committee considered. The committee considered the evidence provided during consultation. It concluded that the provided unpublished study did not demonstrate that the Reveal LINQ and BioMonitor devices were comparable in detecting atrial fibrillation in a cryptogenic stroke population (see section 4.6 of the diagnostics consultation document). The

			data from CRYSTAL-AF to model the performance of BioMonitor 2-AF.	committee therefore concluded that it is not appropriate to use data from CRYSTAL-AF to model the performance of BioMonitor 2 AF or Confirm Rx (see section 4.7 of the diagnostics consultation document).

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THEME: General comments on economic modelling

Comment number	Name and organisation	Section number	Comment	NICE response
10	Royal College of Physicians	3.53	I am surprised that the EAG have dismissed the paper by Diamantopoulos et al paper as this is a standard approach to health economic modelling. This is probably the best published economic data available. The results of this paper are taken into account in 4.14.	Thank you for your comment which the committee considered. Diamantopoulos et al was critiqued by the EAG in their review of existing models. The committee discussed this paper during each of the meetings for the topic, and was keen to understand how this analysis differed from the EAG's (described in section 4.14 of the updated diagnostics consultation document).
11	Medtronic	General comment	Medtronic would like to thank NICE for the opportunity to comment on the draft guidance, 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 concerns on what we believe to be a general lack of transparent decision-making, and as a stakeholder our limited opportunity to respond in a timely manner. The EAG model initially provided generated ICERs within the acceptable willingness to pay range. However, the identification of an error, subsequently corrected, generated ICERs above this threshold. We believe the resultant committee meeting lacked public slides that clearly explained how this model worked, the comprehensive list of inputs parameters when compared to the model Medtronic submitted or alternative sources, and importantly clear	Thank you for your comment which the committee considered. The committee heard from the NICE team that stakeholder concerns relating to the transparency of the model has resulted in the NICE Decision Support Unit being commissioned to validate the EAG's model. The committee were reassured by the report and amendments provided by the Decision Support Unit. Stakeholders are invited to submit detailed responses to the committee at specific points in the process. This is in accordance

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			illustrations of relevant model results such as life years gained and the Markov traces. Having subsequently gained access to a functioning model, many inputs and associated rationales are still not fully clear given the complexity of the model and the three separate lengthy supporting documents that the parameters are derived from. Acknowledging that it is for Industry to review these models and seek the expertise necessary, we do not believe it should be as complicated as this current process. Certainly, were this to have been a formal Industry model submission in other NICE programmes, we would quite rightly expect clarification questions seeking insight and possibly simplification tables of these input comparisons to aid public and transparent decision-making. This we know could then be explored by the committee with the invited independent clinical experts. We have provided elsewhere in our response our concerns on the inputs used in the model and their subsequent outputs to further illustrate our concern, particularly some of which lack face validity and certainly contradict conventional clinical wisdom according to our clinical expert feedback. We also wish to express our concerns on the timelines and our ability to engage with NICE with fact-based arguments in the process. Given that the initial model generated ICERs similar to that within our own submitted model, it will not come as a surprise that the EAG model was not scrutinized by Medtronic to the degree of the subsequently corrected model. However,	with NICE process that models are provided to stakeholders at specified points in the process for comment, and the opportunity to review models is available to all stakeholders equally. NICE would like to thank Medtronic for highlighting the difficulties with running the economic model. NICE rectified this by requesting an updated version of the model from the EAG which was circulated to stakeholders allowing them the standard 20 working days to comment on the model.

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THEME: General comments on economic modelling

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			when we requested an updated executable model (7th June), we were told that this was not possible because "it is important that all stakeholders receive the same information" and we subsequently did not receive a fully executable model until the 12th July because the previous version did not run because of missing input files. . Again acknowledging that this may be a process issue, and not wishing to overstate the point, NICE and committee members, quite rightly so, would not expect such oversight or tardiness from an Industry submission. We can only speculate that the overly complicated nature of the EAG model led to this delay.	

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Comment number	Name and organisation	Section number	Comment	NICE response
12	NHS professional	General	The model also assumes only 16 strokes are prevented per 1000 LINQ patients, which differs largely from the current accepted model by Diamantopolus et al where 44 strokes are prevented per 1000 LINQ patients. There is no explanation as to how this figure has been derived and I would like to see some further clarification to understand why both models differ so greatly, as this will have a large impact on the cost-effectiveness.	Thank you for your comment which the committee considered. In advance of the third committee meeting, errors were identified in the model by a stakeholder relating to the rate of treatment discontinuation which were corrected (described in section 4.13 of the updated diagnostics consultation document). NICE commissioned a review of the model by the Decision Support Unit. The Decision Support Unit checked the model coding and corrected a further error relating to inconsistent application of sex-specific weightings across parameters. Updated model results, following the Decision Support Unit's work, were presented at the third committee meeting. The updated model estimated that the number of strokes that would be avoided by using an implantable cardiac monitor was 52 per 1,000 people with cryptogenic stroke (see section 4.14 of the updated diagnostics consultation document). The methodology used by the Decision Support Unit in calculating the number of

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Comment number	Name and organisation	Section number	Comment	NICE response
				strokes avoided is set out in their report (on page 10).
13	NHS professional	General	2. I can also see that the model assumes only 16 strokes are prevented per 1000 LINQ patients, which differs largely from the current accepted model by Diamantopolus et al where 44 strokes are prevented per 1000 LINQ patients. There is no explanation as to how this figure has been derived and I feel further clarification is required to understand why both models differ so greatly, as this will have a large impact on the cost-effectiveness.	Thank you for your comment which the committee considered. In advance of the third committee meeting, errors were identified in the model by a stakeholder relating to the rate of treatment discontinuation which were corrected (described in section 4.13 of the updated diagnostics consultation document). NICE commissioned a review of the model by the Decision Support Unit. The Decision Support Unit checked the model coding and corrected a further error relating to inconsistent application of sex-specific weightings across parameters. Updated model results, following the Decision Support Unit's work, were presented at the third committee meeting. The updated model estimated that the number of strokes that would be avoided by using an implantable cardiac monitor was 52 per 1,000 people with cryptogenic stroke (see section 4.14 of the updated diagnostics consultation document). The methodology used by the Decision

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				Support Unit in calculating the number of strokes avoided is set out in their report (on page 10).
14	NHS professional	Economic model	We also presume the stated 16 strokes prevented per 1000 patients in the EAG model to be very low when compared to Diamontoplous Model of 44 strokes prevented. We would like to further understand how this number has been reached by the EAG model as it could have a significant impact on the over ICER.	Thank you for your comment which the committee considered. In advance of the third committee meeting, errors were identified in the model by a stakeholder relating to the rate of treatment discontinuation which were corrected (described in section 4.13 of the updated diagnostics consultation document). NICE commissioned a review of the model by the Decision Support Unit. The Decision Support Unit checked the model coding and corrected a further error relating to inconsistent application of sex-specific weightings across parameters. Updated model results, following the Decision Support Unit's work, were presented at the third committee meeting. The updated model estimated that the number of strokes that would be avoided by using an implantable cardiac monitor was 52 per 1,000 people with cryptogenic stroke (see section 4.14 of the updated diagnostics consultation document).

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				The methodology used by the Decision Support Unit in calculating the number of strokes avoided is set out in their report (on page 10).
15	NHS professional	General	It is rather surprising that NICE's decision was largely based upon â€œitâ€™s not clear how much it will reduce the number of further strokes or TIAs compared with current practice.â€œ The Diagnostic Assessment program was specifically created as a separate assessment route to acknowledge the fact that outcome studies often don't exist for diagnostics. As long as there is a clear causal chain between the diagnosis and the treatment, NICE normally accepts that long term outcomes can be modelled. Specifically here long term outcomes can be modelled as NOACs are initiated in all CS patients with detected AF. The NOAC studies have shown significant stroke risk reduction in patients with prior stroke (Diener et al 2012). There is also a recent meta-analysis on prolonged AF monitoring in CS patient, showing a 55% [0.21â€“0.97] reduction in secondary strokes (Tsivgoulis et al 2019).	Thank you for your comment which the committee considered. The External Assessment Group reviewed the Tsivgoulis et al. (2019) paper and the estimate of a 55% reduction in secondary strokes, which relates to a reported risk ratio of 0.45 (prolonged cardiac monitoring vs conventional cardiac monitoring). The meta-analysis included 2 RCTs, one of which is CRYSTAL-AF and two observational studies. With CRYSTAL-AF, the stroke data presented does not distinguish for patients diagnosed with atrial fibrillation as a result of having the ICM and as such is not detailed enough for the long-term model. Furthermore, the Tsivgoulis et al. paper pools the data from the RCTs and the observational studies to estimate the risk ratio of 0.45. If the subgroup analysis for the RCTs is considered, the risk ratio reported is 0.69. Thus, the observational data, which is not

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				as robust as RCT data, is driving the results. But again, there is no subgroup analysis for reduction in stroke risk for cryptogenic stroke patients diagnosed with AF as a result of prolonged cardiac monitoring that are being treated with anticoagulants, which is what would be needed for the long-term model. The committee agreed that, in the absence of long-term data on this, the EAG's approach of linking evidence on the extent of atrial fibrillation detection, the impact of diagnosis on treatment choice, and the effect of treatment on the incidence of subsequent clinical events such as stroke and TIA in the economic model was suitable for decision making (see section 4.8 of the diagnostics consultation document).
16	NHS professional	General	The Diagnostic Assessment program was specifically created as a separate assessment route to acknowledge the fact that outcome studies often don't exist for diagnostics. As long as there is a clear causal chain between the diagnosis and the treatment, NICE normally accepts that long term outcomes can be modelled. It is undisputed that stroke patients with an AF diagnosis should be prescribed OAC to	Thank you for your comment which the committee considered. The committee agreed that, in the absence of long-term data on this, the EAG's approach of linking evidence on the extent of atrial fibrillation detection, the impact of diagnosis on

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			reduce their stroke risk. The OAC studies have shown significant stroke risk reduction in patients with prior stroke (Diener et al 2012).	treatment choice, and the effect of treatment on the incidence of subsequent clinical events such as stroke and TIA in the economic model was suitable for decision making (see section 4.8 of the diagnostics consultation document).
17	Medtronic	EAG MODEL (*R-Model)*	Our following comments are provided in two sections. Firstly, we describe what we suspect is an error in the code of the DOAC model, which under-estimates the number of strokes avoided with Reveal LINQ. ***Treatment switching error*** The EAG model assumes that a proportion of patients allocated to DOAC will switch to warfarin or "no treatment "following acute events such as stroke and major bleeds, including Intra-cranial hemorrhage (ICH). Similarly, patients on antiplatelet therapy will also switch to "no treatment "following the same events. The implementation of treatment switching rules in the model appears to contain an error. The original EAG model does not generate Markov traces, and because we were concerned about the treatment switching rules, we adapted the model code to generate Markov traces to assess what proportion of patients switch treatment and ultimately end up on "no treatment ". The figures below represent the movement of patients who start on DOAC and antiplatelet, respectively, through the model to different treatments. These diagrams capture merely what treatment patients are on at any	Thank you for your comment which the committee considered. The EAG explained to the committee that they agreed that the R-code for treatment switching for transient events was not specified correctly and the new code suggested by Medtronic corrects the error. While reviewing the model, the EAG also identified a further error. The EAG has provided an addendum document with revised base case results, scenarios and sensitivity analyses. NICE also commissioned a review of the model by the Decision Support Unit. The Decision Support Unit checked the model and corrected a further small error in the model. Updated model results were provided in a Decision Support Unit report and were presented at the third committee meeting (see

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			given time, not what health states they are in (i.e. stroke or MI+stroke, etc).	sections 3.68 to 3.73 of the updated diagnostics consultation document). The committee considered the updated cost effectiveness results at the third committee meeting (see sections 4.15 and 4.16 in the updated diagnostics consultation document). The committee concluded that, based on the updated model results, Reveal LINQ is likely to be a cost-effective use of NHS resources and recommendation 1.1 has been amended to reflect this.

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			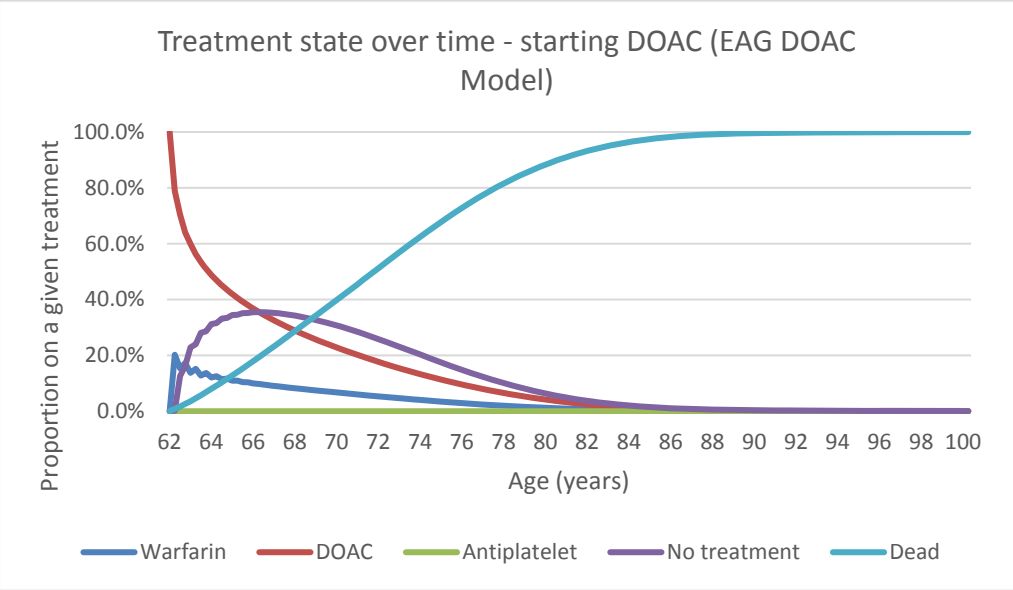 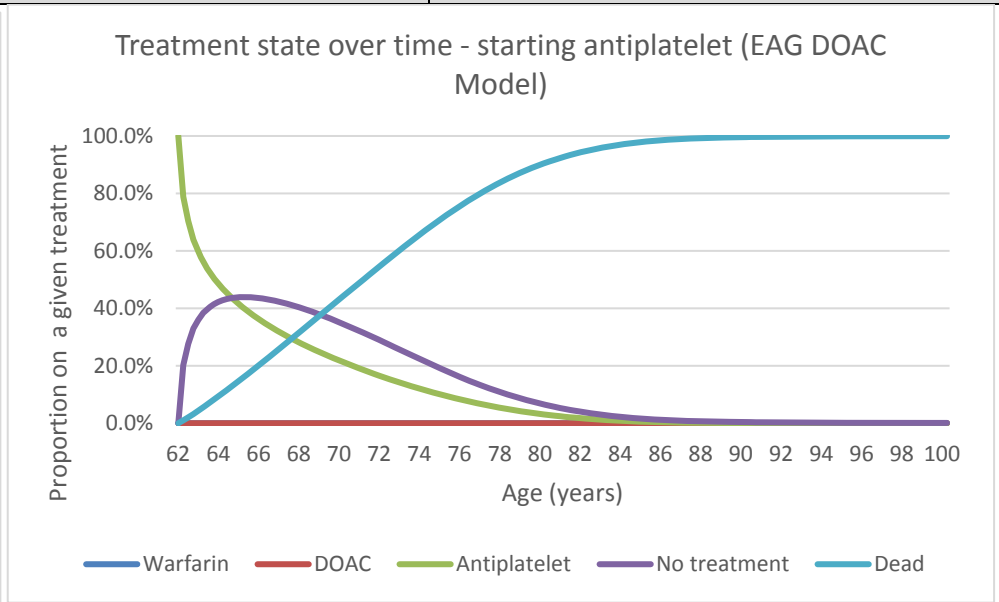
(continued)			Based on these plots, a substantial proportion of patients switch treatment and end up in "no treatment "very quickly. For example, 1 year after starting DOACs, only 60% are expected to still be receiving	

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			DOACs, because 14% are receiving warfarin and 29% are on "no treatment "; the remainder are dead (see first figure). After 2 years, fewer than half of patients who started on a DOAC are still receiving it and more than 30% are receiving nothing. In the antiplatelet therapy arm, only 60% of patients are still receiving treatment after 1 year and fewer than 50% after 2 years; the rest are dead or on "no treatment " (see second figure). This swift move to "no treatment "in both patients groups on DOAC (i.e. those in whom AF has been detected) and on antiplatelet therapy (i.e. those in whom AF has gone undetected) negates the benefits of detecting AF and putting patients on DOACs in the first place. This negative impact is also shown in the table below which presents the event incidence and life years for patients initiating treatment with a DOAC, Warfarin, antiplatelets or no treatment. Regardless of which treatment patients start on, the incidence rates and life years tend towards the values reported for no treatment (values generated from the EAG model).	

Event	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Antiplatelet (high dose)	Antiplatelet (low dose)	No treatment
Bleed	0.275	0.298	0.31	0.3	0.311	0.275	0.259	0.239
ICH	0.059	0.061	0.061	0.062	0.064	0.051	0.053	0.05
MI	0.06	0.061	0.065	0.062	0.061	0.062	0.06	0.059

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
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<tr><td>Life years</td><td>8.346</td><td>8.609</td><td>8.591</td><td>8.591</td><td>8.608</td><td>8.349</td><td>8.34</td><td>8.15</td></tr>
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</td></tr>
<tr><td>(continued)</td><td></td><td></td><td>We suspect that an error in the code of the EAG model may be causing the rush to "no treatment ". We describe it below and request that it be investigated. We have also attempted our own "fix" in an effort to show the sensitivity of the model results to the potential error.

The suspected error relates to how transition probabilities are calculated in the R model. The probabilities of staying in a state if a patient experiences a transient ischemic attack (TIA), systemic embolism (SE) or no event are calculated on lines 344-348 of the generate.transition.matrix script. In this calculation, the probability of experiencing these events (and no event) are multiplied by the probability of these events causing a patient to switch treatment. As the Markov model does not remember transient events, there is no need for patients who experience a transient event (TIA or SE) to switch states while on the same treatment. Therefore, patients can either stay in the same state of the same treatment or move to the same state within a different treatment (e.g. DOAC-well to Warfarin-well if a patient experiences a TIA). The probability of switching if a patient has a TIA is approximately 10%, if a patient has an SE it is approximately 10% and the probability of a patient switching after no event is 0%. The current</td><td></td></tr>
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			model sums these probabilities together (10% + 10% + 0%) and multiplies this by the sum of the probabilities of having a TIA, SE or no event. This means that the total probability of patients switching from their current state to the corresponding state in the next line of treatment is approximately 20%. This probability is being applied at every cycle of the model, causing patients to move to the next line of treatment with around a 20% probability, even if they are in the "well" health state. Additionally, summing together the TIA and SE switching probabilities occasionally results in a probability greater than one as there is no upper bound on this result. We implemented a change to the code that we believe addresses this problem. In the original version of the model the total sum of the transient and no event probabilities are multiplied by the total sum of the event switch probabilities for TIA, SE and no event. We adapted this code so that each transient event probability and the no event probability are multiplied with their corresponding event switch probability first, and then the results of this multiplication are summed. This corrects the total switch probability by accounting for the relative probability of each patient experiencing TIA, SE or no event. The original code and adapted code excerpts are provided below.	

Original code

```
# Probability stay (always sum of "Stay" and transient states
# If no discontinuation/switching
```

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transition.matrix[[age]][,i.state,i.state]<-transition.matrix[[age]][,i.state,i.state]+rowSums(probability.matrix[[age]][,i.state,event.state.codes=="" & event.names!="Death (all causes)"])*(1-rowSums(event.switch.probs[,event.state.codes==""])) # If discontinuation/switching (sum of transient event switching probabilities and no event switching probability) transition.matrix[[age]][,i.state,i.state+treatment.switch.indices[i.treatment]]<- transition.matrix[[age]][,i.state,i.state+treatment.switch.indices[i.treatment]]+rowSums(probability.matrix[[age]][,i.state,event.state.codes=="" & event.names!="Death (all causes)"])*rowSums(event.switch.probs[,event.state.codes==""]) **Adapted code** # Probability stay (always sum of "Stay" and transient states # If no discontinuation/switching transition.matrix[[age]][,i.state,i.state]<-transition.matrix[[age]][,i.state,i.state]+ rowSums(probability.matrix[[age]][,i.state,event.state.codes=="" & event.names!="Death (all causes)"]*(1-event.switch.probs[,event.state.codes==""])) # If discontinuation/switching (sum of transient event switching probabilities and no event switching probability) transition.matrix[[age]][,i.state,i.state+treatment.switch.indices[i.treatment]]<- transition.matrix[[age]][,i.state,i.state+treatment.switch.indices[i.treatment]]+rowSums(probability.matrix[[age]][,i.state,event.state.codes=="" & event.names!="Death (all causes)"]*(event.switch.probs[,event.state.codes==""]))				
(continued)			After applying the "fix" described above, we regenerated the Markov traces and EAG model outputs in order to compare them to the original model. The Markov traces following correction to the code are presented below. Far more patients on both DOAC and antiplatelet stay on treatment, with a minority ultimately ending up on "no treatment". Among patients with AF who initiate DOAC, fewer than 10% at any given time will receive warfarin or nothing. Among patients with undetected AF on antiplatelet therapy a maximum of 12% at any given time will be receiving "no treatment". After 5 years, 70% of	

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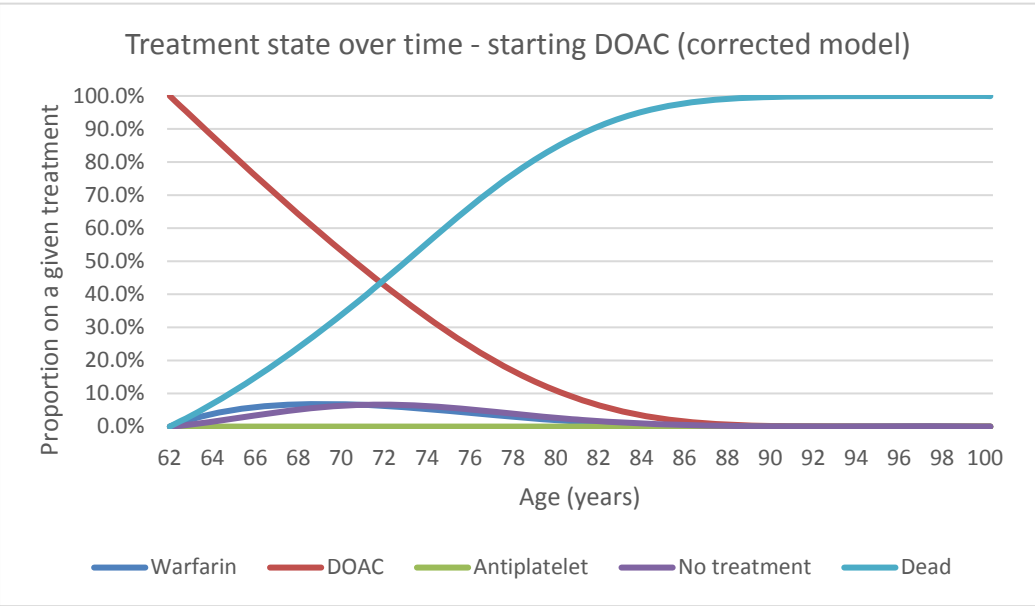
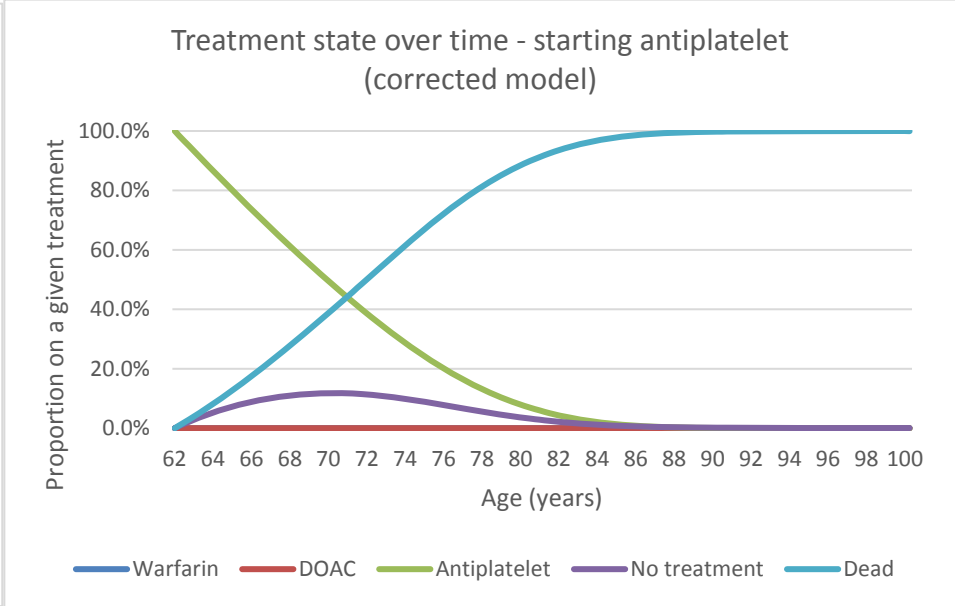
			patients who start on DOAC are still on DOAC and 67% who start on antiplatelet therapy are still receiving antiplatelet therapy.	
			 
(continued)			The event incidence and life years were generated for the revised EAG model, shown in the table below. It appears that these values no longer tend towards the values reported for no treatment.	

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td colspan="5">
<table>
<tr><th>Event</th><th>Warfarin</th><th>Apixaban</th><th>Dabigatran</th><th>Edoxaban</th><th>Rivaroxaban</th><th>Antiplatelet (high dose)</th><th>Antiplatelet (low dose)</th><th>No treatment</th></tr>
<tr><td>Bleed</td><td>0.475</td><td>0.450</td><td>0.518</td><td>0.461</td><td>0.524</td><td>0.484</td><td>0.374</td><td>0.239</td></tr>
<tr><td>ICH</td><td>0.123</td><td>0.090</td><td>0.089</td><td>0.094</td><td>0.119</td><td>0.056</td><td>0.071</td><td>0.050</td></tr>
<tr><td>MI</td><td>0.071</td><td>0.071</td><td>0.095</td><td>0.074</td><td>0.066</td><td>0.079</td><td>0.066</td><td>0.059</td></tr>
<tr><td>Stroke</td><td>0.144</td><td>0.120</td><td>0.113</td><td>0.127</td><td>0.130</td><td>0.188</td><td>0.217</td><td>0.217</td></tr>
<tr><td>Life years</td><td>9.800</td><td>10.886</td><td>10.680</td><td>10.665</td><td>10.864</td><td>9.876</td><td>9.658</td><td>8.150</td></tr>
</table>
.
</td></tr>
<tr><td>(continued)</td><td></td><td></td><td>We fed the corrected EAG model outputs into the Excel-based detection model in order to assess how the change in long-term costs and outcomes of OACs would impact the cost-effectiveness of ICMs versus Standard of Care. New deterministic results are presented in the table below. Incremental costs between each device and Standard of Care have increased, but so too have incremental QALYs. The ICERs for each device versus standard of care in this corrected model are significantly lower than in the previous version of the model.</td><td></td></tr>
</table>

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td colspan="3">
<table>
<tr><th>Intervention</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER (£) vs. SoC</th></tr>
<tr><td>Standard of care</td><td>£7,709</td><td>1.75</td><td></td><td></td><td></td></tr>
<tr><td>Reveal LINQ</td><td>£9,577</td><td>1.89</td><td>£1,869</td><td>0.13</td><td>£14,051</td></tr>
</table>
.
</td><td colspan="2"></td></tr>
<tr><td>(continued)</td><td></td><td></td><td>To the best of our knowledge, we have identified and corrected what we interpreted to be an error in the code. If this was not an error, it implies an implausibly high level of discontinuation among patients with a history of stroke who are benefiting from treatment, which lacks face validity according to our clinical advisors and the rationale hasn't been described in the model or supporting documentation.</td><td></td></tr>
</table>

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Comment number	Name and organisation	Section number	Comment	NICE response
18	Medtronic	General comment	It is an important distinction to make from the outset, the purpose of the assessment is to examine the use of implantable cardiac monitors in secondary stroke prevention in the cryptogenic stroke patient population in the UK. However not fully explained and explored in the public section of the meeting was that, the EAG cost-effectiveness analysis is based on a pre-existing model principally designed for primary prevention situations in a different patient population – initially to examine the cost-effectiveness of novel oral anticoagulants (NOACs), and subsequently adapted to evaluate the cost-effectiveness of screening strategies for AF. We believe insufficient adjustments have been made to several assumptions and inputs within the adapted DOAC model, such that it does not represent well enough the cryptogenic stroke population in this assessment. As a result, we believe the model significantly under-estimated the health benefits of using ICMs in the treatment pathway for these patients.	Thank you for your comment which the committee considered. The committee was aware that the model had been adapted to a secondary stroke population.
19	NHS professional	3.56	'For the subsequent long-term anticoagulation model, the EAG adapted a published economic model to model the long-term effect of people with detected atrial fibrillation (anticoagulant treatment) or undetected atrial fibrillation (remain on antiplatelet therapy with clopidogrel). This is the â€˜adapted direct oral anticoagulant (DOAC) modelâ€™ (Sterne et al. 2017 and Welton et al. 2017). People enter the model after having atrial fibrillation in an â€˜atrial fibrillation wellâ€™ state. After this, clinical events can occur. These are TIA, ischaemic stroke, intracranial haemorrhage, myocardial infarction, clinically relevant (extracranial) bleed or systemic embolism (multiple events can happen to one person over the course of the model). '	Thank you for your comment which the committee considered. The EAG explained at the second committee meeting that the initial cohort that enters the short-term model are people who have had a cryptogenic stroke and have not had atrial fibrillation detected. Patients will then either be given an implantable cardiac monitor or receive standard monitoring. It is only if their given intervention detects atrial

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Comment number	Name and organisation	Section number	Comment	NICE response
			Is it appropriate to use the model stated above for the second stage of the economic analysis? The model assumes that patients, at the time of inclusion, are in â€˜atrial fibrillation well stateâ€™, which they are not as they have already had a cryptogenic stroke or a TIA. Do the results of the economic analysis alter if this is taken into consideration?	fibrillation or if they are a patient with undetected atrial fibrillation (based on the prevalence of atrial fibrillation in the cryptogenic stroke population) that they enter the long-term model in the "atrial fibrillation well" state, with "well" indicating no event after their initial stroke event.
20	Medtronic	Assessment report section 4	*Assumptions and inputs in the EAG model we politely request NICE and Committee to reconsider* **(1) The risk of most adverse events and all-cause mortality is over-estimated in the model due to these data being sourced from a network meta-analysis of patients with different characteristics** All long-term clinical outcomes are based on data used in the pre-existing model for primary prevention of stroke and contains safety and efficacy data from trials that included patient cohorts that were significantly older and had symptomatic AF, and usually persistent or permanent AF, compared to the cryptogenic stroke patient population. It is not representative for the cryptogenic stroke population in the UK, which was acknowledged by clinical experts as being similar to the CRYSTAL-AF trial cohort, having generally asymptomatic AF and an average age of 62 years. Patient characteristics in studies used to inform the Sterne model are summarized in Table 1. In addition to mean age and type of AF, we also report the relatively high rates of heart failure in the trials, as heart failure is associated with increased rates of mortality, and this may be contributing to the EAG model projecting shorter life expectancy than we would expect for patients in CRYSTAL-AF.	Thank you for your comment which the committee considered. The EAG explained that as the long-term model is primarily a treatment model that people enter once they have been categorised as having atrial fibrillation (whether detected or undetected), the EAG considered that the NMA methodology to estimate adverse events and all-cause mortality employed by Sterne et al., was robust as it accounts for all the trial data published up to date of the review for each DOAC to be accounted for and included in the estimates. Furthermore, an NMA limits the bias in selecting favourable estimates from single RCTs. As mentioned in the note to Table 1, the NMA was based on the 23

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				trials. The benefit of the DOAC model is that the age of the starting cohort, the type of atrial fibrillation and history of stroke can be, and was, adjusted to reflect the population of CRYSTAL AF. Thus, the model was specified for a cohort with a mean age of 62, secondary stroke with paroxysmal atrial fibrillation.

Table 1: Patient characteristics in studies used to inform the Sterne model

Study	Sample Size	Mean Age	Type of AF	Heart Failure[1]
ARISTOTLE	18,201	70	15% PAF, 85% persistent/permanent	35%
AVERROES	5,599	70	27% PAF, 21% persistent, 52% permanent	38%-40%
ENGAGE AF-TIMI 48	21,105	72	25% PAF	57%-58%
RE-LY	18,113	71	32% PAF, 31%-32% persistent, 35%-36% permanent	32%
ROCKET AF	14,264	73	17-18% PAF, 80-81% persistent, 1% new onset	62%-63%
CRYSTAL-AF	441	61	History of AF or atrial flutter an exclusion criteria	4%-7% (labelled CAD)

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Note: The Network Meta-Analysis included 23 trials with a total of 94,656 patients. The five trials in Table 1 included 77,282 patients (82% of the total) 1) The term "heart failure" generally refers to "congestive heart failure" except for the CRYSTAL-AF study which reported "Coronary Artery Disease" instead of CHF. CAD may lead to CHF, so it is still included here.				
(continued)			As a consequence of sourcing data from a NMA with an older and sicker patient population, the risk of all-cause mortality and of all adverse events, except for ischaemic strokes, appears to be over-estimated in the EAG model. The EAG model does adjust stroke risk to be lower than the rate in the NMA, on the basis that patients with paroxysmal AF have a lower risk of stroke than patients with persistent or permanent AF. This appears to be an inconsistency of the model: the stroke risk is adjusted downwards for patients with paroxysmal AF, while other adverse event rates were not adjusted. Table 1 present the risk of adverse events in the EAG model.	The EAG commented that in the DOAC model, stroke, transient ischemic attack and systemic embolism risks are adjusted for paroxysmal atrial fibrillation. Clinically relevant extracranial bleed risk is as a consequence of treatment with DOACs.

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td colspan="5">Table 2: Risk of adverse events in the EAG model.
<table>
<tr><th></th><th colspan="2">Annual Risk of Adverse Event in EAG Model</th></tr>
<tr><th>Event</th><th>Clopidogrel (low dose)</th><th>DOAC</th></tr>
<tr><td>Ischaemic stroke</td><td>9.7%</td><td>4.2%</td></tr>
<tr><td>Clinically-relevant bleed[1]</td><td>6.0%</td><td>7.1%</td></tr>
<tr><td>TIA/SE</td><td>20%</td><td>4.9%</td></tr>
<tr><td>ICH</td><td>0.7%</td><td>0.7%</td></tr>
<tr><td>Death</td><td>2.65%</td><td>2.14%</td></tr>
</table>
Notes: 1) Clinically relevant bleeds (CRB) are defined as CRNM (clinically relevant non-major) bleeding or major bleeding</td></tr>
<tr><td>(continued)</td><td></td><td></td><td>When considering patients on DOACs and patients on clopidogrel, the cumulative risk of clinically-relevant bleeds (CRB) is in fact very similar to the cumulative stroke risk in the model. At the same time, the model assumes the impact of CRBs and strokes are the same on a patient's life because CRBs and strokes have the same impact on mortality and quality of life.</td><td></td></tr>
<tr><td colspan="5"></td></tr>
</table>

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td colspan="5">Table 3: Comparison of quality of life and mortality impact of strokes and bleeds
<table>
<tr><td>Adverse Event</td><td>Quality of life after adverse event</td><td>Mortality Hazard Ratio applied after adverse event</td></tr>
<tr><td>Recurrent ischaemic stroke</td><td>0.7</td><td>1.32</td></tr>
<tr><td>Clinically-relevant bleed</td><td>0.7</td><td>1.32</td></tr>
</table>
.</td></tr>
<tr><td>(continued)</td><td></td><td></td><td>Thus, a patient who has had two strokes has the same quality of life as a patient after one bleed. While we acknowledge that CRBs are serious, it seems highly unrealistic that the impact of a CRB and a stroke on a patient's life are the same given that only a share of the CRBs are major bleeds. At the same time, the costs of a stroke are assumed to be 10 times as much as a CRB (£14,522 for a stroke compared to £1,397 for a CRB).

The problem of over-estimating adverse events is augmented in the model because every adverse event increases the risk of incurring subsequent adverse events. These assumptions are based on data from the Swedish Atrial Fibrillation cohort study which excluded asymptomatic AF patients (Friberg et al 2012). Although the multipliers were taken from a specific subgroup of patients with a prior stroke in the study, 88% of patients with prior stroke were</td><td>The EAG commented that the utility values outlined in Table 3 reflect post-event health state values (i.e. quality of life after an acute event of ischaemic stroke or a major bleed). The costs quoted in the comment relate to the acute event costs (that is, the cost of treating an acute event of ischaemic stroke or major bleed). Acute events only last for one cycle of the model and, as such, the cost is only applied for one model cycle. For an acute event of ischaemic stroke, the utility value applied is 0.64, compared with a utility decrement of -0.03 for a major bleed.</td></tr>
</table>

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			> 75 years. As an example, the multiplier for having another CRB if patients experienced a previous bleeding is 3.32. Taking data from this study results in a CRB risk of 23% for patients on DOACS who had one prior bleed. While CRBs are serious, this seems to over-estimate the risk of bleeding in the CRYSTAL-AF patient population with average age of 62 years. As a result of over-estimating the likelihood of CRBs and modeling them the same as a stroke in terms of patient outcomes, DOACs provide only a smaller benefit in the model. In summary, a major flaw of the EAG model is that the risk of several adverse events may be over-estimated since it is based on data from a significantly older and AF patient population with more advanced disease. While the risk of stroke was adjusted downwards for a paroxysmal AF population, other adverse event risks and all-cause mortality were not adjusted. To model all-cause mortality and CRB risk, an appropriate alternative would be to source adverse event rates from the recent trials NAVIGATE ESUS (Hart et al, 2018) and RE-SPECT ESUS (Diener et al, 2019). These studies included patients with a cryptogenic stroke which were only slightly older than patients in the Crystal AF trial (average age was 64 in RE-SPECT ESUS and 67 in NAVIGATE ESUS). Table 3 compares bleeding rates in the EAG Model to the rates in the RE-SPECT ESUS trial.	Therefore, an acute event of ischaemic stroke has a greater utility value decrement than an acute major bleed and also higher costs. The EAG further explained that it is a known risk that patients taking anticoagulation treatment are at a higher risk of bleeding than patients on antiplatelet treatment, as reflected in the model and based on an NMA of trial data for each DOAC considered in the model. The EAG noted that RESPECT-ESUS was published in May 2019, after the submission of the EAG report, and so it could not be reviewed for inclusion in the NMA. However, Deiner et.al., reported a hazard ratio of 1.19 for major bleeding on dabigatran compared with aspirin, which compared with the NMA hazard ratio 1.07 for major bleeding on dabigatran, is relatively higher. The NAVIGATE ESUS trial assessed only rivaroxaban vs. aspirin and was terminated early because of lack of benefit regarding

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Comment number	Name and organisation	Section number	Comment	NICE response
				stroke risk and because of bleeding associated with rivaroxaban (Hart et al., 2018). Table 3 presents the aggregate for all DOACs, however in the model each DOAC is modelled separately and results are weighted according to DOAC usage, thus using single risk estimates from one trial of a specific DOAC was not considered by the EAG to be robust and introduces selection bias.

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td colspan="5">Table 4: Comparison of assumed CRBs in EAG to results from RE-SPECT ESUS trial
<table>
<tr><td></td><td>EAG Model</td><td>RE-SPECT ESUS trial)[2]</td></tr>
<tr><td></td><td colspan="2">Risk of Clinically Relevant Bleedings[1] (p.a.)</td></tr>
<tr><td>Patients on DOACs</td><td>7.1%</td><td>3.3%</td></tr>
<tr><td>Patients on antiplatelet[3]</td><td>6.0%</td><td>2.3%</td></tr>
</table>
Table notes: 1) Clinically relevant bleeds (CRB) are defined as CRNM (clinically relevant non-major Bleeding) or major bleeding. 2) Bleedings in the NAVIGATE ESUS trial were defined differently: Major bleeding (according to ISTH definition) is reported separately from CRNM bleeding, and there may be overlap, thus they cannot be directly compared. The annualized rate of major bleeding (ISTH definition) on DOAC was 1.8% and the annualized rate of clinically relevant nonmajor bleeding was 3.5% on DOACS. 3) The type and dose of antiplatelets taken differ in the trials, the rates however do provide an indication of the magnitude of CRBs.</td></tr>
<tr><td>(continued)</td><td></td><td></td><td>Lastly, there is an inconsistency in the overall approach versus the AF detection rates in the model: the incidence of AF rises with age, so the detection rates with LINQ would be much higher in an older cohort.</td><td></td></tr>
</table>

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Comment number	Name and organisation	Section number	Comment	NICE response
21	Medtronic	Assessment report section 4	**(2) Severity of secondary strokes** Primary and secondary strokes are modelled very similarly in terms of severity and mortality impact, despite literature that shows secondary strokes to be more severe. A recurrent stroke in the EAG model has a zero probability of acute mortality, despite literature that shows case fatality after a secondary stroke to be high. Case-fatality after secondary stroke has been estimated to be 42% (Hardie et al, 2004). Jørgensen et al, 1997 found that the relative risk of death was almost doubled following recurrent vs. first ever stroke – yet the EAG only applied a multiplier of 1.32 to all-cause mortality after a stroke. The result of not modeling case fatality after a secondary stroke means that the benefits of preventing it (additional QALYs) are not appropriately accounted for. In addition, the EAG assumes that patients still have a rather high quality of life after a second stroke: patients have a quality of life of 0.7 after a secondary stroke – the same level that patients were documented to have after a primary stroke in the OXVASC study which the EAG used to estimate quality of life values (Luengo-Fernandez et al, 2013). Experiencing a recurrent stroke lowered quality of life in the OXVASC study below the level of 0.7. It seems rather unrealistic to assume that secondary strokes have the same severity distribution as primary strokes given that they have been shown to be very disabling. As an example, patients who survived a recurrent stroke experienced substantially more severe functional disability if they had a contralateral recurrence (Jørgensen et al, 1997). The lack of granularity in the model on this aspect means the model does not	Thank you for your comment which the committee considered. The EAG commented that it is incorrect to state that the model has zero probability of acute mortality due to a recurrent stroke. In the model, acute mortality is not explicitly modelled as a probability; it's modelled as an increase in hazard. Therefore, the next model cycle will have an increased proportion of patients who have died following a stroke compared to not having a stroke, so this reflects the acute mortality as well as the increased long-term mortality risk. With regards to the utility value for stroke used in the model, the EAG commented that in the OX-VASC study (Luengo-Fernandez *et al*., 2013) the overall estimate does include both patients with primary and recurrent stroke. In Luengo-Fernandez *et al*., 2013 a utility decrement was reported for recurrent stroke (-0.15 at 1 month and -0.068 at 5 years). However, adding the utility decrement would potentially be double counting for the proportion of patients in the overall estimate

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			realistically reflect the true impact a secondary stroke has on a patient's quality of life.	with secondary stroke and as such the EAG did not include it in their model. Furthermore, the time point for the long-term decrement was not suitable for the model. The EAG considered that the probabilistic sensitivity analyses captured the uncertainty around the utility estimates.
22	Medtronic	General comment	**New data on stroke costs not used** Costs of ischaemic strokes are based on data from 153 patients from a single source (Luengo-Fernandez et al, 2013) despite new data from Xu et al, 2018 based on 84,184 patients in the National Audit Programme. While it is a strength that Luengo-Fernandez provides data for AF patients specifically as strokes for patients with AF are considered to be more severe, the study did not include all health- and social care costs relevant to stroke care. Acute costs of strokes are estimated to be £14,522 and post stroke annual costs are £4,514 in the EAG model. Xu et al, 2018 estimate mean total health and social costs after 5 years to be slightly higher, £41,432. Importantly, they find that stroke costs varied widely (ranging from £19,101 to £107,336) and that costs increased with stroke severity. Costs of secondary strokes were not reported separately in this study but are likely to be higher than primary stroke costs as shown in (Luengo Fernandez 2012) and based on higher rates of disability (Jørgensen et al, 1997).	Thank you for your comment which the committee considered. The EAG commented that mean healthcare costs at 1 year reported in Xu et al. was £13,452, rising to £17,963 after 5 years, similar to what has been used in their long-term model. However, the Xu et al. study also estimates costs for social care, which the authors acknowledge may include costs that would be funded by the patient and not the NHS. Therefore, the EAG maintained that the Luengo-Fernandez *et al* estimates are appropriate as they are solely for hospitalisation and healthcare costs that are likely to be more reflective of NHS resource use. The committee considered that, given the updated ICERs presented at the third

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<tr><td></td><td></td><td></td><td></td><td>committee meeting, using data from Xu et al. for costs was unlikely to change conclusions.</td></tr>
<tr><td>23</td><td>NHS professional</td><td>General</td><td>There are a couple of issues with the EAG cost-effectiveness model:

1) Cost-effectiveness was modelled using an existing primary prevention model. (Sterne et al, 2017; Welton et al, 2017 both NIHR HTAs).

2) Insufficient adjustments were made to represent a secondary stroke population, although there are important differences in the clinical outcomes of primary and secondary strokes: there are greater number of strokes, these are more likely to be disabling with significantly higher healthcare costs (Luengo Fernandez et al 2013) and also much higher mortality (Joergensen et al, 1997). The Diamantopoulos model also accounted for heterogeneity of strokes to account for higher costs with more severe strokes. In the EAG model no-one seems to die from their stroke which has an effect on the QoL assessment, whilst the QoL assessment is also skewed by the inclusion of primary strokes (which have a lesser effect on QoL than secondary strokes).

[Additional comments here relate to other topic themes and have been included elsewhere]

It is not generally accepted that the risk of stroke is lower in people with paroxysmal AF than persistent AF, yet the EAG assume a 0.78 risk</td><td>Thank you for your comment which the committee considered.

The EAG commented that the model was adjusted appropriately to reflect the risks associated for a secondary stroke population with paroxysmal atrial fibrillation, as well as the costs and utilities for this population.

Below are the hazard ratios that were applied to the baseline risk of events in the model to adjust for prior stroke.
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<tr><th>Risk factor</th><th>Hazard ratios -Prior stroke</th></tr>
<tr><td>Future ischaemic stroke</td><td>4</td></tr>
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Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 27 November 2019

THEME: Modelling of a secondary stroke population in the EAG's model: Stroke-related parameters used in the EAG's model

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<tr><td></td><td></td><td></td><td>(Hohnloser 2007, Vanassche 2015, Steinberg 2015).

[Additional comments here relate to other topic themes and have been included elsewhere]</td><td>The EAG explained that primary strokes were not included in the model, as the population under consideration (cryptogenic stroke patients) by definition have already had a first stroke. Mortality due to strokes and other events has been included in the model.</td></tr>
<tr><td>24</td><td>NHS professional</td><td>General</td><td>Dear NICE Diagnostics Advisory Committee,

I am writing in response to the recent draft guidelines for the use of implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke. I would like to make some comments on the new model that has been used to conclude that ICMs are not cost-effective in the cryptogenic stroke patient cohort.

1. From what I can see, the model claims to be assessing the cost-effectiveness of LINQ to detect atrial fibrillation following cryptogenic stroke. The purpose of using LINQ for this indication, is so we can initiate anticoagulation to reduce the risk of secondary stroke. However, the model that has been described in the guidance is for primary stroke prevention and makes the assumption that the patient outcomes and related costs are the same for primary stroke as they are for secondary stroke. We see these patients day in-day out in the HASU and I can assure you that this is not the case. A secondary stroke, particularly if AF-related, is hugely debilitating and</td><td>Thank you for your comment which the committee considered.

The EAG commented that the model was adjusted appropriately to reflect the risks associated for a secondary stroke population with paroxysmal atrial fibrillation, as well as the costs and utilities for this population.

Below are the hazard ratios that were applied to the baseline risk of events in the model to adjust for prior stroke.
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Comment number	Name and organisation	Section number	Comment	NICE response
			life-changing. Immediate case fatality and mortality have been shown to be higher after secondary stroke (Hardie et al 2014, Joergensen et al 1997). Consequently, I believe the model should be based on secondary stroke outcomes data. *[Additional comments here relate to other topic themes and have been included elsewhere]* 4. The final comment I would like to make is around the variation in stroke risk of paroxysmal vs persistent AF. The model has assumed the stroke risk to be lower since Crystal AF patients are detected with paroxysmal AF and not persistent. Multiple studies have not observed a difference in stroke risk between patients with paroxysmal and persistent AF or find that differences are more due to associated risk factors such as age that tend to be more prevalent in patients with persistent AF. (Hohnloser 2007, Vanassche 2015, Steinberg 2015). The UCLH HASU provides world-class treatment to all our stroke patients. AF is a well-documented cause of ischemic stroke and causes a fivefold increase in the patient's risk of a stroke (Wolf et al, 1987). The detection of AF allowing the initiation of an OAC, reduces the patient's risk of a secondary stroke by 73% (Diener et al, 2012). We have approximately 1200 ischemic stroke admissions a year and will be uncomfortable denying high-	<table><tr><td>**Future TIA/SE**</td><td>3.61</td></tr><tr><td>**Future ICH**</td><td>1.64</td></tr><tr><td>**Future Bleed**</td><td>1.39</td></tr><tr><td>**Future Death**</td><td>5.87</td></tr></table> .

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Comment number	Name and organisation	Section number	Comment	NICE response
			risk cryptogenic stroke patients, a form of AF detection and subsequent secondary stroke risk prevention, when the technology is readily available. Kind regards, Dr [redacted]	
25	NHS professional	3.56	'The risks of these events happening in the model were based on a population with a history of ischaemic stroke and paroxysmal atrial fibrillation.' A number of reports in the scientific literature point to a lower burden of stroke in patients with paroxysmal rather than persistent or permanent AF. What is the effect on the economic analysis if rates of stroke, on follow-up, are varied depending on the type of AF diagnosed?	Thank you for your comment which the committee considered. The EAG commented that the adjustment for paroxysmal atrial fibrillation in the model results in a lower risk of recurrent stroke compared with permanent or persistent atrial fibrillation. Permanent and persistent atrial fibrillation is out of scope as the population under consideration is patients with cryptogenic stroke, that is where no cause can be identified after standard ECG monitoring. It is therefore assumed that all atrial fibrillation detected is paroxysmal.
26	NHS professional	General	Dear NICE Diagnostics Advisory Committee, I would like submit some comments on the recent draft guidelines for the use of ILRs in cryptogenic stroke/TIA patients.	Thank you for your comment which the committee considered.

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<tr><td></td><td></td><td></td><td>I can see that the model used is based on primary prevention even though the guidelines are for secondary prevention. After a secondary stroke, the costs are higher and the outcomes are much more disabling, so I believe the model needs to be updated to reflect this. Immediate case fatality and mortality have been shown to be higher after secondary stroke (Hardie et al 2014, Joergensen et al 1997).

[Additional comments here relate to other topic themes and have been included elsewhere]

The model has also assumed the stroke risk to be lower since Crystal AF patients are detected with paroxysmal AF and not persistent. Multiple studies have not observed a difference in stroke risk between patients with paroxysmal and persistent AF, or find that differences are more due to associated risk factors such as age that tend to be more prevalent in patients with persistent AF. (Hohnloser 2007, Vanassche 2015, Steinberg 2015).

I hope this feedback is helpful.

Many thanks,

Dr [redacted] (Clinical Scientist)</td><td>The EAG commented that the model was adjusted appropriately to reflect the risks associated for a secondary stroke population with paroxysmal atrial fibrillation, as well as the costs and utilities for this population.

Below are the hazard ratios that were applied to the baseline risk of events in the model to adjust for prior stroke.
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<tr><td>27</td><td>NHS professional</td><td>Economic model</td><td>We use these devices for patients who have already had an unexplained ischemic stroke as a tool to help prevent secondary strokes, therefore we assume the cost-effectiveness was incorrectly modelled by the EAG using an existing primary prevention model and we are concerned that the adjustments made do not
reflect the cryptogenic stroke population. (Sterne et al, 2017; Welton et al, 2017 both NIHR HTAs).

There are important differences in the clinical and economic outcomes of primary and secondary strokes:
• A 41% case fatality in secondary stroke patients at 30 days has been reported (Hardie et al 2014)
• Secondary stroke mortality was twice as high as primary stroke mortality (Joergensen et al, 1997)
• 5-year hospital care costs are significantly higher for secondary strokes indicating that secondary strokes are more severe (Luengo Fernandez 2012).</td><td>Thank you for your comment which the committee considered.

The EAG commented that the model was adjusted appropriately to reflect the risks associated for a secondary stroke population with paroxysmal atrial fibrillation, as well as the costs and utilities for this population.

Below are the hazard ratios that were applied to the baseline risk of events in the model to adjust for prior stroke.
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<tr><td>28</td><td>NHS professional</td><td></td><td>The external research group (EAG) commissioned by NICE presented a cost-effectiveness model with an ICER of Â£24,875. They have taken an existing model which was developed for primary prevention and made little adjustment to represent a secondary stroke population. They unfortunately do not account for the important differences in the clinical outcomes of primary and secondary strokes.

In contrast, previous developed models for ILRs in secondary stroke prevention showed ILRs to be a cost-effective. (ICER Â£17,175). While all models aren't truly accurate â€“ some are more useful than others.

In the EAG model, there were a lot fewer recurrent strokes than a meta-analysis has shown. In addition, the recurrent strokes modelled do not reflect the severity shown in the secondary stroke literature. Thus, the model is more applicable to Reveal LINQ in primary stroke prevention â€“ which is NOT the question of this assessment.

Due to these reasons (too low number of avoided strokes, severity of secondary strokes are not captured) I feel this is, unfortunately, not a fair assessment of the benefit of ILR in these patients.</td><td>Thank you for your comment which the committee considered.

The EAG commented that the model was adjusted appropriately to reflect the risks associated for a secondary stroke population with paroxysmal atrial fibrillation, as well as the costs and utilities for this population.

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Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 27 November 2019

THEME: Amount of monitoring for atrial fibrillation done in conventional-follow up arm of the EAG's model

Comment number	Name and organisation	Section number	Comment	NICE response
29	NHS professional	General	3. I would also like to challenge the conclusion that in the Crystal AF study, â€œthe base case may overestimate how much monitoring for atrial fibrillation is done in current practiceâ€ so therefore all future AF monitoring costs have been removed. One point to note is that the additional AF monitoring in Crystal AF is actual data where it was left entirely down to physician's choice. We are ordering further AF monitoring in these patients via Holter monitoring and patches daily, both of which incur costs to the NHS and also burden our cardiology departments. Without the option of implanting ICMs, we will be left with no choice but to order more of these other tests, which will have a significant impact on the quality of our service, the well-being of our patients and furthermore, the efficiencies within the hospital.	Thank you for your comment which the committee considered. Clinical experts at the committee meeting reiterated their opinion that in current practice the amount of testing for atrial fibrillation varies if an implantable cardiac monitor is not used, but it is likely to be less than occurred in CRYSTAL-AF. The committee further concluded that the EAG's scenario with no monitoring in the standard monitoring arm of the model may be too extreme, in that some monitoring is likely to be done in the NHS for people with no implantable cardiac monitor fitted. However, the amount of assessment for atrial fibrillation in current practice is likely to have been overestimated in the base case model. Assuming no further monitoring in the model for current practice increased the base case ICER by about £1,300 per QALY gained (see

Comment number	Name and organisation	Section number	Comment	NICE response
				section 4.11 of the updated diagnostics consultation document).
30	NHS professional	General	It also states that in the Crystal AF study, â€œthe base case may overestimate how much monitoring for atrial fibrillation is done in current practiceâ€ so therefore all future AF monitoring costs have been removed. We see a increasing demand of post-stroke Holter monitor requests and this places an immense burden on our cardiology department.	Thank you for your comment which the committee considered. Clinical experts at the committee meeting reiterated their opinion that in current practice the amount of testing for atrial fibrillation varies if an implantable cardiac monitor is not used, but it is likely to be less than occurred in CRYSTAL-AF. The committee further concluded that the EAG's scenario with no monitoring in the standard monitoring arm of the model may be too extreme, in that some monitoring is likely to be done in the NHS for people with no implantable cardiac monitor fitted. However, the amount of assessment for atrial fibrillation in current practice is likely to have been overestimated in the base case model. Assuming no further monitoring in the model for current

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THEME: Amount of monitoring for atrial fibrillation done in conventional-follow up arm of the EAG's model

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				practice increased the base case ICER by about £1,300 per QALY gained (see section 4.11 of the updated diagnostics consultation document).
31	Medtronic	Draft Guidance Section 4.16	**No more additional AF monitoring done in conventional arm** The NICE committee expressed the uncertainty around the amount of further monitoring for AF. The base case of the model had assumed the same amount of additional AF monitoring as the CRYSTAL-AF study reported. In the CRYSTAL-AF study, additional AF monitoring was left at the physician's discretion. The total number of additional tests in the CRYSTAL-AF trial per patient per year are shown in the Table below	Thank you for your comment which the committee considered. Clinical experts at the committee meeting reiterated their opinion that in current practice the amount of testing for atrial fibrillation varies if an implantable cardiac monitor is not used, but it is likely to be less than occurred in CRYSTAL-AF. The committee further concluded that the EAG's scenario with no monitoring in the standard monitoring arm of the model may be too extreme, in that some monitoring is likely to be done in the NHS for people with no implantable cardiac monitor fitted. However, the amount of assessment for atrial fibrillation in current practice is likely to have been overestimated in the base case model. Assuming no further

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<tr><td colspan="5">Table 1: Tests performed per person per year in control arm of CRYSTAL-AF

<table>
<tr><th>Period</th><th>No test</th><th>ECG</th><th>Holter 24H</th><th>Holter 48H</th><th>Holter 7D</th><th>Mean per cycle cost</th></tr>
<tr><td></td><td></td><td colspan="4">£136.79[a]</td><td></td></tr>
<tr><td>0-12 months</td><td>0.307</td><td>0.549</td><td>0.063</td><td>0.022</td><td>0.058</td><td>£29.74</td></tr>
<tr><td>12-24 months</td><td>0.508</td><td>0.398</td><td>0.036</td><td>0.007</td><td>0.051</td><td>£19.56</td></tr>
<tr><td>24-36 months</td><td>0.582</td><td>0.314</td><td>0.021</td><td>0</td><td>0.084</td><td>£15.96</td></tr>
</table>
.</td></tr>
<tr><td>(continued)</td><td></td><td></td><td>The committee had concluded that in Crystal-AF more monitoring for atrial fibrillation was done than would be done in the NHS. This is a fair point as physicians might have done more monitoring in the study setting of Crystal AF (Hawthorne effect). However, it appears to be rather unrealistic that in the future, no further AF monitoring would be performed in the conventional arm (committee considerations DCD 4.16). The patient representative on the committee mentioned that patients will visit the GP for re-assurance after CS if no diagnosis is found (Draft Guidance, p. 32,33). Given that AF is an important risk factor for recurrent strokes, it would be surprising if no additional monitoring was done when</td><td></td></tr>
</table>

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Comment number	Name and organisation	Section number	Comment	NICE response
			a cryptogenic stroke patient came back for future visits. The NICE committee notes stated that their assumption "may be too extreme and that some monitoring may be done" (Draft Guidance DAP42 p.38). Acknowledging the uncertainty around the further monitoring question, we have provided below data that we hope will illustrate that the extreme is highly unlikely, and the trend is that additional monitoring will be untaken. In order to get a more general picture, we consulted the NHS Hospital Episode Statistics Data. In the analysis, HES data for 2017/18 was used and patients between 51 and 73 with a primary stroke were followed for 12 months and all the cardiac monitoring in addition to the initial stroke work-up was documented. (The age range is based on taking the average age ± 1 standard deviation from the Crystal AF study. Patients who had a previous diagnosis between 2013/14 – 2017/18 were excluded from the analysis.) Patients with a new stroke diagnosis were identified through ICD-10 diagnosis codes I630-I636, I638, I639 and I64X. As cryptogenic stroke patients cannot be identified in the HES data since there is no associated code, all patients post initial stroke were included. 24h Holters and other extended cardiac monitoring are coded as HRG code EA47Z or EY51Z "Electrocardiogramm monitoring or stress testing" depending on the setting (inpatient or outpatient). The code also includes stress testing. However, since stress testing entails recording an ECG during an exercise (like running on a treadmill) it seems less likely to be done in stroke patients. We thus assume that the majority of these tests will be for ECG monitoring.	

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<tr><td></td><td></td><td></td><td>The results show that 24.5% of all primary stroke patients go on to have further ECG monitoring done during the 12 months post stroke in addition to their initial stroke work-up. A total number of 8,398 ECG monitoring tests were done in these patients (Table 2). The analysis includes all stroke patients, not only CS patients, however, it seems more likely that patients without a diagnosis of the underlying cause of their primary stroke would undergo more cardiac testing than patients with a stroke diagnosis. We do acknowledge that patients might receive cardiac monitoring due to other reasons. Nevertheless, a share of these tests are likely to be undertaken for AF monitoring which would contradict the assumption that no more AF monitoring is done in conventional care.</td><td></td></tr>
<tr><td colspan="5">Table 2: Additional Cardiac Monitoring Performed in Patients After Primary Stroke
<table>
<tr><td>Total patients with a new stroke diagnosis in 2017/18</td><td>Total patients with additional cardiac monitoring 12 months post diagnosis (%)</td><td>Total additional cardiac monitoring tests 12 months post diagnosis</td></tr>
<tr><td>27,212</td><td>6,669 (24.5%)</td><td>8,398</td></tr>
</table></td></tr>
<tr><td>(continued)</td><td></td><td></td><td>Based on the Crystal data, additional short-term external monitoring is unlikely to be a cost-effective use of resources due to the low AF detection yield. In the Crystal-AF study, 202 ECGs, 52 24-hr Holters and one 1 Event Recorder were done to detect 5 patients with AF (Sanna et al, 2014). The AF detection yield of different monitoring strategies have also been simulated based on the individual patient level data from Crystal-AF (Choe et al, 2015).</td><td></td></tr>
</table>

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Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 27 November 2019

THEME: Additional benefits of implantable cardiac monitors

Comment number	Name and organisation	Section number	Comment	NICE response
32	Medtronic	General comment	Based on research performed by the market research company ZS for Medtronic, a substantial share of cryptogenic patients will start OAC medication even if no AF has been found. ZS interviewed 97 cardiologist and neurologists in the UK in 2015 to understand the patient care pathway of cryptogenic stroke patients. They found the surprising result that even without detecting AF, neurologists would prescribe OACs in 29% of patients and cardiologists in 21% of patients. The result indicates that physicians are concerned about the recurrent stroke risk in these patients, at the same time, better AF detection options might be needed to identify the patients who actually benefit from OAC treatment. The recent trials NAVIGATE ESUS (Hart et al, 2018) and RE-SPECT ESUS (Diener et al, 2019) have shown that there is no benefit in terms of stroke reduction in an overall cohort of CS patients, and NAVIGATE-ESUS showed significantly higher bleeding rates. Thus, it is important to detect AF.	Thank you for your comment which the committee considered.
33	NHS professional		One other comment has come to mind: there are no options for these somewhat younger patients to diagnose AF reliably. The lack of other options should be taken into account.	Thank you for your comment which the committee considered.
34	NHS professional	General	As a practicing stroke physician for over 6 years I find this document very depressing and backward. We see the impact of AF causing major strokes and the diagnostic value of short term cardiac monitoring being very poor and time consuming. I have seen so many cases of recurrent TIA's or major stroke where it takes multiple attempts of short term monitoring with huge time delays to prove that they have paroxysmal AF. And by this time they end up with major stroke	Thank you for your comment which the committee considered. In light of the updated cost effectiveness modelling, recommendation 1.1 has been updated to state that Reveal LINQ is

DIAGNOSTICS ASSESSMENT PROGRAMME

Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke

Diagnostics Consultation Document – Comments

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THEME: Additional benefits of implantable cardiac monitors

Comment number	Name and organisation	Section number	Comment	NICE response
			which is absolutely unacceptable in this era. I have constantly fought locally to get our fair share implantable reveal LINQ devices for these patients, which certainly have a much better yield and its only common sense that the longer you monitor the better chances of picking up paroxysmal AF. There are numerable numbers of "Crypogenic" strokes which I'm sure would be PAF related if appropriate long term monitoring is done with these implantable LINQ devices. At present we just do short monitoring and give up early as we cannot afford these devices for a major proportion of patients. This as far as I am concerned is incomplete work but we donâ€™t have a choice. So rather than promoting better practice for the future it's sad that NICE is proposing a backward idea, citing costs and poor/ non- convincing evidence which in my opinion will cost lives. Finally I would like to ask the committee members this. What would you prefer if you or your relatives have a stroke or TIA with no cause found? Would you prefer short term monitoring which returns as normal or an implantable LINQ device to continually pursue evidence of PAF? .....Please help us clinicians to monitor better and prevent strokes.	recommended for use to help to detect atrial fibrillation after cryptogenic stroke.
35	NHS professional	General	We here at Addenbrooke's Hospital feel that by making the decision not to recommend Reveal LINQ, NICE leave the cryptogenic stroke (CS) patient population with no alternative since there is no other long-term diagnostic test	Thank you for your comment which the committee considered.

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THEME: Additional benefits of implantable cardiac monitors

Comment number	Name and organisation	Section number	Comment	NICE response
			for them. These recommendations assume the current SoC is acceptable. We know from our own data presented at EHRA in 2017 that in this patient population of unexplained ischemic strokes that we have achieved a 43.2% yield of AF in patients receiving an ILR. This is by far greater than any alternative monitoring method and has led to a higher rate of appropriate NOACs.	In light of the updated cost effectiveness modelling, recommendation 1.1 has been updated to state that Reveal LINQ is recommended for use to help to detect atrial fibrillation after cryptogenic stroke.
36	NHS professional	General	*[Additional comments here relate to other topic themes and have been included elsewhere]* The committee appears to have underestimated the impact of a stroke on a younger person i.e. lost economic productivity, the lived experience and care giver burden. Importantly, the reason we look for AF is to avoid subsequent stroke (s). The model seems to use first event opposed to second or third event with cumulative neurological damage and higher dependency and care giver burden with a resulting lower health state. Hence the model used is likely to increase the ICER. There are some assumptions made about the impact of false alerts. These can be largely negated by correct positioning of the device and correct programming of the device. The committee acknowledges that this technology gives superior yield compared to service monitoring. In the absence of an alternative, acknowledging the devastating physical and fiscal impact of stroke (the RCP recently suggested combined health and social costs of Â£18.5k in the first annum) by not approving these devices we are left with little clinical options. In Lincolnshire less than 50% of	Thank you for your comment which the committee considered. The committee noted that people who have had a cryptogenic stroke tend to be younger than people who have had a stroke with a known cause. Therefore, they're more likely to be working and have dependants, such as elderly parents or children (see section 4.1 of the diagnostics consultation guidance). The EAG commented that the model is adjusted for a secondary stroke population and as such, considered second stroke events. Below are the hazard ratios that were

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<tr><td></td><td></td><td></td><td>GP practices have a 12-lead ECG and the idea of serial ECGs and Holters post stroke is not feasible due to lack of primary care capacity, long journey times and the fact that it is not commissioned. Lincoln shire is not alone in struggling with primary care provision. Importantly, this also raises an equality issue that in a localities with little or no public transport. Patients with disabilities post event will experience significant difficulties accessing monitoring via local hospitals/ GP consortia that could be provided from home using telemedicine and as such will be disadvantaged. This was not included in the costing model. I ask the committee to reconsider their recommendations given the uncertainty and either review the economic inputs or acknowledge the limitations and while we await further research support the use of ILS as currently there is no feasible alternative.</td><td>applied to the baseline risk of events in the model to adjust for prior stroke.
<table>
<tr><th>Risk factor</th><th>Hazard ratios -Prior stroke</th></tr>
<tr><td>Future ischaemic stroke</td><td>4</td></tr>
<tr><td>Future TIA/SE</td><td>3.61</td></tr>
<tr><td>Future ICH</td><td>1.64</td></tr>
<tr><td>Future Bleed</td><td>1.39</td></tr>
<tr><td>Future Death</td><td>5.87</td></tr>
</table>
At the third committee meeting on this topic, based on corrections made to the economic model (described in section 4.13 of the updated diagnostics consultation document), the committee recommended the Reveal LINQ for use to help to detect atrial fibrillation after cryptogenic stroke (recommendation 1.1 updated diagnostics consultation document).</td></tr>
</table>

DIAGNOSTICS ASSESSMENT PROGRAMME

Implantable cardiac monitors to detect atrial fibrillation after cryptogenic stroke

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 27 November 2019

THEME: Recommendations

Comment number	Name and organisation	Section number	Comment	NICE response
37	Medtronic	DCD 1.1	The draft recommendations state that ….."Reveal LINQ is not recommended for detecting AF after cryptogenic stroke because it is not cost effective". If the recommendations are to remain unchanged, after addressing the comments we have raised. We believe 1.1 requires clarification, most explicitly that the uncertainties mean it is not a cost-effective use of NHS resource at present. This is important to address as the wider literature clearly illustrate that it is cost effective, albeit in this assessment using differing modeling techniques it may not be for WTP threshold the NHS accept. The distinction needs to be made for differing health care settings in the UK and internationally	Thank you for your comment which the committee considered. In light of the updated cost effectiveness modelling, recommendation 1.1 has been updated to state that Reveal LINQ is recommended for use to help to detect atrial fibrillation after cryptogenic stroke.
38	Royal College of Physicians	4.16	I feel that the conclusion is too strong for the data presented 'the most plausible ICER for Reveal LINQ is too high for the committee to recommend routine adoption'. The available data does not provide sufficient evidence to be able to make a recommendation about the clinical effectiveness and cost-effectiveness of this intervention.	Thank you for your comment which the committee considered. In light of the updated cost effectiveness modelling, recommendation 1.1 has been updated to state that Reveal LINQ is recommended for use to help to detect atrial fibrillation after cryptogenic stroke.
39	NHS professional	General	As a cardiologist who has worked closely with stroke colleagues on improving the post stroke pathway for nearly two decades I was disappointed by the committees preliminary recommendations. The recommendation that ILRs are not cost effective given the data and some of the inputs used in the sensitivity analysis is concerning and flies sin the face of several European Guidelines and deserves to be scrutinised further. Crystal AF used a combined sample of TIA and stroke. By definition, TIAs do not leave you with a prolonged neurological	Thank you for your comment which the committee considered. In light of the updated cost effectiveness modelling, recommendation 1.1 has been updated to state that Reveal LINQ is

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<table>
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<tr><td></td><td></td><td></td><td>deficit and hence any changes in health state are lower than those post stroke and stroke health states differ if you have suffered a stroke on stroke. Moreover, the consultation document was concerned with cryptogenic stroke not TIA.

[Additional comments here relate to other topic themes and have been included elsewhere]</td><td>recommended for use to help to detect atrial fibrillation after cryptogenic stroke.

The EAG commented that the model is adjusted for a secondary stroke population and as such, considered second stroke events. Below are the hazard ratios that were applied to the baseline risk of events in the model to adjust for prior stroke.
<table>
<tr><th>Risk factor</th><th>Hazard ratios -Prior stroke</th></tr>
<tr><td>Future ischaemic stroke</td><td>4</td></tr>
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THEME: General comments and comments on clarity

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40	Abbott		One thing to consider is that if the published data show mean or median times to detection being well short of 2 years, then a battery life in excess of 2 years ceases to have relevance. The 95% confidence interval or percentile range may be useful, depending on whether mean or median is reported.	Thank you for your comment which the committee considered. The EAG commented that despite the mean or median time to atrial fibrillation detection being less than 2 years, the upper range maybe beyond 2 years, in which case a proportion of patients will get benefit from an implantable cardiac monitor with a battery life longer than 2 years. In CRYSTAL-AF 4 patients with an implantable cardiac monitor were diagnosed with AF between 24 and 36 months.
41	Medtronic		References: (not provided in the Sterne and Welton reports) 1. Diamantopoulos A, Sawyer LM, Lip GYH, Witte KK, Reynolds MR, Fauchier L, et al. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. International Journal of Stroke 2016; 11: 302-12. 2. Hardie, Kate, et al. "Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study." Stroke 35.3 (2004): 731-735. 3. Jørgensen, H. S., et al. "Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study." Neurology 48.4 (1997): 891-895.	Thank you for your comment which the committee considered.

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			4. Luengo-Fernandez, Ramon, Alastair M. Gray, and Peter M. Rothwell. "A population-based study of hospital care costs during 5 years after transient ischemic attack and stroke." Stroke 43.12 (2012): 3343-3351. 5. Tsivgoulis, Georgios, et al. "Prolonged Cardiac Rhythm Monitoring and Secondary Stroke Prevention in Patients With Cryptogenic Cerebral Ischemia." Stroke (2019): STROKEAHA-119. 6. Luengo-Fernandez R, Yiin GS, Gray AM, Rothwell PM. Population-based study of acute- and long-term care costs after stroke in patients with AF. Int J Stroke. 2013;8(5):308-14. 7. Xu, Xiang-Ming, et al. "The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke." European Stroke Journal 3.1 (2018): 82-91. 8. Hart, Robert G., et al. "Rivaroxaban for stroke prevention after embolic stroke of undetermined source." New England Journal of Medicine 378.23 (2018): 2191-2201. 9. Diener, Hans-Christoph, et al. "Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source." New England Journal of Medicine 380.20 (2019): 1906-1917 10. Choe, William C., et al. "A comparison of atrial fibrillation monitoring strategies after cryptogenic stroke (from the Cryptogenic Stroke and Underlying AF Trial)." The American journal of cardiology 116.6 (2015): 889-893.	
42	Royal College of Physicians	1	Suggest change the wording ‘but it not clear how much it will reduce the number of further strokes’. The device only identifies AF and does not treat the condition.	Thank you for your comment which the committee considered.

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			Perhaps reword – it is not clear how many further cases of strokes or TIA will be prevented by identify patients with AF using this method and treating them with anticoagulants.	The section on 'Why the committee made these recommendations' has been amended to clarify that use of the devices can reduce further strokes by identifying people for anticoagulant treatment.
43	Royal College of Physicians	3.2	Only 1 study met the initial eligibility criteria and observational studies of the same population were then included. The quality of the observational studies was not assessed. I feel that the quality of studies should be reported as the results of these studies are reported in the text. Summary table of the studies would be helpful.	Thank you for your comment which the committee considered. The EAG commented that the observational studies were not quality assessed as the majority were single-arm studies and there is no standardised quality assessment tool suitable for assessing single-arm clinical effectiveness studies. It also highlighted that that their results were only reported narratively or in tables (no evidence synthesis conducted using them) and in Section 3.3 of the EAG report there is a narrative discussion around the observational studies along with

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				summary tables of the study characteristics and results.
44	Royal College of Physicians	3.14	Table 1 provides interesting data about detection of AF over time. I am unclear throughout the document is the pick-up rate of AF in the general/non stroke population.	Thank you for your comment which the committee considered. The EAG commented that the detection rate estimated in CRYSTAL AF (table 1) and used in the economic model is specific to a cryptogenic stroke population.
45	Royal College of Physicians	3.32	Is the data available from CRYSTAL-AF investigators re in stroke or TIA events occurred in those who were and who were not diagnosed with AF? How many of these strokes were found to have AF at time of recurrent stroke or TIA?	Thank you for your comment which the committee considered. The EAG commented that data from CRYSTAL AF only presents the number of atrial fibrillation events detected in patients with and without the implantable cardiac monitor device. CRYSTAL-AF data on strokes does not distinguish between patients with and without a diagnosis of atrial fibrillation.
46	Royal College of Physicians	3.51	There are two ongoing randomised controlled trials which seek to address this research question which are due to report in 2019. How and when will these data be incorporated into the review?	Thank you for your comment which the committee considered.

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				If this evidence does become available during consultation, please submit it as part of your response to the updated diagnostics consultation document for consideration by the committee at their next meeting. NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.
47	Royal College of Physicians	4.16	The cost-effectiveness of these devices is uncertain but some data suggests that they may be cost-effective (and come within the NICE threshold). It would be helpful for the EAG to submit the model they have developed as a peer review paper for wider scrutiny. I would also be keen to hear the views of health economists about the work undertaken.	Thank you for your comment which the committee considered. The EAG's model is made available to stakeholders who request it for review. In addition, for this assessment NICE commissioned a review of the model by the NICE Decision Support Unit. Their findings are set out in a report to accompany the guidance.

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