BMJ Open

Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in large- or small-vessel disease ischaemic stroke in the USA

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To cite: Reynolds MR, Pollit V, Schwamm L, *et al*. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in large- or small-vessel disease ischaemic stroke in the USA. *BMJ Open* 2026;**16**:e103766. doi:10.1136/bmjopen-2025-103766

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-103766).

Received 15 April 2025
Accepted 26 March 2026

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ABSTRACT

Objectives To evaluate the cost-effectiveness of insertable cardiac monitors (ICMs) compared to standard of care (SoC) to detect atrial fibrillation (AF) in patients with stroke of presumed known cause of large-artery atherosclerotic disease (LAD) or small-vessel occlusive disease (SVD) from a US payer perspective.

Design A lifetime Markov model assessed cost-effectiveness of ICM versus SoC from a US payer perspective. Patient characteristics and AF detection rates were based on the STROKE AF trial (NCT02700945): 3-year diagnostic yield was 21.7% (95% CI 16.7% to 27.9%) for ICM and 2.4% (1.0%–5.7%) for SoC. AF detection resulted in a switch from aspirin to direct oral anticoagulant unless precluded by prior bleeding. Subsequent risks of ischaemic strokes (ISs) and bleeding events were modelled based on published literature. Costs and effects were discounted at 3% annually. Specific SoC short-term monitoring strategies (STMs) were explored as scenarios.

Setting US healthcare system perspective.

Participants Hypothetical cohort of patients with IS believed to be due to LAD or SVD.

Interventions Patients received an ICM within ten days of the index stroke or SoC involving conventional follow-up.

Main outcome measures Stroke and bleeding risk, mortality, health-related quality of life and healthcare cost and utilisation.

Results ICM was associated with a gain of 0.176 quality-adjusted life years (QALYs) compared with SoC per patient, representing a reduction of 53 strokes per 1000 patients. The lifetime incremental cost of ICM was $6736 per patient. This resulted in an estimated incremental cost-effectiveness ratio (ICER) of $38 346 per QALY gained, making ICM a cost-effective intervention at willingness-to-pay thresholds of $50 000–$150 000 per QALY in the USA. ICMs were also cost-effective compared with various individual STMs, with ICERs ranging from $29 814 to $38 941 per QALY gained. The mean probabilistic ICER across 5000 samples was $46 910 per QALY (97.5% CI$45 421 to $53 523). Results were sensitive to anticoagulant uptake on AF detection and underlying stroke risk. Model findings were robust to both probabilistic sensitivity analysis and sensitivity analyses where inputs tested were considered within plausible ranges, as ICM was found cost-effective in these analyses.

Conclusions ICMs are highly likely to be a cost-effective diagnostic tool for secondary prevention of stroke related to AF in US patients with prior stroke attributed to LAD or SVD. However, further research is needed to understand the efficacy of secondary stroke prevention treatments in patients with stroke attributed to LAD or SVD and subclinical AF.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A key strength of this analysis is that it builds on existing cost-effectiveness analyses of insertable cardiac monitor (ICM) in the USA for cryptogenic stroke by considering its efficacy in a new patient population, meaning that it presents novel research that is methodologically comparable to previous economic evaluations.

⇒ The analysis is limited by simplifying model assumptions owing to absence of data, such as true oral anticoagulation uptake following atrial fibrillation (AF) detection and uptake of alternative treatment options following AF detection.

⇒ The model makes use of a number of sensitivity and scenario analyses to explore different clinical thresholds at which ICM is considered cost-effective under the US healthcare perspective, as well as to mitigate data uncertainties.

INTRODUCTION

In the United States America (USA), about 690 000 people have an ischaemic stroke (IS) annually, 185 000 of which are recurrent.[1] About 40% of all IS are attributable to large-artery atherosclerotic disease (LAD) or small-vessel occlusive disease (SVD).[1] Another aetiology, atrial fibrillation (AF), portends a fivefold increase in IS risk.[2] Oral anticoagulation (OAC) is effective in preventing IS in patients with AF and is recommended by

clinical guidelines for patients with AF at risk of thromboembolism, but not for stroke survivors without AF.[1 2]

Recent AF management guidelines recommend prolonged monitoring for AF in patients with embolic stroke of undetermined source (also known as cryptogenic stroke (CS)) to inform treatment decisions (Class I, level of evidence B).[2] Previously, insertable cardiac monitor (ICM) was shown to be 8.8 times more effective than standard of care (SoC) at detecting AF over 3 years for CS patients in the CRYSTAL AF randomised trial (95% CI 3.5 to 22.2).[3] More recently, the STROKE AF randomised trial was conducted to assess AF detection rates with ICM versus SoC in 492 patients with stroke attributed to LAD or SVD, finding that ICM was 10.0 times more likely (95% CI 4.0 to 25.2) to detect AF compared with SoC (note: patient with STROKE AF population characteristics are provided in online supplemental table S2).[4]

The relative increase in AF detection with ICM versus SoC in the STROKE AF cohort was similar to that found in patients with CRYSTAL AF CS with radiographic patterns of suspected embolic infarction. ICM-based AF detection in patients with CS or suspected AF is cost-effective in several geographies including the USA, Canada, Australia and the UK.[5–7] The aim of the current study, therefore, is to evaluate the cost-effectiveness of ICM to detect AF in patients with stroke of presumed known cause of LAD or SVD, from a US payer perspective. The US healthcare system relies on a complex mixture of various private and public insurance payers, each making independent decisions that lead to different perspectives on health economic value. As such, we assess the cost-effectiveness of ICM against the range of willingness-to-pay thresholds considered in the USA ranging from $50 000 to $150 000 per quality-adjusted life year (QALY).[8]

METHODS

Model origin and design

We adapted a previously published US cost-utility analysis of ICM for AF detection in patients with CS,[9] preserving the model structure and US payer perspective (figure 1). We estimated QALYs, healthcare costs, life-years gained and stroke events avoided. Guided by the Institute for Clinical and Economic Review (ICER) reference case,[8] we used a lifetime horizon to capture all possible costs and health outcomes, given the chronic nature of the disease area. A discount rate of 3% per annum was applied to cost and health outcomes, also in line with the ICER reference case.

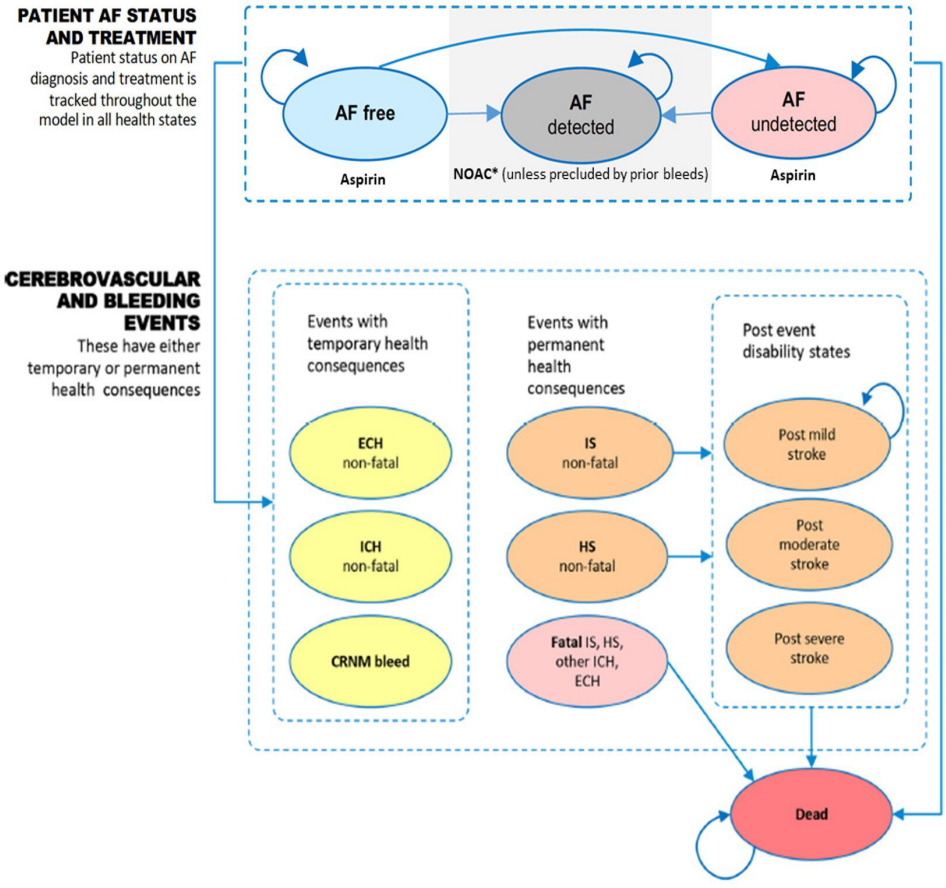

Figure 1 Markov model flow. Sourced from figure 1: Model schematic by Laura M Sawyer, Journal of Comparative Effectiveness Research, licensed under CC BY-NC-ND 4.0, DOI: 10.2217/cer-2020-0224). AF, atrial fibrillation; CRNM, clinically relevant nonmajor; ECH, extracranial haemorrhage; HS, haemorrhagic stroke; ICH, intracranial haemorrhage; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant.

This section focuses on input parameters used, emphasising key changes to the original CS model and evidence base. A more detailed overview of the modelling methodology is provided in the supplemental material, including: key features of the economic evaluation (online supplemental table S1); an overview of the modelled population characteristics based on the STROKE AF trial (Clinicaltrials.gov NCT02700945; online supplemental table S2); the population baseline characteristics stratified by CHA_2DS_2-VASc score (online supplemental tables S3 and S4); the parameterisation of AF detection in the model (online supplemental table S5) and expected proportions of patients with AF detected under several scenarios (online supplemental tables S6–S8).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this analysis. The study did not involve human participants and no ethics approval or consent to participate were required.

Population and treatment strategies

The analysis models a hypothetical cohort of patients who had an IS within the past 10 days believed to be due to LAD or SVD. Patients were allocated to receive either: (i) an ICM inserted within 10 days of the index stroke, (ii) SoC involving conventional follow-up (ie, ECGs/Holter monitors at the discretion of the treating provider) which could include short-term monitoring (STM) with external patch cardiac monitors of various durations.

Model structure and flow

Patients move through the model's health states in a fixed cycle length of 3 months, reflecting the approach of prior economic evaluations in AF treatment.[7 9 10] Two aspects of relevance, AF detection status and health state changes, are simulated in parallel. In each 3-month cycle, patients have a probability of having AF detected, developing it without detection or remaining AF-free. If AF is detected, patients commence OAC therapy. If AF is not detected, regardless of whether it occurred, patients continue to receive aspirin.

Strokes and bleeds are based on estimated cerebrovascular risks for this cohort with or without AF, as well as the efficacy and safety of OAC treatments administered. Patients can experience up to two recurrent strokes within the model (online supplemental table S16). First and second recurrent strokes each have an associated level of temporary or permanent disability captured in distinct 'poststroke' health states. AF detection and treatment change can still occur in each of the two poststroke states, but patients cannot exit these states except by transitioning to the 'death' state.

Baseline risk stratification and subgrouping

Stroke and bleeding risks

The probability of the model cohort's primary health state transition, namely to recurrent stroke events, was first stratified according to baseline risk. STROKE AF captured CHA_2DS_2-VASc scores at baseline[4]; this score distribution was applied to the model cohort from day 0. Since STROKE AF did not collect scores on bleeding risk, this was not stratified at baseline in the current model cohort. Instead, a global baseline risk of bleeds was applied, increasing by a factor of 1.97 (95% CI 1.79 to 2.16) for every 10 years lived in the model.[11] Additional bleed risks were applied if a patient commenced OAC.[11–13]

AF detection

Rates of AF detection were taken from the STROKE AF trial, which had an AF duration threshold of ≥30 s; however, it is important to note that due to the ICM's automatic detections all detected episodes in the ICM group were 2 min in duration. Subgroup analyses, informed by data from the STROKE AF trial, were undertaken to explore the impact of potentially different AF detection rates on the main analysis:

- *by duration of AF episode*: we undertook scenario analyses where AF detection was modelled only for patients with STROKE AF with longer AF episode durations of ≥6 min or of ≥1 hour;
- *by clinical risk factors understood to increase likelihood of AF*: we analysed a subgroup of patients with documented presence of any congestive heart failure, left atrial enlargement, QRS interval >120 ms and/or body mass index >30.[14]

Clinical inputs

AF detection and monitoring

The STROKE AF study provided 3-year follow-up data from which we derived probabilities of detecting AF in ICM and SoC strategies. In the base case, detection rates were derived from the trial data for the duration of follow-up, and thereafter a low constant detection of incident AF was modelled using linear extrapolation, using the average detection rate of 0.46% per 3-month cycle as observed in the STROKE AF trial between years 2 and 3 of follow-up (please see supplemental methods for additional information). The likelihood of undetected AF was approximated through back calculation using STROKE AF detection rates and the sensitivity of the Reveal LINQ ICM (of 99.7%) (online supplemental table S6).[4 15] We assumed that an expert clinician was reviewing the ECG data in the study and as such the diagnostic specificity in both arms was effectively 100%. Additionally, as specificity would not impact the outcomes relevant to this study (ie, clinical outcomes and costs driven by rates of AF diagnosis and therapeutic intervention), any clinician workload/efficiency to assess false positive detections was not considered to be within the scope of this model.

On battery expiration (assumed to be 4.5 years, reflecting the current LINQ II model), or explantation, it was assumed that the ICM would not be replaced and thereafter, detection rates would mirror SoC. The annual probabilities of explantation and likelihood of infection on implant were derived from STROKE AF

data (corresponding to 1.1% and 0.45%, respectively; Medtronic data on file). Various other extrapolation scenarios, inclusive of no detection following the trial period, were explored (online supplemental table S8).

Scenario analyses exploring differing SoC detection rates were also conducted. These rates were based on a simulation study of ICM compared with various STM strategies, including: a one-time 24-hour, 48-hour, 7-day, 21-day or 30-day monitor or a quarterly 24-hour, 48-hour or 7-day monitor.

Modifying risks of IS and bleeding events

The risk of IS was conditional on the following factors:

- *Baseline CHA_2DS_2-VASc score distribution*—patients with higher scores had a higher IS risk than those with lower scores.
- *Age*—risk of IS increased with age.
- *Presence of AF*—patients with AF had a higher IS risk than those without AF.
- *Treatment administered*—patients' IS risks were reduced depending on the treatment received.

The association of baseline CHA_2DS_2-VASc score and IS risk was sourced from a retrospective Swedish study (online supplemental table S9).[16] Risk of IS was thereafter increased progressively with age by a factor of 1.46 per decade.[9] For presence of AF, a published HR from a UK community study was applied to baseline risks of IS to distinguish patients with and without AF (HR=0.662 for AF-free vs AF present).[17]

IS risk reduction and bleed event risk associated with OAC therapy administered after AF detection were modelled based on a meta-analysis by Tawfik *et al*, which were applied to baseline risks (online supplemental tables S10–S15 for detail regarding IS and bleed event risks and treatment effects, respectively).[18] Use of the Tawfik *et al* study represents an update from the previously published CS model, which performed its own indirect comparisons using multiple evidence sources.[9] These previous values were, however, tested in a scenario analysis. The ability of OAC to modify the distribution of IS or intracranial haemorrhage events (categorised as mild, moderate, severe or fatal), was also modelled, based on two cost-effectiveness analyses of OAC therapies (online supplemental tables S12, S13, S16 and S17) for more detail of proportions applied and derived in regards to estimation of severity of IS and bleed events, with the same source informing the likelihood that an extracranial haemorrhage would be a gastrointestinal bleed (online supplemental table S18).[12 13]

Uptake and discontinuation of OAC

OAC uptake after AF detection was assumed to be 100% (under the assumption of full concordance to treatment guidelines) in the base case. Scenario analyses explored the impact of 90% uptake,[9] as well as the 76% uptake value observed in the STROKE AF 36-month follow-up analysis.[4]

Patients experiencing haemorrhagic stroke (HS) while on OAC therapy were conservatively assumed to permanently discontinue OAC and switch to aspirin. Patients who had HS while on aspirin were precluded from ever changing to OAC therapy, even if they were later diagnosed with AF. Patients with HS who may have been unable to take OAC (or patients without HS who had another reason not to take OAC, eg, cost, contraindications, intolerance) and instead received left atrial appendage closure (LAAC) were not included in this analysis. For non-fatal 'other intracranial haemorrhage' or extracranial haemorrhage, a proportion of patients could temporarily discontinue OAC before resuming after 6 weeks, while the remainder permanently discontinued (online supplemental table S19) contains more detail of the percentages discontinuing OAC after a specific event).

Mortality

Age-dependent all-cause mortality statistics were sourced from the Social Security Actuarial Life Table for 2019,[19] excluding cerebrovascular deaths to avoid double-counting. These were sourced separately for males and females, and the percentage of males in the economic model was applied to the statistics to derive a weighted average all-cause mortality risk per age band (online supplemental table S20). All-cause mortality risk was adjusted according to severity of IS experienced (online supplemental table S21) and according to the type of preventive therapy received (aspirin, warfarin or direct oral anticoagulation (DOAC)) using point estimates derived from Tawfik *et al* (online supplemental table S22),[18] with alternative estimates derived from randomised trial subgroup analyses of secondary patients with stroke tested in a scenario analysis, as used in the CS model (online supplemental table S23).[9] Bleed events were associated with a case fatality probability (online supplemental table S24).

Health-related quality of life (HRQoL)

Utilities derived for economic modelling are summarised in table 1 and online supplemental tables S25–S28. Health state utilities were derived using a multiplicative approach to align HRQoL estimates to the age and sex profile of the cohort using a US baseline dataset.[20]

Costs and healthcare resource use

Broadly, the resource use component of the model covered: AF detection costs (for ICM or SoC), stroke prevention therapy costs after AF detection, and costs associated with clinical events such as strokes and bleeds (with sources summarised in table 1 and detailed in the supplemental methods and online supplemental tables S29–S34).

Estimates of ICM and SoC resource use, including surgical procedures required for implantation and explantation, monitoring and device interrogation were based on STROKE AF trial data on file. Unit costs were based on 2022 US Medicare national average payment

Table 1 Summary of key costs and utilities of interventions, events and health states

	Cost mean, US$*	Utility mean	Source for costs	Source for utilities
Stroke events				
Mild IS	$25 092	0.760	Miller *et al* 2016[22]	Gage *et al* 1996[33]
Moderate IS	$29 231	0.390		
Severe IS	$37 555	0.110		
Fatal IS	$37 555	0.000		NA
Mild HS	$27 483	0.757		Gage *et al* 1996[33] with Oxvasc study derived multiplier[34]
Moderate HS	$38 869	0.454		
Severe HS	$50 255	0.336		
Fatal HS	$50 255	0.000		
Other events				
Other intracranial haemorrhage event	$29 259	0.700	Miller *et al* 2016[22]	Oxvasc study[34]
Clinically relevant nonmajor bleed	$1353	−0.181		Sullivan 2006, Sullivan *et al* 2005[35]
Other extracranial haemorrhage/ gastrointestinal bleed	$13 794	−0.181		Sullivan 2006, Sullivan *et al* 2005[35]
Health states before any event				
Starting utility and No-AF	NA	0.774	NA	Derived from Sullivan *et al* 2005[35]
Disutility for presence of AF	NA	−0.014		Oxvasc study[34]
Poststroke health states				
Annual post mild stroke (IS or HS)	$14 733	0.757	Shireman *et al* 2017[23]	Relative difference derived between health states informed by the OxVasc[34] 60-month data applied to Gage *et al* 1996[33] values
Annual post moderate stroke (IS or HS)	$28 068	0.454		
Annual post severe stroke (IS or HS)	$70 165	0.336		
One-time intervention costs				
ICM acquisition and implantation†	$8362	NA	2022 US Medicare national average payment rates.‡,[21]	NA
ICM removal	$559	NA		
Summary of 3-month monitoring costs§				
ICM remote and in-person follow-up	$133	NA	2022 US Medicare national average payment rates.‡,[21]	NA
SoC monitors and follow-up	$108	NA		
Drug costs (annual)				
Aspirin	$615	NA	Optum analysis (data on file, 2018).	NA
DOAC (weighted)	$3214	NA	Medicare Part D spending by Drug 2019–2020.[24]	NA

Full details regarding utility and cost calculations, assumptions and sources are available in the supplemental methods (see online supplemental tables S25–S34) for more details regarding utilities and costs, respectively).
*Where appropriate, costs were inflated to 2025 values using health inflation indices from the Bureau of Labour Statistics medical care index.
†The cost of ICM implant was calculated based on the site of service for real-world ICM implants in 2019–2020 (29.7% in-office vs 70.3% in-hospital; Medtronic data on file); please see online supplemental table S29 for additional detail on ICM-related costs.
‡The analysis took a balanced perspective with respect to funding, with an assumed 60%/40% split between public (Medicare) and private (commercial insurance) funding based on data from 2019 to 2020 ICM patients. Private payer costs were assumed to be 125% that of Medicare.
§The frequency of monitoring in the SoC arm was based on STROKE AF trial data on file and summarised in online supplemental table S30.
AF, atrial fibrillation; CRNM, clinically relevant nonmajor; DOAC, direct oral anticoagulation; HS, haemorrhagic stroke; ICM, insertable cardiac monitor; IS, Ischaemic stroke; SoC, standard of care.

rates, inflated to 2025 values.[21] The cost of LINQ implantation was calculated based on the proportion of patients receiving the ICM in-office (29.7%) versus in-hospital (70.3%) and based on calendar year 2019–2020 LINQ implantation data. Acute care costs of clinical events (eg, treating an IS) and poststroke health state costs originated from published studies.[22 23] Unit costs of stroke prevention medication including aspirin, warfarin and DOACs, were sourced from Medicare and inflated to 2025 values.[24]

The analysis took a balanced perspective with respect to funding, with an assumed 60%/40% split between public (Medicare) and private (commercial insurance) funding based on data from patients receiving a LINQ between 2019 and 2020. Private payer costs were assumed to be 125% of Medicare costs. Where appropriate, unit costs were inflated to reflect 2025 values.

Sensitivity, scenario and subgroup analyses

Sensitivity analyses, including a threshold analysis of the AF episode duration detection threshold, were carried out to explore the impact of uncertainty on the expected cost-effectiveness of ICM. A probabilistic sensitivity analysis was also performed (5000 samples) with suitable statistical distributions applied to model variables.

RESULTS

Base case

The ICM strategy was associated with fewer strokes than SoC. Improved AF detection led to better stroke prevention, equivalent to an additional 53 strokes avoided per 1000 patients in the ICM arm compared with SoC (equivalent to 19 ICM patients to prevent one stroke). This clinical benefit helped to partly offset the higher diagnostic and device costs of ICM, by reducing both acute hospital and permanent health state costs. Associated improvements in HRQoL and survival also produced QALY gains. The incremental cost-effectiveness ratio (ICER) of ICM compared with SoC was $38 346 per QALY gained. Relative to various STM strategies, the ICER for ICM ranged between $29 814 and $38 941 per QALY, with the ICER versus typical 7-day Holter strategy estimated at $35 292 per QALY (table 2 and online supplemental table S35). This falls below the lowest of the ICER willingness-to-pay threshold of $50 000 per QALY, indicating the intervention is considered highly cost-effective in the USA.[8]

Sensitivity analyses

One-way sensitivity analysis results suggested that the ICER was most sensitive to the assumed relative efficacy of DOACs, and the cost of ICM implantation. However, ICM remained cost-effective when using upper or lower

Table 2 Base case results per patient for ICM vs SoC, and ICM vs STM (exemplified by a 7-day Holter strategy)

Estimated lifetime average values per patient	Results by strategy			Incremental results	
	SoC	STM	ICM	ICM vs SoC	ICM vs STM
Clinical and HRQoL outcomes					
Ischaemic strokes	0.482	0.481	0.429	−0.053	−0.052
Detections	0.022	0.027	0.193	0.171	0.166
CRNM bleeds	0.791	0.792	0.843	0.052	0.048
Major bleeding events	0.317	0.317	0.328	0.011	0.010
Life years	9.068	9.073	9.258	0.190	0.173
QALYs	6.562	6.567	6.737	0.176	0.162
Disutility due to non-fatal events	0.045	0.045	0.042	−0.003	−0.003
Cost estimates					
Diagnostic and device costs	$376	$1199	$10 692	$10 316	$9 493
Cost of stroke events	$14 663	$14 618	$13 028	-$1635	-$1590
Cost of bleed events	$6669	$6674	$6871	$202	$197
Combined event costs	$21 332	$21 292	$19 899	−$1433	−$1393
Health state costs	$43 188	$43 118	$41 041	−$2147	−$2077
Total costs	$64 896	$65 610	$71 632	$6736	$6022
Cost-effectiveness estimates for ICM vs comparator					
ICER per life year				$35 386	$32 554
ICER per QALY				$38 346	$35 292
Incremental net monetary benefit (threshold $100 000 per QALY)				$10 830	$11 041

CRNM, clinically relevant non-major; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ICM, insertable cardiac monitor; QALY, quality-adjusted life year; SoC, standard of care; STM, short-term monitoring strategy.

Table 3 Sensitivity analyses and subgroup results

Model parameter	ICERs	
Comparison	**ICM vs SoC**	**ICM vs STM**
Base case	$38 346	$35 292
Subgroups and scenarios		
CHA_2DS_2-VASc score 2 and 3	$162 425*	$56 961*
CHA_2DS_2-VASc score 7	ICM dominates	ICM dominates
'High risk of AF' subgroup†	$22 500	$29 323

Analyses with ranges of inputs						
	Lower input value	**Upper input value**	**ICER Lower**	**ICER Upper**	**ICER Lower**	**ICER Upper**
Threshold of AF duration	>6 min	>1 hour	$43 370	$59 611	$42 043	$56 976
ICM costs (implant, explant)	–30%	+30%	$23 411	$53 652	$20 770	$50 187
OAC uptake‡	76%	90%	$54 925	$44 177	$52 372	$41 234
HR for IS with DOAC vs aspirin	0.200	0.710	$23 887	$82 939	$21 447	$77 911
Cost of ICM device and implantation	$5854	$10 871	$24 064	$52 628	$20 590	$49 995
Health state utilities	–20%	+20%	$48 332	$31 694	$44 483	$29 169

Please see supplemental methods for full range tested within threshold analysis (see online supplemental tables S36–S42).
*Indicates where results are no longer considered cost effective using ICER's highest threshold of $150 000 per QALY.
†Defined as having at least one of: history of left atrial enlargement, congestive heart failure, high body mass index or abnormal QRS duration.
‡STM based on simulated detection findings of 7-day Holter strategy.
AF, atrial fibrillation; DOAC, direct oral anticoagulation; ICER, incremental cost-effectiveness ratio; ICM, insertable cardiac monitor; IS, ischaemic stroke; OAC, oral anticoagulation; SoC, standard of care; STM, short-term monitoring strategy.

estimates of parameter values, as detailed in table 3 and figure 2.

A range of scenarios and subgroup analyses were devised to assess model sensitivity to:

- Subgrouping by CHA_2DS_2-VASc score or 'high risk of AF' (online supplemental table S36).
- Uptake of OAC (online supplemental table S37, supplemental methods).
- Alternative assumptions, evidence sources or modelling methods for key parameters such as detection rates, treatment effect, HRQoL, cost and resource use (online supplemental tables S38–S42, supplemental methods).

Subgroup analyses examining specific categories of baseline stroke risk (as defined by CHA_2DS_2-VASc score) found that the ICER for ICM reduced as the starting risk of stroke increased, with ICM becoming dominant (more effective and less costly) vs SoC in patients with a higher baseline risk of stroke (baseline CHA_2DS_2-VASc scores of 7 or 8), and not cost-effective in patients with a lower baseline risk of stroke (baseline CHA_2DS_2-VASc scores of 2 or 3). Further analyses addressed uncertainty around true baseline risk of IS risk in the model population, by varying baseline IS risk associated with three alternative CHA_2DS_2-VASc scores (scores 2, 5 and 7; noting the STROKE AF median score of 5). These analyses also

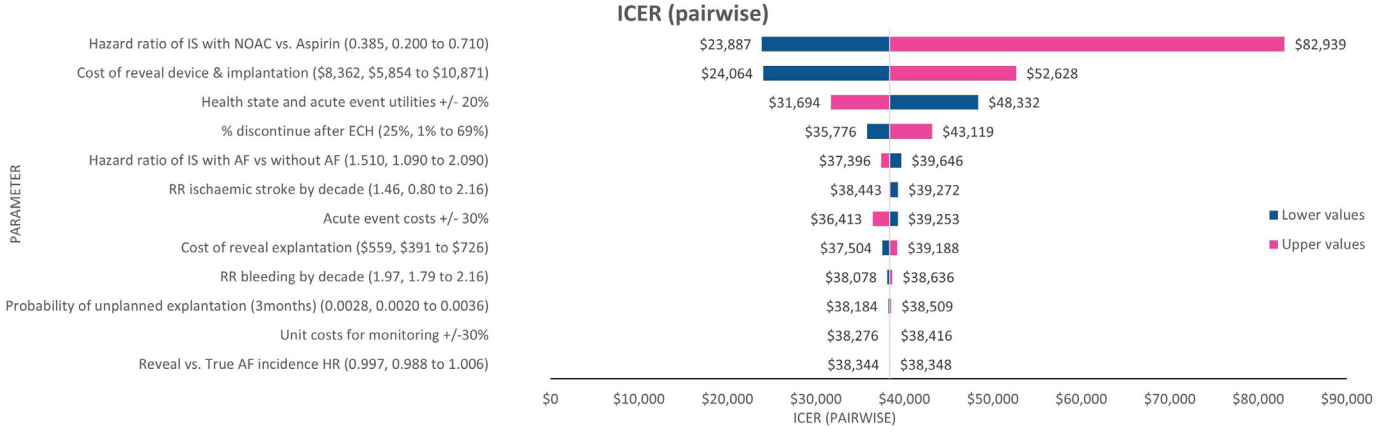

Figure 2 Tornado diagram. AF, atrial fibrillation; ECH, extracranial haemorrhage; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IS, ischaemic stroke; RR, relative risk.

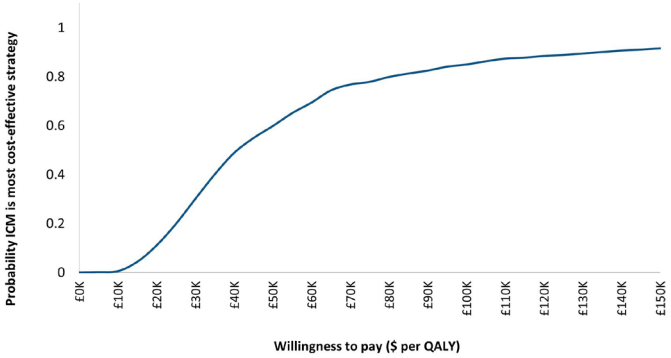

Figure 3 Cost-effectiveness acceptability curve (ICM vs SoC). $K, US dollars in thousands; ICM, insertable cardiac monitor; QALY, quality-adjusted life years; SoC, standard of care.

demonstrated the trend that ICM is expected to become increasingly cost-effective with increased baseline risk of stroke (online supplemental figure S1).

Patients in the 'high risk of AF' subgroup had a more cost-effective ICER than the base-case population. Running the model with data for patients categorised by alternative definitions of AF, namely, episodes of ≥6 min or ≥1 hour, produced ICER values comparable to the base case.

Excepting exploratory scenarios involving very low risk of IS or very poor OAC uptake on diagnosis, all scenarios returned ICERs below a threshold of $100 000 per QALY, with the majority of scenarios resulting in an ICER below $50 000 per QALY.

Probabilistic sensitivity analysis (PSA) reported a mean ICER of $46 910 per QALY over 5000 PSA samples, with ICM being cost-effective compared with SoC in 91%, 85% and 60% of runs at willingness-to-pay thresholds of $150 000, $100 000 and $50 000 per QALY, respectively (see figure 3).

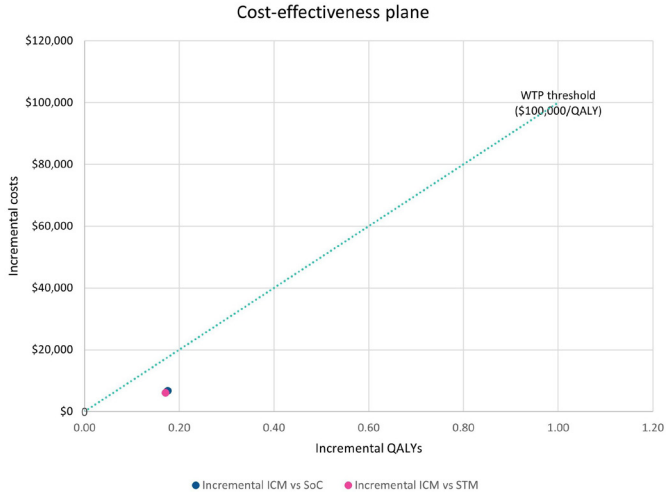

Figure 4 Cost-effectiveness plane. $K, US dollars in thousands; ICM, insertable cardiac monitor; QALY, quality-adjusted life years; SoC, standard of care; STM, short-term monitoring strategy; WTP, willingness-to-pay.

Visual representation of the cost-effectiveness plane (figure 4) indicated that the ICM strategy was cost-effective versus SoC and versus STM, with the ICER of both comparison falling below the willingness-to-pay threshold of $100 000 per QALY.

DISCUSSION

Main findings

Overall, the model demonstrated the cost-effectiveness of ICM as a method of detecting AF in patients with stroke attributed to LAD/SVD, given a willingness-to-pay threshold of $50 000 to $150 000 in the USA. With a few exceptions involving either high ICM cost, low OAC uptake/efficacy or very low baseline stroke risk, the ICER was robust to sensitivity tests.

Comparison to previous analyses

The results of our analysis are specific to the US perspective, although similar cost-effectiveness has been demonstrated for ICM in other healthcare settings.[5–7] Our findings were similar to those in other cost-effectiveness evaluations of ICM in suspected AF or CS populations.[6 9 25] The base-case ICER, although marginally higher than in other evaluations, remains below $50 000 per QALY and considered a high-value, cost-effective intervention.[8] The model structure was based on a previous model for a CS population, but with some key differences around evidence sources and implementation. These differences, notably in baseline risk stratification and HRQoL modelling, as well as a lower average rate of AF detection, may have caused the slightly higher ICER ($38 346) compared with the CS study ($31 345).[9]

LIMITATIONS

Compilation of evidence sources from diverse sources to build the model involves necessary compromises. The key limitations in this model were:

The underlying (untreated) rate of secondary ischaemic stroke and the risk reduction with DOACs, in the poststroke subclinical AF population specifically, is uncertain.

Recent trials have provided some insights regarding the untreated rate of secondary IS and risk reduction with DOACs in the poststroke subclinical AF population; however, to date the evidence remains inconclusive. The Post-Embolic Rhythm Detection with Implantable versus External Monitoring (PER DIEM) trial[26] found numerically fewer recurrent strokes in patients with IS monitored with ICM compared with external loop recorder; however, the study was underpowered to compare this outcome. The Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS) trial,[27] conducted in a CS population, compared DOAC therapy to ICM-monitored aspirin therapy, which switched to DOAC on AF detection. Although a difference in the primary outcome of new ischaemic lesions was not found, the

study was underpowered for detecting differences in recurrent stroke rate. In the Apixaban for the Reduction of Thrombo-embolism in Patients with Device-detected Sub-clinical Atrial Fibrillation (ARTESiA) trial, the DOAC apixaban reduced stroke or systemic embolism by 37% compared with aspirin in a population with subclinical AF and CHA_2DS_2-VASc score of 3 or higher, but increased the risk of major bleeding 1.8 times.[28] A prespecified subgroup analysis of patients with ARTESIA with a history of IS or TIA showed that this cohort had a high risk of recurrent stroke or systemic embolism (3.1% per year in the aspirin group), and seemed to derive overall benefit from DOAC (1.2% per year) despite an increase in major bleeding events (1.2% and 2.3% per year, respectively).[29] However, the ARTESIA cohort consisted mainly of patients with underlying cardiac conditions requiring a pacemaker or a defibrillator. A second subgroup analysis of this trial, only including patients with ICM (n=209), half of whom had a history of stroke/TIA, did show a lower rate of stroke/systemic embolism when treated with DOAC (annual rate of 0.3% vs 2.6% with aspirin).[30]

Post-Embolic Rhythm Detection With Implantable Versus External Monitoring

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The recent studies demonstrate a potential benefit of DOACs for secondary stroke prevention in the poststroke subclinical patient population with device-detected AF, although more research is needed. This analysis attempts to account for uncertainty around the reduction in risk of stroke with DOACs by varying the HR for IS with DOAC vs aspirin in one-way sensitivity analysis (HR 0.39, 95% CI 0.20 to 0.71). While this is the most influential parameter in the model, variation using the CIs results in cost-effective ICERs given a willingness-to-pay threshold of $150 000 in the USA.

No modelling of 'DOAC failures' which may increase stroke risk—recurrent IS in patients with known AF and already prescribed DOAC (so-called 'DOAC failures')—is an ongoing clinical conundrum.[31] Reasons for 'DOAC failures' include non-compliance, untreated SVD or LAD, malignancy, severe atrial disease 'atriopathy' with high AF burden, or pharmacogenomic dysfunction of DOAC absorption, metabolism or clearance.[31] Nuanced evaluation of 'DOAC failures' was beyond the scope of this study but represents a real-world limitation seen clinically at the bedside.

No lifelong modelling of comorbidities which may increase stroke risk—comorbidities such as hypertension, diabetes, and others listed within the CHA_2DS_2-VASc score were only considered at baseline and did not evolve over time.

No modelling of thromboembolic events besides stroke—anticoagulation therapy would probably mitigate these events, some of which are fairly common in the modelled population, thus potentially further decreasing the ICER.

Limit of up to two potential stroke events—the analysis models the risk of up to two recurrent stroke events (either IS or HS), due to the lack of empirical data on the risk and severity of potential subsequent (ie, third) recurrent events. This is a conservative assumption as additional recurrent events could theoretically be prevented with OAC therapy.

The uptake of OAC following AF detection is uncertain—assuming all patients initiate OAC treatment on AF detection per clinical guidance[1 2] may be optimistic. It is acknowledged that in clinical practice, OAC treatment uptake following AF detection is likely to be lower given refusal for treatment, contraindications, follow-up deviations and bleeding complications. However, sensitivity analysis showed even when uptake was halved, expected ICERs were below $100 000 per QALY threshold (online supplemental table S37 and figure S2).

AF detection rates beyond 3 years—there is uncertainty around the rate of AF detection after the duration of the STROKE AF trial follow-up (3 years) through the battery life of currently available ICMs (4.5 years). To estimate the detection rate in long-term follow-up, this analysis linearly extrapolated the AF detection rate observed towards the end of the trial follow-up period (during years 2–3), which was a lower rate compared to the initial several months of the trial. Additionally, the previously published analysis using the model engine used a similar approach, and found that results were robust even when reducing the extrapolated AF detection rate by 50%.[9]

Stroke risk modelling not fully aligned with trial population—after stratifying the cohort's underlying stroke risk at baseline, the risk of each stratum was only modified by an age coefficient (plus the main factors associated with AF and anticoagulation). The CHA_2DS_2-VASc risk score is a more nuanced predictor of stroke risk, which could

potentially have been implemented as a continuously changing set of parameters in the model. However, this would have involved highly detailed observations about each score component, which were not collected regularly in STROKE AF. Given the age and generally high stroke risk of the model cohort, we considered that this method would, on balance, not have yielded a more accurate ICER.

HS leading to permanent discontinuation of OACs—recent research contradicts this assumption, finding that a proportion of patients with post-HS may resume OAC.[32] Although sensitivity analyses suggest the impact of this parameter is probably low due to relative infrequency of OAC resumption, future models may improve accuracy by accounting for it.

HS or other DOAC contraindication leading to implantation of LAAC device—many patients with AF cannot receive OAC due to cost, side effects, bleeding/coagulopathy, thrombocytopenia, chemotherapy, cerebral amyloid angiopathy, advanced age, fall risk or hazardous employment; this population who may have received LAAC instead of OAC was not included in the analysis. LAAC implantation rates were unknown in this study and LAAC may not have been available at all participating sites. Similarly, catheter ablation is an alternative treatment option to OAC following AF detection. As uptake of catheter ablation was not captured in this study, this too was excluded in the analysis.

CONCLUSIONS

This economic evaluation suggests that, in the US setting, ICM monitoring to detect AF in people who have had an IS attributed to LAD or SVD is likely to be a highly cost-effective strategy. This finding is predominantly driven by the appropriate stroke prevention treatment that follows timely detection of AF. When compared with SoC or STM, an ICM strategy for the detection of AF is expected to reduce the number of ISs and therefore increase average life expectancy and quality of life, while also reducing downstream healthcare costs. This conclusion was robust to several sensitivity analyses whereby key parameter values were changed within their plausible range. However, further research is needed to understand the efficacy of secondary stroke prevention treatments in patients with stroke attributed to LAD or SVD who have ICM-detected subclinical AF.

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Acknowledgements Erika Pouliot (Medtronic, Mounds View, NJ, USA) greatly enriched the manuscript with her clinical insights and input. Cori Blauer-Peterson provided technical review and completed the CHEERS checklist. Jana Tillotson provided meticulous editorial assistance. Joe Whitaker (Novo Nordisk) provided guidance in conceptual development and research support. Laura Sawyer (Symmetron Limited, London, UK) generously shared her extensive scientific knowledge in cardiac health and technical expertise in health economic modelling. Sophie Degraeve (Symmetron Limited, London, UK) provided invaluable support in managing author correspondence, communications and manuscript preparation.

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Funding The STROKE AF trial and this cost-effectiveness analysis were funded by Medtronic. As the sponsor, Medtronic personnel were involved in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review and approval of the paper and decision to submit the paper for publication.

Competing interests MRR: consultant to Medtronic. LS: STROKE AF co-PI and consultant to Medtronic, Genentech. KKW: Consultant to Medtronic, Cardiac Dimensions, Abbott, Bayer, Microport, Finapres Medical. SY: none. DZR: Consultant/speaker for Medtronic, Atricure, Boston Scientific, Chiesi and Viz. RAB: STROKE AF co-PI and consultant to Medtronic. VP, SC and JC: employees/former employees of Symmetron Limited. SCR, PDZ, KN and NCF: employees of Medtronic.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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