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Cost-effectiveness of insertable cardiac monitors for diagnosis of atrial fibrillation in cryptogenic stroke in Australia

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Abstract

Introduction: Detection of atrial fibrillation (AF) is required to initiate oral anticoagulation (OAC) after cryptogenic stroke (CS). However, paroxysmal AF can be difficult to diagnose with short term cardiac monitoring. Taking an Australian payer perspective, we evaluated whether long-term continuous monitoring for 3 years with an insertable cardiac monitor (ICM) is cost-effective for preventing recurrent stroke in patients with CS.

Methods: A lifetime Markov model was developed to simulate the follow-up of patients, comparing long-term continuous monitoring with an ICM to monitoring by conventional care. We used a linked evidence approach to estimate the rates of recurrent stroke when AF detection leads to initiation of OAC, as detected using ICM during the lifetime of the device or as detected using usual care. All diagnostic and patient management costs were modeled. Other model inputs were determined by literature review. Probabilistic sensitivity analysis (PSA) was undertaken to explore the effect of parameter uncertainty according to $CHADS_2$ score and OAC treatment effect.

Results: In the base-case analysis, the model predicted an incremental cost-effectiveness ratio (ICER) of A$29 570 per quality-adjusted life year (QALY). Among $CHADS_2$ subgroups analyses, the ICER ranged from A$26 342/QALY ($CHADS_2 = 6$) to A$42 967/QALY ($CHADS_2 = 2$). PSA suggested that the probabilities of ICM strategy being cost-effective were 53.4% and 78.7%, at thresholds of $30 000 (highly cost-effective) and $50 000 per QALY (cost-effective), respectively.

Conclusions: Long-term continuous monitoring with an ICM is a cost-effective intervention to prevent recurrent stroke in patients following CS in the Australian context.

KEYWORDS

atrial fibrillation, cost-effectiveness, cryptogenic stroke, insertable cardiac monitor, oral anticoagulation

1 | INTRODUCTION

Ischaemic stroke is a major cause of prolonged disability in adults with a significant societal cost burden.[1] About 30% of stroke survivors in Australia are of working age, and 65% require assistance with daily living activities.[1] Poststroke care costs about $5 billion each year in Australia.[1] Stroke survivors are also at high risk of suffering additional strokes. Among risk reducing strategies, antithrombotic therapy plays a crucial role. The choice of agent, whether an antiplatelet or oral anticoagulation (OAC), relies on the presumed stroke etiology at the time of occurrence. However, in 25%–40% of cases, the underlying cause of ischemic stroke remains undetermined, despite multiple investigations.[2–8]

Between 15% and 38% of patients with ischaemic stroke will have atrial fibrillation (AF), a common cardiac arrhythmia which confers a fivefold to sixfold increased risk of a subsequent ischaemic stroke.[9–14] The true proportion of AF may be even higher because of difficulties in detecting asymptomatic and intermittent forms of AF. Identifying patients with underlying AF is important because these patients should be treated with OAC therapy rather than antiplatelet therapy, which is not recommended in the prevention of AF-related stroke due to inferior risk reduction.[15]

Several short-, middle-, and long-term monitoring strategies exist for detection of AF in stroke patients.[16] Due to the difficulty in detecting asymptomatic and intermittent AF by conventional tests such as telemetry and 24-hour ambulatory Holter monitoring[10,17–21] and compliance issues of longer external monitorig, long-term continuous monitoring with insertable cardiac monitors (ICMs), also known as implantable loop recorders, is proposed to optimize detection of AF and consequently improve secondary stroke prevention and patient outcomes.

A randomized, controlled study of 441 patients with stroke of unknown etiology after a standardized work up (cryptogenic stroke [CS]) was performed to assess whether long-term monitoring with an ICM is more effective than standard of care (SoC) follow-up for detecting AF. In this study, the ICM detected a near ninefold increase in AF compared to the control arm. Real-world data additionally confirm that ICM similarly detect high rates of AF in patients with CS.[21] The objective of this study was to evaluate whether long-term continuous monitoring with ICMs is cost-effective for preventing recurrent stroke in patients with CS, from an Australian payer perspective, compared to the current Australian SoC.

2 | METHODS

2.1 | Model overview

A lifetime Markov model was developed to estimate quality-adjusted life years (QALYs) and costs from an Australian healthcare perspective, discounted at 5% annually.[19] The model compared a cohort of patients with recent CS, monitored with an ICM or SoC as reported in the CRYSTAL AF trial.[22] A lifetime horizon was used to ensure that mortality benefits arising from ICM-associated secondary stroke prevention were fully represented in the cost-effectiveness results. It also allowed evaluation of the costs and quality of life (QoL) impacts associated with permanent disability and dependency associated with stroke. Outcomes were assessed in the model every 3 months corresponding to the visit schedule in the CRYSTAL AF trial. The CRYSTAL AF study has 3 years of follow-up corresponding to the ICM battery life. In the model, we assumed single use of an ICM with monitoring for AF for 3 years after insertion. Once the ICM battery was depleted, any patients not already diagnosed with AF were transitioned to SoC monitoring.

The employed model was similar to that used by Diamantopoulos et al to examine the long-term cost-effectiveness of ICMs from a UK National Health Service perspective.[23] Many elements of the UK model such as concepts, fundamental modeling approach, and health state definitions were adapted by the current Australian model. The model was specifically redesigned to meet the requirements of the Australian Medical Services Advisory Committee (MSAC) evaluation process. Data inputs such as healthcare resource costs were modified for the Australian setting. Sensitivity analyses were undertaken to explore the effect of parameter uncertainty on the results of the economic model.

2.2 | Model structure

The cost-effectiveness of ICM was determined by its ability to accurately detect AF and the effect of appropriate treatment decisions on health outcomes. We modeled the diagnosis of AF, events related to AF, and treatment selection (Figure 1). The model also considered possible QoL and cost implications of adverse events such as bleeding caused by OAC therapy. The model assumed that all OACs used were direct oral anticoagulants (DOACs).

In each cycle, the cohort faced a probability of having AF detected or developing it without detection. If AF was detected, patients received OAC therapy. If AF remained undetected, patients received aspirin. Stroke recurrence and bleeding risks were based on the cohort's cere brovascular risk and the efficacy and safety of the treatments received. Patients experiencing a new stroke, either ischaemic or haemorrhagic, entered a poststroke health state, and they were assumed to remain there and face no further stroke or bleeding risks (Figure 1). Nonfatal bleeding events were associated with temporary consequences of cost and disutility. Some of those with intracranial hemorrhage and major bleeds became ineligible for further OAC therapy due to their assumed high bleeding risks.

2.3 | Input parameters

Event probabilities used in the model are given in Table 1. The risk of ischaemic stroke recurrence is dependent on whether

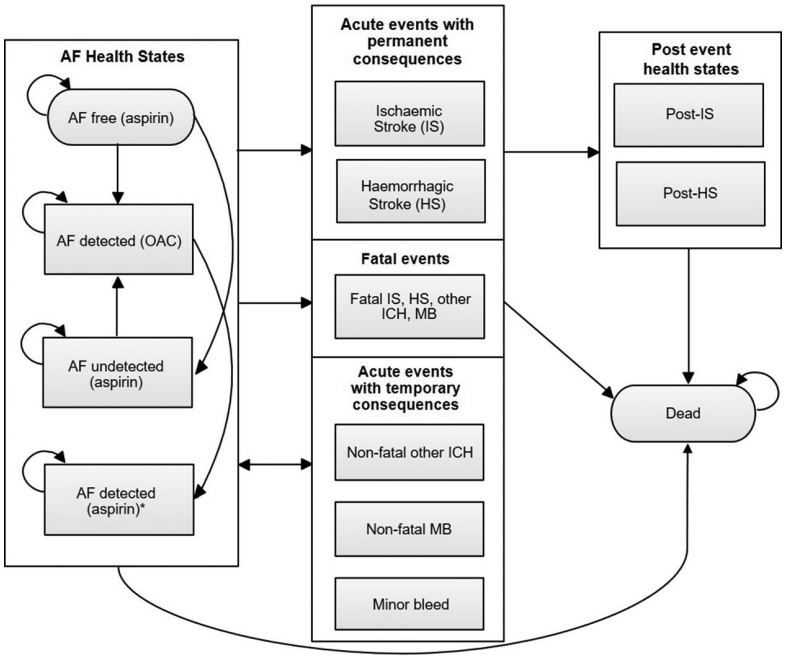

FIGURE 1 Model schematic of the current economic model. AF, atrial fibrillation; HS, hemorrhagic stroke; ICH, intracranial hemorrhage; IS, ischemic stroke; MB, major bleed; OAC, oral anticoagulant

TABLE 1 Event risks employed in the economic model

Events	AF free treated with aspirin	AF undetected treated with aspirin	AF detected treated with warfarin	AF detected treated with DOAC	Case fatality
Ischaemic stroke	HR 0.662[36]	0.0785	HR 0.38 (indirect comparison)[31,37]	OR 1.03 (vs warfarin)[28]	0.222 (pooled estimate)[23]
Hemorrhagic stroke	Assumed equal to AF undetected, treated with aspirin	HR 0.46 (indirect comparison)[31,37]	0.0071	OR 0.47[28]	0.372 (pooled estimate)[23]
Bleeds					
ICH (non-HS)	Assumed equal to AF undetected, treated with aspirin	HR 0.46 (indirect comparison)[31,37]	0.0048	OR 0.47[28]	0.13 (pooled estimate)[23]
Other major bleeding	Assumed equal to AF undetected, treated with aspirin	HR 1.04 (indirect comparison)[31,37]	0.0266	OR 1.22[28]	0.02 (pooled estimate)[23]
Minor bleeding	Assumed equal to AF undetected, treated with aspirin	HR 0.870 (vs DOAC)[23]	0.1012	HR 0.847[37]	0.00 (assumption)

Note: AF, atrial fibrillation; DOAC, non vitamin-K antagonist oral anticoagulants; HR, hazard ratio; HS, hemorrhagic stroke; ICH, intracranial bleed; OR, odds ratio.

the patient experienced AF and the choice of treatments administered. The reference risk was represented by the $CHADS_2$-based stroke risk for patients treated with aspirin, and effects of the administered treatments were based on DOAC randomized controlled trials.[24–29] Bleeding risks were also affected by the choice of treatment.[28,30–32] Published DOAC randomized controlled trials were used to inform the reference risks and treatment effects. Event-related QoL decrements were informed by a published regression model[33] and other published estimates.[23,34,35]

2.3.1 | Incidence and detection of AF

The baseline prevalence of AF was estimated to be 8.3%, and a constant probability of 2.6% per 3 months was applied to model the development of new AF in the patient cohort. These values were based on the rate of detection by ICM in the CRYSTAL AF study adjusted by an ICM sensitivity of 96.1%.[38] The model therefore assumed that 96.1% of these AF cases were detected with ICM. The sensitivity of the SoC strategy was assumed to be 9.6%, also informed by the CRYSTAL AF study.

2.3.2 | Ischaemic stroke risk

The risk of ischemic stroke in the model depends on AF status, virtual $CHADS_2$ score,[1] and treatment administered. The term "virtual" is used because the presence of AF must be confirmed to assign a $CHADS_2$ score to a patient; that is, every patient in the model is assigned a hypothetical $CHADS_2$ score assuming they are associated with AF, and for patients without AF their stroke risk is adjusted downwards for the absence of AF.[26,36,39] As performed in the UK model, relative efficacies of the treatment administered were synthesized from published evidence.[25,27–29,31,32,37] The choice of treatment was assumed to have no impacts on the severity of secondary stroke experienced.

2.3.3 | Bleeding risk

Bleeding risks included in the model depend entirely upon the treatment the patient received (aspirin or DOACs). The reference risk for estimation of bleeding risks is informed by the pooled data from randomized clinical trials of DOACs and warfarin.[24,25,27,28,30–32]

2.3.4 | All-cause mortality

Age-specific all-cause mortality in the model was based on Australian life tables (Australian Bureau of Statistics, Life table 3302.0.55.001). Mortality rates were adjusted to prevent double counting cerebrovascular events, some of which were captured in the model. Adjustment was also made to account for the elevated mortality risk of patients with a prior history of stroke.[23] The model captured case fatalities associated with stroke recurrence and bleeding events.

2.3.5 | Resource use and costs

In relation to the provision of ICM, costs included ICM implantation, follow-up every 6 months, and explantation at 3 years. The current SoC was assumed to consist of periodical follow-up investigations involving doctor consultation plus electrocardiogram (ECG) and/or Holter monitor. The frequency of these investigations was informed by the CRYSTAL AF study. The cost of OAC therapy to the Australian payer was based on the current Australian Pharmaceutical Benefits Scheme (PBS) price for DOACs, with assumptions made to account for price arrangements between the Australian Government and manufacturers. The impact of the full PBS price was also explored in a sensitivity analysis.[2] The costs of treatment of clinical events were estimated based on data from Australian observational studies[39–41] or published hospitalization costs.[42] Costs are in Australian dollars and based on 2016 prices (Table 2). Any unplanned ICM explantations due to adverse events were modeled based on the rates observed in CRYSTAL AF. Upon explantation, patients incurred the cost of the explant procedure and were assumed to subsequently receive SoC monitoring for AF.

2.3.6 | Utility inputs

The QoL decrements associated with clinical event (ischaemic stroke, haemorrhagic stroke, other intracranial hemorrhage, major bleeding, and minor bleeding) reflected in QALY calculations were based on published evidence.[23,33–35] Ischaemic stroke and haemorrhagic stroke caused permanent impacts, whi le events were associated with temporary impacts (assumed 3 months, 2 weeks, and

TABLE 2 Cost inputs for interventions employed in the economic model

Intervention	Cost (AUD$)
ICM-related services	
Implantation, total	$4204.61[a]
Follow-up, total per episode	$77.75[b]
Explantation, total	$285.46[c]
AF investigation under SoC	
Between 0 and 6 months, 3 monthly	$22.24[d]
After 6 months, 3 monthly	$11.38[e]
Aspirin and OAC	
Aspirin	$45.93[f]
Oral anticoagulation	$675.38[g]

Note: AF, atrial fibrillation; GP, General Practitioner; ICM, insertable cardiac monitor; MBS, Medicare Benefit Schedule; OAC, oral anticoagulant; PBS, Pharmaceutical Benefits Scheme; SoC, standard of care.

[a]ICM device benefits (Part C of the Prosthesis List) and relevant MBS benefits and consumables.

[b]Relevant MBS benefits. Assumed to occur every 6 months. Also applied upon AF detection.

[c]Relevant MBS benefits and consumables.

[d]Mean costs per patient. Investigation frequencies as per CRYSTAL AF.

[e]Mean costs per patient. Investigation frequencies as per CRYSTAL AF.

[f]Based on PBS item 1010E (300 mg per day).

[g]Including GP consultations for script renewal. Price arrangements between the Australian Government and manufacturers are commonly known in Australia; this analysis assumed 40% reduction vs PBS price based.

TABLE 3 Cost and utility inputs for clinical events employed in the economic model

Clinical event	Cost (AUD$)	Utility
Baseline	—	0.774[34,a]
Ischaemic stroke		
Acute impact	$39 986 per episode in first 12 months[40]	−0.075 per episode (regression analysis)[33, b]
Long-term impact	$1647 per annum after first 12 months[43,44]	−0.068, ongoing (regression analysis)[33]
Death	$16 624 per death[42]	
Hemorrhagic stroke		
Acute impact	$45 189 per annum in first 12 months[40]	−0.075 per episode (regression analysis)[33]
Long-term impact	$1647 per annum (assumed equal to ischaemic stroke)	−0.068, ongoing (regression analysis)[33]
Death	$16 624 per death (assumed equal to ischemic stroke)	
Other intracranial hemorrhage	$12 967 per episode or $4126 if fatal[42]	−0.038 per episode (the acute decrement of stroke, as above, but assumed to persist for 3 months)[33]
Major bleeding	$5351 per episode	−0.0058 per episode[23]
Minor bleeding	$3259 per episode	−0.00032 per episode[23]

[a]Baseline EQ-5D.
[b]Assumed to persist for 6 months.

2 days for other intracranial hemorrhage, major bleeding, and minor bleeding, respectively) (Table 3).

2.4 | Analytical methods

The cost-effectiveness of ICM compared to SoC was estimated with the incremental cost-effectiveness ratio (ICER) over the cohort's lifetime. The ICER is expressed as incremental costs per QALY gain. A Markov cohort analysis, based on CRYSTAL-AF patients' characteristics, was performed to produce base case results. Patients with AF were switched to DOAC therapy. A series of univariate deterministic sensitivity analyses were conducted on the base case by altering data inputs for key variables. Probabilistic sensitivity analysis (PSA) was also performed, fitting distributions to model variables relating to the risks of ischaemic stroke recurrence (function of the underlying reference risks and efficacy of administered treatments; Table S1). These variables were selected because the recurrence risk was considered the key determinant of ICM's cost-effectiveness. Specification of parameter distributions for the relevant model variables was as per Diamantopoulos et al[23] All calculations were performed using TreeAge Pro software (Williamstown, MA, USA).

3 | RESULTS

3.1 | Base-case analysis

The overall costs and outcomes, and incremental costs and outcomes for the ICM and SoC arms, from the base case deterministic analysis, are shown in Table 4. Lifetime cumulative incidence of ischaemic stroke and bleeding events estimated in the model is given in Table S2. ICM for the detection of AF after CS was cost-effective when compared with SoC with an estimated ICER of AUD$29 570 per QALY gained. Underlying the favorable cost-effectiveness of ICM vs SoC was the reduction in the lifetime risk of ischaemic stroke recurrence in the ICM arm (40.1%) compared to that in the SoC arm (45.3%).

3.2 | Sensitivity analyses

The univariate deterministic sensitivity analyses suggested that the base case results were robust, generally insensitive to changes made to costs of strokes, bleeds drugs, disutility values, rate of AF, and risks of stroke with AF (see Table S1). Among CHADS2 subgroups analyses, the ICER ranged from A$26 342/QALY ($CHADS_2 = 6$) to A$42 967/QALY ($CHADS_2 = 2$). Cost-effectiveness acceptability curve derived from 5000 iterations suggested that the probabilities that the ICM strategy would be cost-effective under thresholds of A$30 000 (highly cost-effective) in 53.4% of the scenarios and A$50 000 per QALY (cost-effective) in 78.7%, of the scenarios (Figure S1).

4 | DISCUSSION

Appropriate targeting of antithrombotic medication is essential for prevention of stroke recurrence. Antiplatelets and OACs are associated with bleeding risks, and generally, anticoagulation has higher risk of major bleeding but has been found superior in preventing

TABLE 4 Total costs and quality-adjusted life years over patient lifetime

	Patient follow-up under SoC	ICM-assisted patient follow-up	Difference
Interventions including follow-up appointments	A$326	A$4927	A$4601
Management of IS recurrence	A$20 888	A$18 465	−A$2423
Management of bleeding events including HS	A$4 174	A$4586	A$412
Cost of stroke prevention (aspirin or OAC)	A$767	A$2222	A$1455
Total cost	A$26 155	A$30 201	A$4046
Effectiveness	7.791	7.9279	0.1368
ICER			A$29 570

Note: All estimates discounted at 5% per annum.

HS, hemorrhagic stroke; ICM, insertable cardiac monitor; ICER; incremental cost-effectiveness ratio; IS, ischemic stroke; OAC, oral anticoagulant; QALY, quality-adjusted life year; SoC, standard of care.

stroke, especially in patients with AF. Thus, anticoagulation should be offered only to patients with diagnosed AF or other factors that warrant it instead of making it available to all patients. This was verified by the NAVIGATE and RE-SPECT Embolic Stroke of Uncertain Source (ESUS) trials, which found that in patients with CS, the DOAC treatment strategy was not superior to aspirin for secondary stroke prevention[45,46] and led to increased bleeding (in the case of rivaroxaban). Identification of AF in patients with a CS is therefore important to target OAC to those who might benefit, while avoiding its use in those without AF, as recommended by the Australian guidelines.[47] Our analysis shows that a diagnostic strategy with an ICM to identify AF in CS patients is cost-effective from an Australian payer's perspective. Using a linked evidence approach, a strategy of anticoagulating patients with demonstrated AF detected by an ICM within 3 years after device insertion had an estimated ICER of A$29 570 which is well within the cost-effectiveness thresholds generally accepted by Australian reimbursement decision makers.[19] Compared to usual care, the ICM strategy was associated with higher initial costs for the device and higher costs of treatment of bleeding (due to a greater number of patients treated with DOACs). While the use of ICM generated a modest additional lifetime cost (AUD$4601), more than half of this was offset by the reduction in stroke-related costs resulting from the reduction in ischaemic stroke recurrence (AUD$2423 saved with ICM strategy; Table 4).

The results of the base case economic model hold true across a range of assumptions in terms of event rates, disutility inputs, and costs as shown in our PSA (Table S1). As the prices of DOACs such as apixaban and dabigatran will decline over time due to generic entries and associated price disclosure requirements, the cost-effectiveness of ICM-guided treatment is likely to improve. The current model is based on device insertion taking place in an inpatient setting, which is not needed with newer generation devices. Additional cost reductions may therefore occur when device implantation moves to the outpatient setting. Our findings are in line with a cost-efficacy model in the UK health care setting where the ICER was £17 175.[23]

Our study has some limitations. We did not include discontinuation rates of anticoagulants in our model, except when severe bleeding had occurred. This was based on high treatment persistence in the CRYSTAL-AF study. In a real-world setting, discontinuation of DOACs may reduce the cost-efficacy of long-term continuous monitoring with an ICM. Secondly, we assumed that there would be a 100% specificity of the diagnostic algorithm of the ICM. This occurs only rarely in our experience, but further diagnostic testing may occur if there is uncertainty about the ICM findings and these costs were not included in our model. For simplicity, patients with stroke enter "poststroke" health states and will not experience any further events (except for death), but they continue to incur QoL loss and additional health care costs. Our model assumes similar benefits of OAC compared to aspirin in patients with AF detected through ICM compared to patients enrolled in the clinical trials of DOACs or warfarin vs aspirin.[28,31,37] Perhaps, higher burdens of AF could be associated with relatively higher risk of thromboembolic events. Nevertheless, studies on device-detected AF have showed that in patients such as the ones under study here, even amounts equal to 5 minutes have been associated to increased stroke risk.[48] In later studies, device-detected AF was a strong predictor of clinical AF progression and had substantial ischemic event risk once it exceeded 24 hours.[49] Guidelines published at the time, and now, do not take into account length of AF to decide on anticoagulation. In the CRYSTAL AF study, almost all patients in whom AF was detected were treated with anticoagulants. Nevertheless, the risk of stroke with device-detected AF may be lower than AF detected through routine testing. Future studies will have to establish the stroke risk with device-detected AF in direct comparison with a similar group of patients with routine detected AF treated in the same fashion.

Although ICMs are generally safe, in rare cases adverse events may occur. Our model includes the cost of device explantation in any patients with unplanned early explants based on the rates observed in the CRYSTAL AF trial. We did not include additional costs

related to particularly complicated adverse events in the economic modeling, yet due to the rarity of such circumstances, we estimate that they would not change the conclusion regarding cost-efficacy of ICMs.

Our model was developed prior to the availability of results from the recently terminated NAVIGATE and RE-SPECT ESUS trials such that the results were not included in the analysis inputs.[45,46] However, these trials showed no efficacy improvement over aspirin, further confirming the management approach explored in our model of investigating AF and treating with DOACs when detected. This is also consistent with the recently updated Australian Stroke Management Guidelines as follows: Strong Recommendation: "Routine use of anticoagulation in patients without cardioembolism (eg AF) following TIA/stroke is not recommended".[47]

The NHFA CSANZ Atrial Fibrillation Guidelines were recently updated for the management of AF.[50] The recommendation stipulates that for patients with ESUS,[3] longer-term ECG monitoring (external or implantable) should be used. The Guideline notes a substantial proportion of AF that occurs beyond 30 days, and there is clear evidence that the longer duration of implantable monitoring is associated with a higher frequency of AF detection. This recommendation further aligns with the long-term clinical and economic benefits of long-term monitoring demonstrated in our economic analysis.

5 | CONCLUSIONS

The analysis presented here shows that long-term continuous monitoring with ICM is a cost-effective intervention to prevent recurrent stroke in patients following CS in the Australian context. These results highlight the importance of detecting underlying AF with regards to determining the appropriate treatment strategy for CS patients.

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CONFLICT OF INTEREST

Vincent Thijs has received modest speaker fees from Medtronic not connected with his work on this analysis; Klaus K. Witte has received modest consulting fees from Medtronic for his work on the economic analysis; this was work was based on but not with regards to this adaptation; Carmel Guarnieri, Koji Makino, and Dominic Tilden are employed by THEMA Consulting that received financial support from Medtronic Australasia to conduct the analysis and prepare the MSAC submission. Marianne Huynh is a Medtronic employee and stakeholder. John Gillespie was a Medtronic employee at the time of this analysis.

ENDNOTES

[1] In determining the reference stroke risks for the modeled cohort, the model reflects the trial population's distribution of different "virtual" $CHADS_2$ scores at baseline, that is, everyone is assumed to have AF to assign a hypothetical $CHADS_2$ score. The mean $CHADS_2$ score in this trial was 2.96 at baseline. The term "virtual" is used because the presence of AF must be confirmed to assign a $CHADS_2$ score to a patient. Also, a prior stroke or TIA allocates 2 points in the $CHADS_2$ scheme; meaning that no patients would have a $CHADS_2$ score <2 in the modeled patient population.

[2] Dispensed price for maximum quantity (DPMQ) was used to explore DOAC cost in the absence of price arrangements.

[3] Comparison of the inclusion and exclusion criteria in the CRYSTAL AF trials in CS and in the NAVIGATE and RE-SPECT trial in ESUS demonstrates that the terms CS and ESUS can be considered substantively interchangeable.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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