Published in final edited form as:

J Cardiovasc Electrophysiol. 2016 November ; 27(11): 1304–1311. doi:10.1111/jce.13090.

Cost Effectiveness of Implantable Cardiac Monitor-Guided Intermittent Anticoagulation for Atrial Fibrillation: An Analysis of the REACT.COM Pilot Study

Daniel A Steinhaus, MD¹, Peter J Zimetbaum, MD¹, Rod S Passman, MD, MSCE², Peter Leong-Sit, MD, MSc³, and Matthew R. Reynolds, MD, MSc⁴

¹Division of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

²Bluhm Cardiovascular Institute, Northwestern University Feinberg School of Medicine, Chicago, IL

³Division of Cardiology, Department of Medicine, University of Western Ontario, London, ON, Canada

⁴Harvard Clinical Research Institute, Boston, MA and Lahey Hospital & Medical Center, Burlington, MA

Abstract

Introduction—Anticoagulation guidelines for patients with atrial fibrillation (AF) disregard AF burden. A strategy of targeted anticoagulation with novel oral anticoagulants (NOACs) based on continuous rhythm assessment with an implantable cardiac monitor (ICM) has recently been explored. We evaluated the potential cost-effectiveness of this strategy versus projected outcomes with continuous anticoagulation.

Methods and Results—We developed a Markov model using data from the Rhythm Evaluation for AntiCoagulation With COntinuous Monitoring (REACT.COM) pilot study (N=59) and prior NOAC trials to calculate the costs and quality-adjusted life years (QALYs) associated with ICM-guided intermittent anticoagulation for AF vs. standard care over a 3-year time horizon. Health state utilities were estimated from the pilot study population using the SF-12. Costs were based on current Medicare reimbursement. Over 14±4 months of follow-up 18 of 59 patients had 35 AF episodes. The ICM-guided strategy resulted in a 94% reduction in anticoagulant use relative to continuous treatment. There were no strokes, 3 (5.1%) TIAs, 2 major bleeding events (on aspirin) and 3 minor bleeding events with the ICM-guided strategy. The projected total 3-year costs were \$12,535 for the ICM-guided strategy vs. \$13,340 for continuous anticoagulation. Projected QALYs were 2.45 for both groups.

Conclusion—Based on a pilot study, a strategy of ICM-guided anticoagulation with NOACs may be cost-saving relative to expected outcomes with continuous anticoagulation, with similar

CORRESPONDING AUTHOR: Matthew R. Reynolds, MD, MSc, matthew.reynolds@hcri.harvard.edu, Address: Harvard Clinical Research Institute, 930 Commonwealth Ave, Boston, MA 02215, Phone: 617-307-5489, Fax: 617-307-5600.

Clinical Trial Registration: clinicaltrials.gov NCT01706146

quality-adjusted survival. This strategy could be attractive from a health economic perspective if shown to be safe and effective in a rigorous clinical trial.

Keywords

atrial fibrillation; anticoagulation; implantable cardiac monitor; cost-effectiveness

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults and is a major cause of stroke. Chronic anticoagulation is recommended for patients with AF and additional stroke risk factors to decrease the likelihood of thromboembolic events.¹ Current treatment recommendations are based on fixed risk factors and do not consider the pattern or burden of AF experienced by the patient. However, recent evidence suggests that the risk of stroke in AF patients is likely to be influenced by AF pattern² and possibly burden.³ Moreover, some patients with a history of AF may have very long arrhythmia-free intervals, either spontaneously or as a result of rhythm control interventions, and may have a low risk of thromboembolism during these times.⁴

Recent advances in cardiac monitoring technology have been developed that allow for continuous rhythm evaluation using implantable cardiac monitors (ICM).⁵ The introduction of novel oral anticoagulants (NOAC) has also allowed for rapid onset of anticoagulation. These two developments have led to the proposal of a strategy of targeted anticoagulation around the time of AF episodes rather than continuous treatment. The feasibility and preliminary clinical outcomes of such an approach were recently evaluated in The Rhythm Evaluation for Anticoagulation with Continuous Monitoring (REACT.COM) pilot study.⁶ The study demonstrated a 94% reduction in the time on anticoagulation compared with chronic anticoagulation with a good safety profile and high rate of compliance.

The potential health economic consequences of an ICM-guided intermittent anticoagulation strategy for AF patients are uncertain. ICM implantation and monitoring would generate costs that could potentially be offset by reduced expenditures on medications and the treatment of bleeding events. To explore the potential health economic value of the ICM-guided strategy, we performed a health economic analysis of the REACT.COM pilot study. We hypothesized that a strategy of ICM-guided anticoagulation would be cost saving relative to continuous anticoagulation in low- to moderate-risk AF patients.

Methods

Methodological Overview

We developed a Markov model to compare the costs and quality-adjusted life years (QALYs) of an ICM-guided intermittent anticoagulant strategy in AF patients to the current standard of continuous anticoagulation. Model inputs were obtained from the REACT.COM pilot study for the ICM-guided strategy⁶ and from published literature for the continuous anticoagulation group.^{7–11} Although the REACT.COM pilot study was conducted using the

Medtronic Reveal XT™ ICM system, the current analysis assumes use of the newer generation Reveal LINQ device.

Study Sample

REACT.COM was a single-arm, prospective, multicenter pilot study to assess reduction in anticoagulation utilizing an ICM-guided strategy for patients with non-valvular, non-permanent AF with CHADS₂ scores of 1 or 2. To be enrolled, patients were required to have no AF episodes lasting ≥ 1 hour for 2 consecutive months immediately prior to enrollment and to have demonstrated tolerance to a novel oral anticoagulant drug for a minimum of 30 days. Most patients had been managed with rhythm control interventions including cardioversion, antiarrhythmic drugs, and/or catheter ablation.

Model Structure

The base case model was a Markov cohort simulation with a cycle length of 1 month. The time horizon of the model was 3 years, the expected battery life of a Medtronic Linq ICM. An annual discount rate of 3% was applied to future costs and benefits.¹² All costs were estimated in 2015 U.S. dollars.

The basic model structure is shown in Figure 1. All patients begin in the “Alive & Well” health state. From this state, in a given month patients could experience any of 6 events: recurrent AF, transient ischemic attack (TIA), stroke, minor bleeding, major bleeding, or death. Following an AF recurrence, subjects remain in the recurrent AF health state for remainder of the 3 years. From this state, the risk of additional AF recurrences was increased, but the risk of other events was unchanged. In the model, minor bleeds were considered one-time events, following which patients returned to their prior health state.

Point estimates for model inputs (transition probabilities, costs, and utilities) are shown in Table 1. Model inputs for ICM-guided therapy were drawn from the pilot study where available, although some event probabilities were assumed as described below. For the continuous anticoagulation strategy, inputs were drawn primarily from the RE-LY^{13,10} and ARISTOTLE^{7,9} trials. We did not include inputs from the ROCKET-AF trial¹¹ as it excluded patients with CHADS₂ scores of <2.

Costs were estimated using national reimbursement values obtained from the Centers for Medicare and Medicaid Services using Current Procedural Terminology (CPT) and Ambulatory Payment Classification (APC) codes, the Medicare Provider Analysis and Review (MedPAR) files where applicable, or from prior literature.^{14–16} The cost of NOACs was assumed to be \$10 per day, which is the approximate retail price for dabigatran.

Key Assumptions

The key assumptions of the model were as follows. Patients with an AF recurrence in the ICM-guided arm resumed their NOAC immediately and continued it for 1 month from resolution of the last AF episode, as per the REACT.COM protocol⁶. Observed AF recurrence rates from the pilot study were applied equally to both model arms. No quality of life (QOL) decrement was assumed for AF recurrences, as the majority of observed episodes

were asymptomatic and resolved spontaneously. Patients with TIA or stroke under the ICM-guided strategy were assumed to be placed on indefinite oral anticoagulation and to discontinue ICM arrhythmia monitoring. Patients with minor bleeds were assumed to continue NOAC and incurred a nominal cost for office evaluation. Patients with major bleeds were assumed to discontinue NOAC, where applicable, for the subsequent 3 months, and then return to their previous health state and resume NOAC as guided by ICM. During that time, they faced the standard risk for stroke of their group.

As no strokes were observed in the pilot study, we used the literature-derived annualized risk of stroke on NOAC for patients with a CHADS₂ score = 1 (0.8%) as the assumed background rate for both treatment strategies.^{9, 10} The literature-derived risk of major bleeding for CHADS₂ score=1 was 2.0% while the observed rate in the pilot study was 3.4% -- primarily due to traumatic events.⁶ It seems unlikely on clinical grounds that the rate of major bleeding with the ICM-guided strategy (under which the exposure to OAC was reduced >90%) would be higher than with continuous OAC therapy. Therefore, for the model base case, the rate of major bleeding for the ICM-guided strategy was made equal to that of standard therapy.

Utility values for patients in the “Alive & Well” state were obtained from the REACT.COM pilot study. In the pilot, patients completed the SF-12 quality of life questionnaire¹⁷ at baseline and at subsequent 6-month intervals. The SF-12 raw item responses were used to calculate SF-6D utility scores.¹⁸ There was no significant difference between the baseline and 6-month SF-6D scores, so the baseline scores were used in the model.

Statistical Analysis

The model was programmed using TreeAge Pro 2014 software (Williamstown, MA). The effectiveness measure was quality-adjusted life years (QALYs), estimated by applying utility weights to each health state in the model. One-way sensitivity analyses were performed for key model inputs across their plausible ranges. Where applicable, the threshold where a variation in an individual parameter was found to alter the preferred strategy (generally, the point at which the ICM strategy was no longer cost-saving relative to standard care) was calculated. Selected 2-way sensitivity analyses were performed using only those variables that were found to have definable threshold effects.

In order to explore the potential tradeoff between an increased risk of stroke in the ICM arm and the cost-savings associated with reduced NOAC usage, we performed an additional sensitivity analysis in which the assumed risk of stroke in the ICM group was increased and the resulting incremental cost-effectiveness ratio (ICER) of standard therapy (which would be more expensive but associated with fewer strokes) compared with ICM was calculated. This analysis allowed us to estimate the stroke risk at which standard therapy would become cost-effective relative to ICM based on a conventional U.S. threshold of \$150,000 per QALY gained.¹⁹

Additionally, probabilistic sensitivity analysis was performed by replacing each model input with a probability distribution. For clinical events in the ICM arm, binomial distributions were used based on observed event rates. Log-normal distributions were used for costs, and

beta distributions were used for literature-based probabilities. Second-order Monte Carlo simulation was then performed, in which each probability distribution was independently resampled over 1,000 model iterations, in order to assess overall model uncertainty.

Results

Clinical Results

The clinical results of the pilot REACT.COM study have been published previously.⁶ The baseline patient characteristics are shown in Table 2. In 14±4 months of follow-up, 18 of 59 patients had 35 AF episodes, of which 60% resolved spontaneously and 63% were asymptomatic. Compliance with ICM monitoring was 98.7% and the protocol resulted in a 94% reduction in anticoagulant use relative to standard continuous treatment. During follow-up (median 461 days), there were no strokes, 3 (5.1%) TIAs (two adjudicated as possible, one as definite), 2 major bleeding events (on aspirin) and 3 minor bleeding events with the ICM-guided strategy.

Base Case Analysis

The up-front cost of ICM insertion was estimated at ~\$6500, including physician fees and the acquisition price for the device (Table 2). Based on current US reimbursement, monthly monitoring costs were estimated at \$58. The model projected total 3-year costs of \$12,535 for the ICM-guided strategy vs. \$13,340 for literature-based expected outcomes with continuous anticoagulation, with an estimated cost savings of \$805 per subject. Projected QALYs were 2.45 for both groups.

Sensitivity Analyses

The model was sensitive to several factors. In one-way sensitivity analysis, the model was found to be sensitive to several cost inputs, including the cost of NOAC therapy, the cost of the ICM device and insertion procedure, and the cost of monthly ICM monitoring (Table 3). The model is also sensitive to the rate of TIA in patients not taking a NOAC. With a rate of TIA 1% per month and greater, a large number of patients would initiate continuous NOAC, and the ICM strategy would no longer be cost saving.

Any increase in the ICM-guided stroke risk above 0.8% per year would result in the ICM strategy being less effective (lower projected QALYs) than standard care. However, even with an assumed stroke risk of 1.6% per year, the ICM guided strategy was still found to be cost saving (data not shown). In this circumstance, it is possible to estimate the ICER of the more costly, more effective strategy (standard care) relative to its alternative (ICM-guided) and to see how the ICER is affected by variation in the assumed stroke rate with ICM. This is depicted in Figure 2, which shows that at stroke rates between ~0.8–1.2% per year in the ICM guided group, the ICER for standard care relative to ICM-guided was >\$150,000 per QALY gained. At ICM guided stroke rates >1.2% per year, the ICER for standard care became more favorable.

Overall model uncertainty as evaluated with probabilistic sensitivity analysis is shown in Figure 3, where incremental costs (on the y-axis) and incremental effectiveness (on the x-

axis) for the ICM guided strategy relative to standard care are plotted for each of 1000 model iterations. With simultaneous sampling of all model inputs from probability distributions, a very high (>99%) proportion of model iterations found the ICM guided strategy to be cost saving over 3 years. Much greater uncertainty was present for effectiveness with incremental QALYs ranging from approximately -0.2 to +0.2. The ICM strategy resulted in a net gain in QALYs in 44% of model iterations.

Discussion

This economic analysis based on the REACT.COM pilot study demonstrates that in patients with AF and low- to moderate stroke risk, an ICM-guided strategy of intermittent anticoagulation is likely to be cost-saving compared with standard continuous anticoagulation with a savings of approximately \$800 per patient over three years. In the base case model, we found that there would be no significant difference in effectiveness (measured in QALYs) between the strategies, although this finding is highly uncertain based on probabilistic sensitivity analysis, reflecting the small clinical experience from which our model inputs were drawn. In sensitivity analyses, we found that the model is sensitive to the assumed rates of ischemic stroke, TIA, and costs of NOAC, ICM implant and monitoring.

Oral anticoagulation is the cornerstone of stroke prevention for patients with atrial fibrillation. For at-risk AF patients, warfarin reduces the risk of stroke by approximately two-thirds²⁰ and is highly cost-effective.²¹ The direct thrombin inhibitor dabigatran and several available oral factor Xa inhibitors have distinct clinical advantages and have also been found to be cost-effective relative to warfarin.^{15, 16, 22}

The prevailing paradigm of anticoagulation in AF patients calls for continuous therapy regardless of the arrhythmia pattern or burden, even in patients who may have very long intervals without arrhythmia.¹ There is considerable uncertainty regarding whether or not a clear temporal relationship between AF episodes and the risk of stroke exists. Several studies have demonstrated temporal dissociation between stroke events and recorded AF episodes in patients with implanted cardiac rhythm devices,^{23–25} but in general involved higher risk patients, in some cases with no prior history of AF, than those enrolled in REACT.COM. If this view of the relationship between arrhythmia episodes and stroke is correct for all AF patients, then anticoagulation should probably never be stopped in the presence of stroke risk factors.

On the other hand, recent studies have not only shown that the risk of stroke may vary according to the pattern or burden of AF,² but also that there may be temporary periods of increased risk following AF episodes.^{26, 27} Further, in some patients with long arrhythmia free intervals, the stroke risk may be very low, and the balance of risk and benefit with anticoagulation may be less favorable.

The recent availability of implantable monitors capable of providing continuous long-term arrhythmia surveillance as well as rapidly-acting NOACs have permitted preliminary exploration of a strategy of intermittent, rhythm-based anticoagulation. The REACT.COM

pilot study suggests that there is considerable patient interest in such a strategy, and that implementation of the approach is feasible.

Our analysis suggests that in addition to being feasible, this strategy could also be economically attractive. However, this conclusion depends on a number of factors that could change in the future. While current assumptions suggest that the cost of the ICM device, its implantation and monitoring would be more than offset by avoiding the cost of continuous anticoagulation – including medication cost and the cost of bleeding events – this would change with a moderate reduction in NOAC prices, as will occur when generic alternatives to currently branded agents become available. It is likely that the price of ICMs would have to fall for the ICM-guided strategy to reduce costs relative to continuous treatment with generic NOACs.

Importantly, the clinical safety and effectiveness of intermittent, ICM-guided anticoagulation has not yet been established. Given the low rate of significant events in the REACT.COM pilot study we are able to assume that clinical outcomes between the two strategies in our model are roughly equivalent, but REACT.COM was a small study with no control group, so this assumption remains untested.

The primary risk of the ICM-guided strategy would be an increase in the rate of TIA or stroke compared with continuous therapy. Our model suggests, if the stroke rate did not change, that the number of TIAs would have to increase dramatically (to a rate of 1% per month) for the ICM strategy to become unattractive since, by definition, TIAs have no long-term clinical consequences. By contrast, any increase in the risk of stroke would make the ICM-guided strategy clinically inferior. Our model suggests that if this increase was small (such as 0.2% per year in absolute terms), then the ICM strategy could still be preferred to continuous therapy on health economic grounds, as the ICER for continuous therapy would be very high. However, we believe that the maximum increase in stroke risk that would be considered acceptable will more likely be determined on clinical grounds.

Our study has important limitations. It is possible that strokes have little temporal relationship with AF episodes even in low-risk patients and that the premise of this clinical strategy is therefore flawed. As mentioned, REACT.COM was a pilot study with a small sample size. In this population with relatively low risk, there were few events over the follow-up period. The generalizability of these economic results is limited to patients similar to those enrolled in REACT.COM and given similar treatment protocols. Additionally, although quality of life was measured in REACT.COM, the lack of a control group prevents us from estimating the potential advantage of the intermittent ICM-guided strategy in terms of patient preference or quality of life. It is possible that avoiding continuous anticoagulant exposure itself would result in a QALY gain that we were not able to measure.

The detection of AF by an ICM may not be 100% accurate or timely. The REACT.COM pilot study used the REVEAL XT device, which has an automated AF detection algorithm based on R-R interval variability and was found to have 98% accuracy for detecting AF in a prior study.²⁸ In the REACT.COM pilot study patients were instructed to provide daily remote transmissions from their ICM; the newer generation Linq ICM has wireless

telemetry. Hence, problems with device data storage or timeliness of episode detection are not expected. The diagnostic accuracy of detecting AF using other cardiac rhythm devices (e.g., pacemakers or ICDs) could differ.

We also did not explicitly consider potential decay in protocol adherence over time, which could potentially alter results. It is noteworthy, however, that protocol adherence in the pilot study was 98.7% over a median of 461 days.⁶ The time horizon of our analysis was limited to 3 years. The viability of this strategy over a longer time horizon, which would necessitate replacement of the original ICM devices, is entirely uncertain. It is possible that higher rates of recurrent AF and the need for ICM replacement and continued monitoring would render this strategy less attractive from a health economic perspective over a longer time frame.

Despite these limitations, this is the only economic analysis of ICM-guided anticoagulation for patients with low- to moderate-risk non-valvular, non-permanent atrial fibrillation. This study provides some useful insights into the potential tradeoffs this approach would present.

Conclusion

In summary, in a health economic model constructed using data from a recently completed pilot study, we found that a strategy of intermittent, ICM-guided oral anticoagulation with NOACs was cost-saving relative to expected outcomes with continuous anticoagulation, with similar effectiveness. These findings are sensitive to assumptions about clinical event rates and the costs of ICMs, ICM monitoring and anticoagulant drugs. The ICM-guided strategy may therefore be financially viable, but its efficacy and safety must be established in a much larger, randomized study before it can be recommended.

Acknowledgments

Funding support was received from NIH R34 HL113404-01 & Medtronic, Inc.

Dr. Reynolds is a consultant to and has received research grant funding (to an affiliated institution) from Medtronic. Dr. Zimetbaum is on the advisory board of the REACT study. Dr. Passman has participated on an advisory board for and received honoraria from Medtronic. Dr. Leong-Sit has participated on a research grant supported by Medtronic. Dr. Steinhaus has a family member who is an employee of Medtronic Inc.

List of abbreviations

AF	Atrial fibrillation
NOAC	Novel oral anticoagulant
ICM	Implantable cardiac monitor
ICER	Incremental cost-effectiveness ratio
QALY	Quality-adjusted life years

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Figure 1.

Model state-transition diagram. Each of the key health states represented in the model is shown. Arrows indicate possible transitions between health states allowed within the model. AF = atrial fibrillation; TIA = transient ischemic attack.

Figure 2.

ICERs for standard care vs. ICM-guided anticoagulation, according to stroke risk in the ICM-guided group. The ICER (in dollars per QALY gained) is plotted on the y-axis across a range of stroke rates in the ICM-guided group. As the stroke risk becomes higher, the ICER for standard care relative to ICM-guided becomes more favorable. The base case assumption is a stroke risk for both strategies of 0.8% per year. ICER = Incremental cost-effectiveness ratio; ICM = Implantable cardiac monitor; QALY = Quality-adjusted life year.

Probabilistic Sensitivity Analysis

Figure 3. Probabilistic sensitivity analysis. Incremental costs (y-axis) and incremental QALYs (x-axis) of ICM-guided therapy vs. standard care are plotted for each of 1000 model iterations in which all model inputs are drawn at random from probability distributions. The oval includes 95% of the data points. ICM = Implantable cardiac monitor; QALY - Quality-adjusted life years.

Table 1
Model Inputs

	Source	Point Estimate	Range
Discount rate	US standard	0.03	0–0.05
PROBABILITIES			
First AF recurrence	Pilot study	15/59 patients first 12 months (18 total) 29 episodes first 12 months (35 total)	
Recurrent AF after first	Pilot study	9/18 patients	
AF resolves spontaneously	Pilot study	21/35 episodes	
AF results in cardioversion	Pilot study	9/35 episodes	
AF results in ablation	Pilot study	2/59 patients	
Events off OAC (no AF)			
TIA	Pilot study	3/59 per yr (5.08%)	
Stroke	Pilot study	0/59 per yr	0.4–1.6%/yr
Minor Bleeding	Pilot study	3/59 per yr (5.08%)	
Major Bleeding	Pilot study	2/59 per yr (3.39%)	
Events on OAC			
TIA	Assumed	0.4%/yr	
Stroke	ARISTOTLE ⁷⁹ , RE-LY ¹³¹⁰	0.8%/yr	0.4–1.6%/yr
Minor Bleeding	ARISOTLE ⁷⁹ , RE-LY ¹³¹⁰	14%/yr	10–20
Major Bleeding	ARISOTLE ⁷⁹ , RE-LY ¹³¹⁰	2%/yr	1.0–4.0
Other Events			
Stroke after TIA (on OAC)	Shah et al. ¹⁶	Risk increases 2.6 fold	
Major bleed = fatal	Held C et al. ⁸	14.9% (~9% for extracranial and ~40% for intracranial at 30 days)	
Stroke = fatal	Shah et al. ¹⁶	8.2%	
Relative risk of death post stroke	Shah et al. ¹⁶ and Slot et al. ²⁹	2.3	
COSTS			
Linq ICM implant	APC 0680 CPT 33282	MD = \$246 Facility - \$6223	±20%
ICM monthly monitoring	CPT 93298 + 93299	\$58	25–90
Oral anticoagulant	Average wholesale price	\$300/month	±20%
Cardioversion	Botkin et al., ¹⁴ CPT 92960	\$525+125	±20%
AF ablation	MedPAR (unpublished)	\$16,500	±20%
Admission: major Bleeding	Freeman et al. ¹⁵	\$5250	
Minor bleeding	Assumption	\$100	
Stroke: acute cost	MedPAR (DRGs 64–66)	\$6261	50–200
Stroke: long-term cost	Shah et al. ¹⁶	\$5400	±20%
TIA: acute cost	MedPAR (DRG 069)	\$2768	±20%

	Source	Point Estimate	Range
UTILITIES			±20%
Alive & Well	Pilot study	0.84	
Post Stroke	Shah et al. ¹⁶	0.57	
Post Major Bleed	Shah et al. ¹⁶	0.8*well	
Post Minor Bleed	assumption	No adjustment	

AF – Atrial fibrillation

APC - Ambulatory Payment Classification

CPT - Current Procedural Terminology

DRG – Diagnosis-Related Group

ICM - Implantable cardiac monitor

MedPAR - Medicare Provider Analysis and Review

OAC – Oral anticoagulant

TIA – Transient ischemic attack

Table 2
REACT.COM Patient Characteristics (N=59)

Age, years	67 ± 7.7
Female, %	25.4
Caucasian, %	93.2
AF Pattern	
Paroxysmal	76.3
Persistent	23.7
Previous catheter ablation, %	69.5
Previous antiarrhythmic drug therapy, %	88.1
Hypertension, %	93.2
Diabetes Mellitus, %	22.0
CHADS ₂ score = 1, %	69.5
CHADS ₂ score = 2, %	30.5
Baseline anticoagulant	
Dabigatran	62.7
Rivaroxaban	27.1
Apixaban	10.2
Heart Failure, %	3.4

AF – Atrial fibrillation

Table 3**Threshold Analyses**

Entries in the middle column represent the value at which the ICM strategy is no longer preferred.

Variable	Threshold
Drug cost (\$/month)	<273
ICM monitoring cost (\$/month)	>84
Cost of ICM + insertion	>7274
Probability of TIA off OAC	>1.0%/month