Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices

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Aims
Atrial tachyarrhythmias (ATs) detected by implanted devices are often atrial fibrillation or flutter (AF) associated with stroke. We hypothesized that introduction and termination of anticoagulation based upon AT monitoring would reduce both stroke and bleeding.

Methods and results
We randomized 2718 patients with dual-chamber and biventricular defibrillators to start and stop anticoagulation based on remote rhythm monitoring vs. usual office-based follow-up with anticoagulation determined by standard clinical criteria. The primary analysis compared the composite endpoint of stroke, systemic embolism, and major bleeding with the two strategies. The trial was stopped after 2 years median follow-up based on futility of finding a difference in primary endpoints between groups. A total of 945 patients (34.8%) developed AT, 264 meeting study anticoagulation criteria. Adjudicated atrial electrograms confirmed AF in 91%; median time to initiate anticoagulation was 3 vs. 54 days in the intervention and control groups, respectively (P < 0.001). Primary events (2.4 vs. 2.3 per 100 patient-years) did not differ between groups (HR 1.06; 95% CI 0.75–1.51; P = 0.732). Major bleeding occurred at 1.6 vs. 1.2 per 100 patient-years (HR 1.39; 95% CI 0.89–2.17; P = 0.145). In patients with AT, thromboembolism rates were 1.0 vs. 1.6 per 100 patient-years (relative risk – 35.3%; 95% CI – 70.8 to 35.3%; P = 0.251). Although AT burden was associated with thromboembolism, there was no temporal relationship between AT and stroke.

Conclusion
In patients with implanted defibrillators, the strategy of early initiation and interruption of anticoagulation based on remotely detected AT did not prevent thromboembolism and bleeding.

Clinical trial registration

Keywords
Atrial fibrillation • Arrhythmia monitoring • Oral anticoagulation • Stroke prevention • Randomized controlled clinical trial
Introduction
Implanted cardiac devices can detect atrial tachyarrhythmias (ATs), permitting correlation of atrial fibrillation or flutter (AF) with stroke risk. Contemporary dual-chamber cardioverter-defibrillator (ICD) and resynchronization (CRT) devices can issue remote AT alerts. It is not known whether starting and stopping anticoagulation based upon such data can prevent stroke, systemic embolism, and major bleeding compared with conventional management. We conducted a randomized trial of a specified anticoagulation protocol guided by continuous remote rhythm monitoring compared with usual office-based care.

Methods
Organization
The Steering Committee designed and governed the trial, analysed the data, and takes responsibility for the manuscript. A Clinical Events Committee adjudicated suspected primary events and deaths, and an independent Data Monitoring Committee (DMC) oversaw participant safety.

Study design
The design has been described. This multicentre, single-blinded, randomized trial of wireless telemetry [Home Monitoring (HM); BIOTRONIK, Lake Oswego, OR, USA] monitored cardiac rhythms in patients with implantable cardioverter-defibrillator (ICD) and resynchronization therapy defibrillator (CRT-D) devices. We hypothesized that prompt intervention would reduce both thromboembolism and haemorrhage compared with conventional therapy by initiating anticoagulation early after AT detection and withdrawing it when AT abated. Control patients received usual care, including device interrogations at routine checks.

Outcomes
The primary analysis compared first occurrence of stroke, systemic embolism, or major bleeding in the two arms. Specified secondary analyses included AT burden in relation to events.

Population
Patients with ICD or CRT-D devices, CHADS2 risk score ≥ 1 and ability to tolerate anticoagulation enrolled at 104 arrhythmia centres in North America, Europe, and Australia. Patients with permanent AF or contraindications to anticoagulation were excluded. The protocol was approved by institutional review boards governing human research, and consenting patients enrolled any time after device implantation.

Treatment
Patients were randomized 1:1 to intervention or control, stratified by CHADS2 category (1 to 2, 3 to 4, 5 to 6) and device type (ICD, CRT-D). The control group received standard follow-up and anticoagulation based on clinical criteria as determined by treating physicians. The intervention group was continuously monitored by remote technology that issued notifications when ATs occurred. The Coordinating Centre recorded data for both groups, and provided safety surveillance for malfunctions, elevated lead impedance, energy depletion, replacement indicators, and ventricular arrhythmias. Both groups were followed as recommended for ICD devices, but access to HM differed: Monitoring was fully enabled in the intervention group, but AT information for controls was obtained by conventional diagnostic methods or device interrogation.

A treatment-blinded committee retrospectively reviewed electrograms obtained when protocol-specified anticoagulation criteria were met plus a random sample of periodic transmissions.

Anticoagulation for the intervention group was based on CHADS2 risk score [1 point each for heart failure or left-ventricular ejection fraction (EF) ≤ 0.35, hypertension, age ≥ 75 years, or diabetes; 2 points for previous thromboembolism]. The duration of AT prompting anticoagulation in patients with scores 5 to 6 (previous thromboembolism) was shorter than for patients with scores 1 to 4 without previous thromboembolism (Figure 1). Anticoagulants initially included only vitamin K antagonists (VKA), but dabigatran, rivaroxaban, or apixaban were allowed once approved for use. Dosing of VKA was adjusted per local protocols [goal International Normalized Ratio (INR) 2.0–3.0]. Time in therapeutic range (TTR) was calculated by linear interpolation for prescribed periods and excluded the first 14 days after starting or restarting therapy, and brief periods of interruption for surgical or medical reasons. Other oral anticoagulants were prescribed as labelled. There were no restrictions on device settings, antithrombotic medication, cardioversion, ablation procedures, or other treatments.

If sinus rhythm resumed in the intervention group, monitoring continued for AT (Figure 1) and anticoagulation was stopped according to CHADS2 score and arrhythmia-free periods, but continued for patients with prior thromboembolism. Recurrent AT prompted resuming anticoagulation unless haemorrhage occurred.

To balance sensitivity for event detection, both groups completed stroke symptom questionnaires every 3 months. Blinded specialists assessed patients with suspected endpoint events, and collected data for blinded adjudication.

Definitions
Diagnosis of ischaemic stroke required rapid onset of focal neurological deficit lasting ≥ 24 h and infarction on brain imaging. Haemorrhagic strokes were confirmed by imaging or autopsy. Systemic embolism required acute arterial occlusion without previous arterial disease, confirmed by angiography. Major bleeding was clinically overt and disabling, fatal, or associated with ≥ 5 g/dL haemoglobin decline, transfusion ≥ 2 units, hospitalization, surgery, or a critical anatomical site.

Statistical analyses
Sample size was based on Fisher’s exact test and estimated event rate 2.8/100 patient-years for stroke, systemic embolism, and major bleeding in the control group. The primary analysis assessed for superiority according to intention-to-treat, with 80% power [type I error (2-sided α) 0.044 for the adjusted P-value]. Detection of 40% reduction required 951 patients per arm; compensation for 10%/year attrition brought enrolment to 2718 patients.

Analyses were as-randomized and per-protocol, based on time to first event using Cox proportional hazards modelling stratified for CHADS2 score and device type. The DMC performed group sequential interim analyses at 25, 50, and 75% of requisite primary events to validate rate assumptions and monitor for benefit, harm, or futility. The Lan-DeMets and O’Brien-Fleming α-spending functions had two-sided symmetrical boundaries.

Categorical variables are summarized as number of observations and proportion of participants and continuous variables as mean, standard deviation, median, and interquartile range. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA), SPSS version 21 (IBM Corp., Armonk, NY, USA), and StatXact version 10 (Cytel, Cambridge, MA, USA). Significance was accepted at the 95% confidence level (two-sided P ≤ 0.05) for the primary composite
Results

Recruitment and follow-up

Between 28 February 2008 and 17 May 2013, we randomized 2718 patients. After 75% of expected primary events had occurred, the DMC determined that the anticoagulation protocol was unlikely to influence the primary outcome, and that endpoint differences between the two groups were unlikely to emerge in further follow-up. The Steering Committee concurred, and closed the study on 12 June 2013 with median patient exposure 701 days, and cumulative follow-up 5430 patient-years.

The mean interval from device implantation to enrolment was 121 days (median 4.0 months; range 1 day–64 months), similar in both groups. In the control and intervention groups, 10.2 and 11.2% of patients, respectively, withdrew before endpoints, death, or termination of the study occurred (Figure 2). There were 15 977 follow-up visits (89.9% of expected); 95.3% of patients completed ≥1 visit, and devices were interrogated an average of nine times. Clinical status was confirmed for 99.6% of active patients at study termination; 8 (0.3%) were lost to follow-up.

Clinical outcomes

The primary event rate did not differ between the intervention and control groups (2.4 vs. 2.3/100 patient-years, respectively; HR 1.06; 95% CI 0.75–1.51; P = 0.732; Figure 3). Of 124 total primary events in the study, 22 were strokes, 41 major bleeds, and none extracranial systemic embolic events in the intervention group. Corresponding events in controls were 30, 29, and 2. Nine patients developed more than one primary event (major bleed after ischaemic stroke in two intervention and three control, ischaemic stroke after major bleed in two intervention and one control, and haemorrhagic stroke after ischaemic stroke in one intervention patient), but data were censored after the first event (Figure 3).

Among those with AT, thromboembolism rates were 1.0 and 1.6/100 patient-years in the intervention and control groups, respectively (relative risk reduction 35.3%; 95% CI 0.70–0.87; P = 0.251; Table 2). Ischaemic stroke occurred at 0.7/100 patient-years among patients with AT in the intervention group, vs. 1.3 in the control group (HR 0.55; 95% CI 0.23–1.34; P = 0.188). Major bleeding rates were 1.6 and 1.2/100 patient-years (HR 1.39; 95% CI 0.89–2.17; P = 0.145). Intracranial haemorrhage rates did not differ across groups (0.1/100 patient-years). All-cause mortality was 10.8% in the intervention group vs. 10.3% in controls (5.4 vs. 5.1/100 patient-years).

Patient characteristics

Randomized patients were typical of individuals managed with ICD (64%) and CRT-D (36%) devices (Table 1). The median age was 64.4 years; 26.3% were women. Most had CHADS2 scores 1–2 at entry (53.3%); 41.9% scores of 3–4 and 4.8% scores of 5–6. Groups were balanced for risk factors (Table 1), estimated CHA2DS2-VASc (median 4) and HAS-BLED (median 3) scores,11,12 8.9% had previous ischaemic stroke or thromboembolism, and 71.5% had ischaemic heart disease. Baseline medications were balanced between groups, with 76% taking aspirin, but more in the intervention group took other platelet inhibitors, mainly clopidogrel (34.5 vs. 30.7%; P = 0.037). Devices were implanted predominantly to treat potentially lethal ventricular arrhythmias (83.1%). The mean EF was 0.30 (range 0.05–0.80); median CHADS2 scores were 2 for patients with ICD and 3 for CRT-D devices.

endpoint. Other P-values and confidence intervals for the study results are reported as unadjusted, nominal values without assignment of statistical significance.
years; \( P = 0.662 \); 38.3\% were classified as cardiovascular, 26.1\% non-cardiovascular, and 35.5\% uncertain, similar for both groups.

The ischaemic stroke or thromboembolism rate for control patients with \( \geq 6 \) min of AT on any day was 1.8/100 patient-years (4.3\% of 281 patients with AT \( \geq 6 \) min), and 3.1/100 patient-years with AT \( \geq 5.5 \) h (7.7\% of 143 patients with AT \( \geq 5.5 \) h; \( P\) trend = 0.173). In the intervention group, 2.8\% of 290 patients with \( \geq 6 \) min and 2.5\% of 161 patients with \( \geq 5.5 \) h of AT developed thromboembolism, 1.1 and 1.0/100 patient-years, respectively (\( P\)-trend = 1.000; interaction \( P = 0.470 \)). Taking both treatment groups together, thromboembolism occurred in 3.1\% of patients with AT, not significantly greater than in those without AT (2.3\%, \( P = 0.202 \)), but incremental risk became significant when the burden of AT was \( > 5.5 \) h (4.9\% of patients with AT vs. 2.2\% of those without, \( P = 0.010 \)). The increased risk was driven mainly by the control group with thromboembolism in 7.7\% of patients with AT \( > 5.5 \) h, as opposed to 2.5\% of intervention patients.

### Atrial tachyarrhythmias

During 2 years mean follow-up, 99.0\% of devices transmitted rhythm information; the proportion of days with transmissions was 83.7\%; >70\% of patients had transmission rates \( \geq 80\% \). One percent of periodic transmissions showed AT, which occurred in 945 patients (34.8\%), 36.3\% in the intervention group and 33.2\% in controls (\( P = 0.09 \)). In the intervention and control groups, 138 and 126 arrhythmias, respectively, qualified for anticoagulation. Electrogram adjudication confirmed 91\% diagnostic accuracy, with 60.5\% atrial fibrillation, 30.0\% atrial flutter (cycle length 255 \( \pm \) 31 ms), and 9.5\% false-positive due to far-field over-sensing (6.3\%) or noise (3.2\%). This compares favourably with data reported with other devices.13

### Anticoagulation

In the control group, 25.2\% of ATs met protocol-specified anticoagulation criteria, but because these patients were randomized to conventional management, physicians were not alerted; 60.0\% of these patients began anticoagulants (mean OAC duration 450 days, 48.4\% of follow-up), mainly for AF identified by clinical criteria including device interrogation. The incidence of AT meeting protocol-specified anticoagulation criteria was similar in the intervention group (25.6\%), and 72.2\% began anticoagulants (mean OAC duration 409 days, 43.1\% of follow-up). In the intervention arm, 45.2\% of 126 eligible patients started within the specified timeframe, 23.0\% followed the start-stop-resume plan, and 27.8\% received no anticoagulation. Although overall compliance with the anticoagulation protocol was suboptimal, in those patients who adhered the time-to-initiation of anticoagulation was substantially abbreviated (median 3 days in the intervention group vs. 54 days in controls, \( P < 0.001 \)).

When considering any indication, more of the intervention (13.4\%, n = 182) than control (11.6\%, n = 158) patients initiated anticoagulants (80.9\% VKA, 10.0\% dabigatran, 8.2\% rivaroxaban, and 0.9\% apixaban), with similar distributions across groups (Figure 4). The TTR during VKA therapy (58.8\%) was similar between groups and 61.2\% in intervention patients during protocol-specified periods.

### Relationship between atrial tachyarrhythmia and thromboembolism

There was no temporal association between AT and clinical events. Of 69 thromboembolic events in both groups combined, 20 (29.0\%) followed AT by 1 to 489 days, and 9 (13.0\%) preceded AT (Figure 5). The remaining 40 (58.0\%) occurred without AT detected during the monitoring period.
Discussion

This is the only randomized trial of continuous device-detected atrial arrhythmia information to guide therapeutic intervention for stroke prevention. In this cohort, the strategy of early anticoagulation for incident AF and withdrawal after arrhythmia-free periods did not improve outcomes compared with conventional management. Continuous monitoring over a long period documented clear temporal dissociation of atrial arrhythmias from ischaemic stroke or thromboembolism.

Rhythm-guided anticoagulation

Our data are consistent with observational studies in which the annualized rate of thromboembolism was about 1.3/100 patient-years. The incidence of thromboembolism correlates with
CHADS2 score. Accelerating initiation and withdrawal of anticoagulation based on rhythm monitoring did not prevent stroke and bleeding better than conventional management. Although the anticoagulation protocol was not optimally applied, the impact of this deficiency upon the outcome of the study is mitigated by the low event rate and lack of temporal relationship between AT and stroke (Figure 5). Nevertheless, there were three embolic events that occurred after withdrawal of anticoagulation for patients with previously identified AT episodes, and this provides further support for the long-term continuation of anticoagulation even when the arrhythmia appears to have subsided (Figure 5). Target-specific oral anticoagulants provide more rapid onset and offset of anticoagulation than vitamin K antagonists. Although these were prescribed infrequently, there is little reason to suspect that greater use would have altered the outcome. Temporal dissociation between AF and stroke suggests that the driving hypothesis was unsound and calls for reconsideration of conventional notions of stroke pathogenesis in the patient population studied (Figure 5).

**Burden and timing of atrial tachyarrhythmia in relation to ischaemic stroke or thromboembolism**

The association of AT burden with stroke risk has varied in previous reports, possibly because of the populations studied. Five minutes of AT correlated with elevated risk of stroke and death in the Mode Selection Trial (MOST). After adjustment for other risk factors, patients in an Italian pacemaker registry with AT >24 h were three times more likely to develop thromboembolism than those with shorter episodes. A daily AT burden of 3.8 h raised risk in the HomeCARE and everesT studies. The TRENDS investigators established an AT threshold of 5.5 h in a 30-day period, while AT lasting ≥6 min in the ASSERT study elevated risk 2.5-fold. In a pooled analysis of 10 016 patients adjusted for stroke risk and anticoagulation, even 1 h of AT doubled the rate of stroke. In our trial of patients with ICDs (85% of whom had no history of atrial fibrillation at baseline), there was a clear relationship between AT burden and stroke risk.

**Table 2** Outcomes by treatment group, atrial tachyarrhythmia, and oral anticoagulation at any time during the study

<table>
<thead>
<tr>
<th></th>
<th>Control group N = 1361</th>
<th>Intervention group N = 1357</th>
<th>Hazard ratio (95% CI)</th>
<th>P C vs. I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint c</td>
<td>61 2.3</td>
<td>63 2.4</td>
<td>1.06 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>AT detected</td>
<td>30 2.9</td>
<td>34 3.0</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>No AT detected</td>
<td>31 1.9</td>
<td>29 2.0</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>OAC started</td>
<td>24 6.4</td>
<td>32 7.6</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>No OAC started</td>
<td>37 1.6</td>
<td>31 1.4</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>Thromboembolism d</td>
<td>37 1.4</td>
<td>32 1.2</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>Mortality</td>
<td>140 5.1</td>
<td>147 5.4</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>28 1.0</td>
<td>22 0.8</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>TIA</td>
<td>8 0.3</td>
<td>10 0.4</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>Systemic embolism d</td>
<td>2 0.1</td>
<td>0 0.0</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>3 0.1</td>
<td>3 0.1</td>
<td>1.0 (0.75–1.51)</td>
<td>0.732</td>
</tr>
<tr>
<td>Major bleed</td>
<td>32 1.2</td>
<td>43 1.6</td>
<td>1.39 (0.89–2.17)</td>
<td>0.145</td>
</tr>
</tbody>
</table>

AT, atrial tachyarrhythmia; OAC, oral anticoagulation; TIA, transient ischaemic attack.

1n represents the number of patients with each clinical outcome. Rates are expressed as the number of events per 100 patient-years.

2Hazard ratio provided for comparison of total events in each treatment group.

3Only the first event for each patient (ischaemic stroke, haemorrhagic stroke, systemic embolism, or major bleed for primary endpoint; ischaemic stroke, systemic embolism, or TIA for thromboembolism) is counted toward the total number of events.

4Systemic embolism refers to extracranial thromboembolic events.
While several studies found no temporal relationship between AT and thromboembolism, inferences were limited by selective anticoagulation. This is the first prospective trial to validate temporal dissociation with anticoagulant therapy, a controlled variable. One-third of the cohort developed AT, frequently after, rather than before, clinical events, confirming by comprehensive monitoring what was suggested by smaller observational studies with less rhythm ascertainment. Collectively, these data suggest that better adherence to rhythm-guided anticoagulation or wider use of target-specific anticoagulants may not prevent most events. Temporal dissociation of AT and stroke is strong evidence against discontinuing anticoagulation based on rhythm criteria.

The currently recruiting Rhythm Evaluation for AntiCoagulaTion With COntinuous Monitoring (REACT COM) study addresses this in a different patient population with baseline atrial fibrillation and CHADS2 scores [http://clinicaltrials.gov/show/NCT01706146].

Only 4% of ischaemic strokes occurred in patients with antecedent AT meeting anticoagulation criteria, and 55.8% occurred in patients without AT (Figure 5). Although longer AT episodes more accurately indicated AF than short episodes, the protocol based anticoagulation upon the cumulative duration of AT within a specified timeframe, rather than individual episodes. Modifying criteria to address longer AT and overlooking shorter episodes could yield different results. While some strokes in patients with AF involve mechanisms other than embolism from the left atrium, pathological changes in atrial tissue (such as fibrosis or endothelial dysfunction), as well as increased thrombogenicity of blood may predispose to both AF and stroke, causing clinical events without antecedent AF. The implication is that anticoagulation for device-detected AT should be based on a broader assessment of risk (including co-morbidities) and benefit.

**Stroke and atrial fibrillation**

Patients in this trial differed from those with predominantly sinus node disease enrolled in pacemaker-based studies. Our patients generally had left-ventricular dysfunction, heart failure, and vascular disease (Table I) and were, therefore, at risk of stroke with or without AF. Long-term cardiac rhythm monitoring in victims of cryptogenic ischaemic stroke found AF in only ~30% over 3 years. Consistent with dissociation of AF and stroke, over half the patients developing ischaemic stroke in our study did not exhibit AF during continuous monitoring, and the mechanisms responsible for stroke in patients with more advanced heart disease may differ.

**Limitations**

The main limitation of this study was poor compliance with the anticoagulation plan in the intervention group. Participating sites were specialized arrhythmia management practices, and for a high proportion of patients, other providers managed anticoagulation. In patients receiving VKA, the TTR compared favourably to previous trials, and is representative of common anticoagulation care.

Greater use of antiplatelet therapy, combined with the protocol-specified starting of anticoagulation in the intervention group might have increased bleeding asymmetrically. Whether adherence would improve with a simpler algorithm or different care model is speculative, but the temporal dissociation of AT and thromboembolism makes better application of an anticoagulation strategy such as ours unlikely to yield benefit.

**Conclusions**

Early initiation of anticoagulation based on device-detected AT did not improve outcomes, in part because of temporal dissociation between AF and stroke, and possibly because of stroke mechanisms independent of AF. The results do not support urgent initiation or any later withdrawal of anticoagulation in response to incident AF or its termination, and argue instead for anticoagulation based on more comprehensive, individualized assessment of risk and benefit. Additional studies are needed to elucidate stroke...
mechanisms in patients with advanced heart disease to inform anticoagulation decision for AF detected by implanted cardiac rhythm management devices.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Figure 5 Temporal relationship between daily atrial tachyarrhythmia burden and clinical thromboembolism. Periods of remote monitoring are shown in grey, atrial tachyarrhythmia burden as vertical black lines (y-axis 0–100% burden, logarithmic scale), thromboembolic events in dashed red lines, oral anticoagulation starts as green asterisks and stops as red asterisks. Randomized group is denoted in ID column as subscripted C (control) or I (intervention). Cases in which thromboembolism occurred without atrial tachyarrhythmias are not shown. IS, ischaemic stroke; SE, extracranial systemic embolism; and TIA, transient ischaemic attack.
Conflict of interest: D.T.M., M.M.B., A.L.W., M.S.W., W.K.C., G.Y.H.L., J.L.H., and J.L.H. received honoraria from BIOTRONIK and reimbursement of travel expenses for study-related activities. D.T.M. received consulting fees from St Jude Medical; M.M.B. from St Jude Medical and grants from Medtronic, Bayer, and Sorin; A.L.W. from St Jude Medical, BMS/Pfizer, Daiichi-Sankyo, Biosense Webster, Cardiolight, Bard, Cardionet, and AtriCure, and a grant from Gilead Sciences; M.S.W. from Medtronic; G.Y.H.L. from Bayer, Astellas, AstraZeneca, Sanofi-Aventis, BMS/Pfizer, Portola, and Boehringer Ingehein; R.H. from BIOTRONIK to perform statistical analyses for the study; J.L.H. from Boehringer Ingeheim, Johnson & Johnson, Medtronic, Sanofi, Bayer HealthCare, Daiichi-Sankyo, and Boston Scientific.

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