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Targeted Anticoagulation for Atrial Fibrillation Guided by Continuous Rhythm Assessment with an Insertable Cardiac Monitor: The Rhythm Evaluation for Anticoagulation with Continuous Monitoring ([REACT.COM](http://react.com)) Pilot Study

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Abstract

Introduction—Chronic anticoagulation is recommended for patients with AF and additional stroke risk factors, even during long periods of sinus rhythm. Continuous rhythm assessment with an insertable cardiac monitor (ICM) and use of rapid onset novel oral anticoagulants (NOACs) allow for targeted anticoagulation only around an AF episode, potentially reducing bleeding complications without compromising stroke risk.

Methods—This multicenter, single-arm study enrolled patients on NOAC with non-permanent AF and CHADS₂ score 1 or 2. After a 60-day run-in with no AF episodes 1 hour, NOACs were discontinued but reinitiated for 30 days following any AF episode 1 hour diagnosed through daily ICM transmissions. Major endpoints included time on NOAC, stroke, and bleeding.

Results—Among 59 enrollees, 75% were male, age 67 ± 8 years, 76% paroxysmal AF, 69% had prior AF ablation, and mean CHADS₂ score 1.3 ± 0.5 . Over 466 ± 131 mean days follow-up there were 24,004 ICM transmissions with a compliance rate of 98.7%. A total of 35 AF episodes 1 hour occurred in 18 (31%) patients, resulting in a total time on NOAC of 1472 days. This represents a 94% reduction in the time on NOAC compared to chronic anticoagulation. There were three traumatic bleeds (all on aspirin), three potential transient ischemic attacks (all on aspirin with CHADS₂ score of 1), and no strokes or deaths.

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Conclusions—A targeted strategy of ICM-guided intermittent NOAC administration is feasible. A large-scale trial is necessary to evaluate the safety of this approach.

Keywords

atrial fibrillation; stroke; TIA; implantable cardiac monitor; REVEAL; anticoagulation

Background

Atrial fibrillation (AF) is the most common sustained abnormal rhythm of the heart, affects an estimated 5.5 million individuals in the US, and is a major cause of stroke. For those with a history of AF and other stroke risk factors, chronic anticoagulation is recommended to reduce the risk of thromboembolic events (1). However, this recommendation is applied to patients based on fixed risk factors and fails to consider an individual's AF burden either spontaneously or as a result of rhythm control interventions. This aspect of AF management is based in part on our inability to rapidly recognize and respond to AF episodes that can often be brief and asymptomatic, but results in exposure of patients to the risk of anticoagulant-induced hemorrhage even during prolonged periods of sinus rhythm when the risk of stroke may be low.

Recent advances in cardiac rhythm monitoring technology and drug therapy have the potential to change the way AF is managed. The use of a small, leadless, subcutaneous insertable cardiac monitor (ICM) with remote data transmission capabilities provides the opportunity to remotely and continuously evaluate a patient for AF. In addition, the introduction of oral thrombin or factor Xa inhibitors (novel oral anticoagulants, NOAC) provides a means for rapid onset anticoagulation within hours of a single oral dose. Together, these advances allow for targeted anticoagulation therapy to be administered only around the time of an AF episode, thus potentially reducing bleeding risks associated with chronic anticoagulation while still protecting against thromboembolic events.

The Rhythm Evaluation for Anticoagulation with Continuous Monitoring ([REACT.COM](https://www.react.com)) pilot study was performed to establish the feasibility of using an AF-sensitive ICM to guide intermittent anticoagulation with a NOAC in patients with non-continuous AF. The primary objective was to assess the potential reduction in anticoagulation exposure afforded by ICM device-guided therapy. The secondary objectives were to assess bleeding and stroke rates associated with this novel approach.

Methods

Study Design

The [REACT.COM](https://www.react.com) trial (clinicaltrials.gov NCT01706146) was a single-arm, prospective, multicenter pilot study designed to assess the reduction in anticoagulation utilization using ICM-guided NOAC therapy in response to an AF episode. The study protocol was approved by all institutional review boards and all patients provided written informed consent prior to enrollment. Patients were enrolled from 2 US centers (Northwestern Memorial Hospital, Chicago, IL and Beth Israel Deaconess Medical Center, Boston, MA) and one Canadian

center (University of Western Ontario, London, Canada) between October 2012 and December 2014.

The primary endpoint was anticoagulant utilization as computed by the total number of days on anticoagulation following enrollment divided by the total number of days of follow-up. Key secondary endpoints included stroke, death, and major or minor bleeding. Stroke was defined as an acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death and was categorized as either ischemic, hemorrhagic, or cause unknown (based on CT or MR scanning or autopsy). Major bleeding was defined by 1 of the following criteria: (1) Bleeding associated with reduction in hemoglobin level of at least 2.0 g/dL; (2) Leading to transfusion of at least 2 units of blood or packed cells; (3) Symptomatic bleeding in a critical area or organ such as intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal, intra-articular, or pericardial. A major bleed was classified as life-threatening if it met 1 of the following criteria: (1) Fatal, symptomatic intracranial bleed; (2) Reduction in hemoglobin level of at least 5.0 g/dL; (3) Transfusion of at least 4 units of blood or packed cells; (4) Associated with hypotension requiring the use of intravenous inotropic or vasopressor agents; or (5) Necessitating surgical intervention. Clinical bleeds that did not fulfill the criteria for major bleeds were classified as minor bleeds. Transient ischemic attack (TIA) was considered an adverse event defined as a neurological deficit lasting less than 24 hours and without imaging evidence of infarction, if an imaging study is performed. An independent data and safety monitoring committee reviewed interim results and monitored safety. An independent adverse events committee adjudicated all potential neurologic adverse events including TIAs. Potential TIAs were adjudicated as “no” TIA, “possible” TIA, “probable” TIA, and “definite” TIA by three board-certified stroke neurologists with the majority opinion reported.

The principal investigator designed the study and made the decision to submit the manuscript for publication. The sponsors of the study did not participate in the design of the study, data collection, data analysis, manuscript content, or decision to submit the manuscript for publication. All the authors vouch for the completeness and accuracy of the data and analyses.

Eligibility Criteria

Eligible patients were 18 year of age or older, had received a diagnosis of non-valvular, non-permanent AF, and had a CHADS₂ score of 1 or 2 for which a NOAC was prescribed for thromboembolic prevention. Patients were also required to have an implanted ICM (Reveal XT™, Medtronic, Inc) with no documented AF lasting 1 hour for 2 consecutive months immediately prior to enrollment. A rhythm control strategy was not required but could include cardioversion, Class I or Class III antiarrhythmic drugs, ablation, or surgical AF treatment. Exclusion criteria included mechanical prosthetic heart valve, severe valvular disease, prior stroke or TIA, reversible causes of AF, conditions associated with an increased risk of bleeding (including the need for dual antiplatelet therapy), or comorbidities that rendered the patient high-risk for non-cardioembolic stroke based on the discretion of the treating physician (i.e., extensive carotid artery disease).

Baseline Assessment

The patient's medical history, physical-examination findings, medication history, and prior rhythm control strategies (if any) were recorded. Data from the ICM were analyzed for inclusion/exclusion criteria.

Monitoring Strategy and NOAC Protocol

Enrolled patients underwent reprogramming of their ICM to study-specific settings that included detection "on" for AF only, sensitivity 0.035V, balanced sensitivity, and nominal ectopy rejection. While data from all AF episodes were automatically recorded by the ICM, electrocardiograms were recorded only for AF episodes ≥ 30 minutes for the purposes of the study. Previously prescribed NOAC was discontinued the day of enrollment, and aspirin 81 mg was started or continued if previously prescribed. Patients were instructed to perform daily manual transmissions from their REVEAL XTTM using the standard home CareLink monitor. Patients without landlines were provided with an analog to wireless converter (WireXTM, eDevice Inc.). Use of the standard Patient Activator Device was encouraged to record any symptoms that occurred between daily data transmissions. Data was transmitted over the Medtronic CareLink Network to each study center where it was assessed daily by study staff. For any continuous AF episode ≥ 1 hour, patients were contacted within 2 hours of rhythm adjudication and instructed to resume their previously prescribed NOAC and to discontinue aspirin unless otherwise indicated. Anticoagulation could be administered for episodes < 1 hour at the discretion of the treating physician. For those unable to perform daily transmissions due to inaccessibility to the CareLink Network, decisions on the need for NOAC during the blackout period were made on an individual basis. The study algorithm is shown in Figure 1 and representative patient data in Figures 2 and 3.

Results

Study Population

During the study period, 59 patients were enrolled. Baseline characteristics are shown in Table 1. The mean age was 66.8 ± 7.7 years and fifteen (25.4%) were female. Prior to enrollment, 76.3% had a history of paroxysmal AF while 23.7% had a history of persistent AF. Symptoms were present in 80%. Previous ablation was performed in 41 (69%) patients and 3 patients (5%) had a prior surgical procedure for AF. At the time of enrollment, 33.9% of patients were on antiarrhythmic medications, and the mean CHADS₂ score was 1.3 ± 0.5 . Antiarrhythmic drugs included IC agents (40%) and class III agents (60%), with only one patient receiving amiodarone. Of those with prior ablation, 10 (24%) were also receiving antiarrhythmic drugs at the time of enrollment. Anticoagulants used prior to enrollment included dabigatran (62.7%), rivaroxaban (27.1%), and apixaban (10.2%).

Primary Endpoint

The mean and median follow-up durations were 465.8 ± 131.2 and 461.0, respectively, with a range of 85 to 764 days. During follow-up, a total of 24,004 daily manual transmissions were received, resulting in a transmission compliance rate of 98.7%. A total of 35 AF episodes lasting ≥ 1 hour occurred in 18 (30.5%) patients over a total follow-up duration of

66.6 patient-years. Of the 35 AF episodes, 24 (69%) converted spontaneously; the remainder underwent chemical or electrical cardioversion within a median time of 5 days (mean 14.3 ± 23.6 days, range 2-67 days). Symptoms, predominantly palpitations and shortness of breath, were reported during 13 (37%) of the episodes and the other 63% were asymptomatic. The mean and median times on NOAC per AF episode were 42 ± 21 , and 32 days, respectively. The total time on NOAC for the 18 patients with a qualifying AF event ≥ 1 hour was 1472 days or 6% of the follow-up period. This represents a 94% reduction in the expected time on NOAC had continuous anticoagulation been taken as previously prescribed. There was no significant difference in the total time on NOAC for patients previously treated with AF ablation or surgery compared to those treated with antiarrhythmic drugs or cardioversion alone ($6.3 \pm 0.13\%$ versus $5.1 \pm 0.10\%$; $p = 0.73$).

Withdrawals / Adverse Events

Patients were permanently withdrawn from the trial upon the development of permanent AF (N=1), the need for dual antiplatelet therapy (N=1), or possible TIA (N=3). There was one voluntary withdrawal. The most common adverse event was bleeding. There were two major bleeds following trauma, both occurring on aspirin therapy. Three minor bleeds were also noted, two of which occurred on aspirin and one gastrointestinal bleed on NOAC. There were no strokes or systemic emboli and no deaths. Adjudication of the three potential TIA events by an independent review committee rated two as “possible TIA” and one as “definite TIA”. The CHADS₂ scores in these three patients were all 1 (CHA₂DS₂-VASc scores 2,3 and 3) and all were on aspirin therapy throughout the study period and at the time of the event. ICM data showed that two of the patients had no AF detected within the year prior to the suspected TIA and the third patient had a single 2-minute episode of AF detected one month prior to the TIA, though no ECG was recorded given the brief duration of the episode and the mandated device programming. There were no complications related to device implantation.

Discussion

Balancing the risk of stroke due to AF and the risk of bleeding on anticoagulation continues to be both a focus of attention and a challenge for healthcare providers. The [REACT.COM](#) pilot study demonstrates the feasibility of using a leadless subcutaneous ICM for real-time management of oral anticoagulation in AF patients being successfully rhythm-controlled. The primary finding of this study is that a 94% reduction in time on anticoagulation compared to the current standard of practice can be achieved using the strategy of ICM guided anticoagulation only in response to an AF episode. This small, uncontrolled trial cannot and does not claim to be an effective stroke prevention strategy, but demonstrates that long periods of sinus rhythm are common and raises questions as to the need for chronic anticoagulation in all AF patients with other stroke risk factors.

Trials that defined the efficacy of anticoagulation predominantly enrolled patients with persistent and permanent AF; thus the benefits of these therapies in patients with very low AF burdens have not been explored (2-6). Current guidelines recommend continuous anticoagulation in patients with a history of AF and other stroke risk factors even if a rhythm

control strategy has been adopted. This recommendation is based partially on the limited long-term success rates of rhythm control strategies and the high burden of asymptomatic AF, with the latter underscoring the unreliable nature of symptoms alone to guide medical decision making around anticoagulation (1,7,8). Permanent discontinuation of anticoagulation following a rhythm control strategy with antiarrhythmic drugs has been associated with an increased stroke risk (9). Whether the same is true following AF ablation is presently unknown (10,11). As a result of these issues, guidelines state that the decision to discontinue anticoagulation must be based on a patient's risk of stroke and not whether continuous normal sinus rhythm is thought to be present. Though highly effective in reducing stroke risk, chronic anticoagulation is associated with an annual risk of major bleeds of approximately 2-4%, non-major bleeds of 12-22%, a reduction in quality of life, and significant health care costs (2-6). These issues likely contribute, at least in part, to the frequent underutilization or discontinuation of anticoagulant therapies.

Insertable cardiac monitors with remote data transmission allow for continuous and accurate AF surveillance and near real-time intervention (12). Further advances in ICM technology since the inception of this pilot study include a reduction in device size and automatic daily wireless downloads via cellular technology, thus reducing compliance considerations and eliminating the need for landline access or cellular adaptors. One prior attempt to use remote monitoring of implantable defibrillators to guide anticoagulation initiation and withdrawal did not show a reduction in stroke risk (13). In contrast to the present study, the IMPACT trial enrolled heart failure patients with no known history of AF and used warfarin as the predominant anticoagulant. Other major differences in patient population and study design limit any comparisons with the present study.

A number of adverse events occurred during the trial. Two major bleeds, traumatic in nature, occurred while on aspirin therapy. No strokes or deaths occurred; however, one "definite" TIA and two "possible" TIAs were observed. All three occurred in patients with CHADS₂ score of 1 on aspirin therapy; two of the patients had no device-detected AF in > 1 year prior to their neurological event and one had a possible AF episode 2 minutes in duration one month prior. Given the uncertainties and the large inter-observer disagreement in TIA diagnoses, the use of this endpoint in clinical trials of stroke prevention in AF is inherently problematic and was not used in any of the recent NOAC trials (14). Thus, no safety concerns should be raised by the present findings. It is noteworthy, however, that these potential neurologic events were temporally dissociated from any AF episodes. This temporal dissociation was also observed in the TRENDS and ASSERT studies though the largest study to date contradicts these findings by demonstrating a 5.2-fold risk of stroke within 30 days of an AF episode (15-17). In those cases where a temporal dissociation is observed, several possible explanations exist. First, it is possible that AF episodes are the proximate cause of thrombus formation, but the timing of embolization of an established thrombus may be substantially delayed and dependent on non-traditional risk-factors such as appendage morphology (18, 19). Second, the risk for atrial thrombus formation may occur even in the absence of AF, particularly in patients with multiple additional stroke risk factors. Alternatively, other mechanisms of stroke independent of AF may also exist and are significantly correlated with increasing CHADS₂ and CHA₂DS₂-VASC scores (20,21). This is consistent with the findings in ASSERT where the mean CHADS₂ and CHA₂DS₂-VASC

scores of those with stroke were 2.8 ± 1.1 and 4.5 ± 1.2 , respectively (16). Finally, an inflammatory and/or hypercoagulable state is known to be present during AF episodes (22). Whether such a state persists even during long periods of sinus rhythm and whether prompt initiation of anticoagulation, as afforded by an ICM-guided strategy, can prevent future embolic events is the subject of this study.

Several other issues deserve mention. First, as a feasibility trial, enrollment was limited to patients with a CHADS₂ score of 1 or 2. While patients in these risk categories constitute the majority of AF patients, the safety of this approach in a higher risk cohort remains unexplored. The required screening period and the enrollment of a large portion of patients with prior ablation likely contributed to the observed low rates of recurrent arrhythmia and anticoagulation use. Lastly, uncertainty exists over the minimum duration of AF associated with stroke. Studies that correlated AF duration with thromboembolic risk alternatively suggest that AF episodes greater than 6 minutes, 3.8 hours, 5.5 hours, and 24 hours are all associated with increased risk (23-26). The 1-hour threshold used in this study was chosen to balance the accuracy of the ICM with the risks of untreated AF episodes. Regardless, the study design insured that patients would receive anticoagulation well within the 48-hour period from AF onset currently accepted as the minimum duration associated with thrombus formation.

In summary, the [REACT.COM](#) pilot study establishes the feasibility of using an ICM to guide intermittent anticoagulation with NOAC. This approach may significantly reduce exposure to long-term anticoagulation in select AF patients, though the safety of this approach for stroke prevention cannot be assessed in this small pilot study. A randomized trial of ICM-guided versus chronic NOAC (REACT-AF) is planned in a moderate-risk AF population with non-permanent AF. If a favorable balance between major outcomes can be demonstrated, this personalized approach to stroke prevention in AF may offer an attractive alternative to chronic anticoagulation for the growing AF population and pave the way for targeted, point-of-care anticoagulation management.

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References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice

- Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014; 64:e1–76. 2014. [PubMed: 24685669]
2. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; 361:1139–51. [PubMed: 19717844]
 3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011; 365:883–91. [PubMed: 21830957]
 4. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011; 365:981–92. [PubMed: 21870978]
 5. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013; 369:2093–104. [PubMed: 24251359]
 6. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007; 146:857–67. [PubMed: 17577005]
 7. Strickberger SA, Ip J, Saksena S, Curry K, Bahnson TD, Ziegler PD. Relationship between atrial tachyarrhythmias and symptoms. *Heart Rhythm.* 2005; 2:125–31. [PubMed: 15851283]
 8. Verma A, Champagne J, Sapp J, Essebag V, Novak P, Skanes A, Morillo CA, Khaykin Y, Birnie D. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): a prospective, multicenter study. *JAMA internal medicine.* 2013; 173:149–56. [PubMed: 23266597]
 9. Sherman DG, Kim SG, Boop BS, Corley SD, Dimarco JP, Hart RG, Haywood LJ, Hoyte K, Kaufman ES, Kim MH, Nasco E, Waldo AL, National Heart, Lung, and Blood Institute AFFIRM Investigators. Occurrence and characteristics of stroke events in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) study. *Arch Intern Med.* 2005; 165:1185–91. [PubMed: 15911734]
 10. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, Di Biase L, Schweikert RA, Saliba WI, Horton R, Mohanty P, Patel D, Burkhardt DJ, Wazni OM, Bonso A, Callans DJ, Haissaguerre M, Raviele A, Natale A. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. *J Am Coll Cardiol.* 2010; 55(8):735–43. [PubMed: 20170810]
 11. Riley MP, Zado E, Hutchinson MD, Lin D, Bala R, Garcia FC, Callans DJ, Cooper JM, Verdino RJ, Dixit S, Marchlinski FE. Risk of stroke or transient ischemic attack after atrial fibrillation ablation with oral anticoagulant use guided by ECG monitoring and pulse assessment. *J Cardiovasc Electrophysiol.* 2014; 25:591–6. [PubMed: 24533561]
 12. Hindricks G, Pokushalov E, Urban L, Taborisky M, Kuck KH, Lebedev D, Rieger G, Pürerfellner H, XPECT Trial Investigators. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: Results of the XPECT trial. *Circ Arrhythm Electrophysiol.* 2010; 3:141–7. [PubMed: 20160169]
 13. Martin DT, Bersohn MM, Waldo AL, Wathen MS, Choucair WK, Lip GY, Ip J, Holcomb R, Akar JG, Halperin JL, IMPACT Investigators. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *Eur Heart J.* 2015; 36:1660–8. [PubMed: 25908774]
 14. Kinsella JA, Tobin WO, Cogan N, McCabe DJ. Interobserver agreement in ABCD scoring between non-stroke specialists and vascular neurologists following suspected TIA is only fair. *J Neurol.* Jun; 2011 258(6):1001–7. [PubMed: 21188409]

15. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J, Ziegler PD, TRENDS Investigators. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm*. 2011; 8:1416–23. [PubMed: 21699833]
16. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, Lau CP, Van Gelder IC, Hohnloser SH, Carlson M, Fain E, Nakamya J, Mairesse GH, Halyska M, Deng WQ, Israel CW, Healey JS, ASSERT Investigators. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation*. 2014; 129:2094–9. [PubMed: 24633881]
17. Turakhia MP, Ziegler PD, Schmitt SK, Chang Y, Fan J, Than CT, Keung EK, Singer DE. Atrial Fibrillation Burden and Short-Term Risk of Stroke: Case-Crossover Analysis of Continuously Recorded Heart Rhythm From Cardiac Electronic Implanted Devices. *Circ Arrhythm Electrophysiol*. 2015; 8:1040–7. [PubMed: 26175528]
18. Larsen JA, McPherson DD, Kadish AH, Goldberger JJ. Course of intraatrial thrombi resolution using transesophageal echocardiography. *Echocardiography*. 2003; 20(2):121–8. [PubMed: 12848676]
19. Nedics S, Koutalas E, Kornej J, Rolf S, Arya A, Sommer P, Husser D, Hindricks G, Bollmann A. Cardiogenic Stroke Despite Low CHA2 DS2 -VAsC Score: Assessing Stroke risk by Left Atrial Appendage Anatomy (ASK LAA). *J Cardiovasc Electrophysiol*. 2015; 26:915–921.
20. Cha MJ, Kim YD, Nam HS, Kim J, Lee DH, Heo JH. Stroke mechanism in patients with nonvalvular atrial fibrillation according to the CHADS2 and CHA2 DS2 -VAsC scores. *Eur J Neurol*. 2012; 19:473–479. [PubMed: 21972975]
21. Azarbal F, Welles CC, Wong JM, Whooley MA, Schiller NB, Turakhia MP. Association of CHADS2, CHA2DS2-VAsC, and R2CHADS2 scores with left atrial dysfunction in patients with coronary heart disease (from the Heart and Soul study). *Am J Cardiol*. 2014; 113:1166–1172. [PubMed: 24507169]
22. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol*. 2012; 60(22):2263–70. [PubMed: 23194937]
23. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012; 366:120–9. [PubMed: 22236222]
24. Shanmugam N1, Boerdlein A, Proff J, Ong P, Valencia O, Maier SK, Bauer WR, Paul V, Sack S. Detection of atrial high-rate events by continuous home monitoring: clinical significance in the heart failure-cardiac resynchronization therapy population. *Europace*. 2012; 14:230–7. [PubMed: 21933802]
25. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler PD. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol*. 2009; 2:474–80. [PubMed: 19843914]
26. Capucci A1, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G, Ricci R, Favale S, Zolezzi F, Di Belardino N, Molon G, Drago F, Villani GQ, Mazzini E, Vimercati M, Grammatico A, Italian AT500 Registry Investigators. Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. *J Am Coll Cardiol*. 2005; 46:1913–20. [PubMed: 16286180]

Figure 1.
Study Schema

Cardiac Compass Trends (Oct-2013 to Dec-2014)

Figure 2.
Representative samples of patient data
(A) AF burden over 14-month enrollment period in a 58-year-old male with hypertension (CHADS₂ = 1) with paroxysmal AF on an antiarrhythmic drug. The AF burden trend (A) shows a single episode of atrial fibrillation lasting 5 hours and 14 minutes with corresponding R-R interval plot (Figure 2B) and ECG (Figure 2C) supporting the diagnosis. This patient received one month of NOAC in response to the single AF episode.
(B) R-R interval plot of AF episode shown in Figure 2A

(C) ECG recorded from ICM demonstrating AF episode

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Figure 3.

AF burden histogram of a 68-year-old female with hypertension ($\text{CHADS}_2 = 1$) treated with pulmonary vein isolation. The patient had no recurrences of AF over a 14-month enrollment period and received 0 days of NOAC.

Table 1**Baseline Patient Characteristics**

Age, years	66.8 ± 7.7
Age ≥ 75, %	13.6
Female, %	25.4
White/Caucasian race, %	93.2
Prior AF Pattern, %	
Paroxysmal	76.3
Persistent	23.7
Previous Catheter Ablation, %	69.5
Antiarrhythmic Drug Therapy, %	33.9
Hypertension, %	93.2
Diabetes Mellitus, %	22.0
Heart Failure, %	3.4
Creatinine clearance, mL/min	91.6 ± 33.2
CHADS ₂ Score = 1, %	69.5
CHADS ₂ Score = 2, %	30.5
CHA ₂ DS ₂ VASC score	2.4 ± 1.0
Baseline anticoagulant, %	
Dabigatran	62.7
Rivaroxaban	27.1
Apixaban	10.2