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Patient Activity Decreases and Mortality Increases After the Onset of Persistent Atrial Fibrillation in Patients With Implantable Cardioverter-Defibrillators

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ABSTRACT

OBJECTIVES The study sought to determine the effect of persistent atrial fibrillation (AF) on device-measured activity and mortality.

BACKGROUND Patients with AF often complain of fatigue, which may be reflected in patient activity. Daily activity can be objectively measured by implanted devices.

METHODS We retrospectively studied patients (n = 266, 88% male, 69 ± 10 years of age) from the deidentified Medtronic CareLink database with persistent AF (≥28 consecutive days with ≥23 h of AF/day), dual-chamber implantable cardioverter-defibrillators (ICDs) capable of monitoring daily activity and AF burden, no AF between months 1 and 6 post-implant, and ≥1 year of data.

RESULTS The first persistent AF episode occurred 980 ± 534 days after implant and lasted a median of 87 days (interquartile range: 49 to 161 days). Average daily activity over a week just prior (baseline) to the first persistent AF episode was compared to each of the 4 weeks during the AF episode and to each of the weeks following termination of the persistent AF episode. Daily activity decreased significantly from the baseline week (135 min/day) compared to each of the 4 consecutive weeks after AF onset (8%, 11%, 14%, and 17% decrease, $p < 0.001$). Mortality at 4 years was increased in patients with persistent AF compared to a matched group with no persistent AF (20.6% vs. 8.6%, $p < 0.01$).

CONCLUSIONS Patients with ICDs have a significant reduction in activity following the onset of persistent AF and a significant increase in mortality when compared to a matched group without persistent AF. Objective measures of activity may more accurately reflect the impact of persistent AF on patients' functional status.
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Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, estimated to affect between 2.7 and 6.1 million adults in the United States, a number that is predicted to double over the next 25 years (1-3). The prevalence of AF in patients with implantable cardioverter-defibrillators (ICD) was reported to be as high as 25% (4). Dual-chamber ICDs have algorithms that allow AF detection with high accuracy and have data storage capacity that includes: onset of AF, daily measurements of AF burden, and episode durations (5,6).

Symptom-rhythm correlation is the cornerstone of AF patients evaluation and plays a critical role in the decision-making process to determine the eligibility

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for sinus rhythm (SR) restoration by cardioversion, antiarrhythmic drugs, or AF ablation (7–10). Engagement in activities of day-to-day life is a reflection of the cardiovascular system status and the impact of cardiovascular disease. Little is known on the impact of AF on patient daily activities. ICDs have accelerometers that can provide an objective measure of patient daily activity (11).

The aim of this study was to determine the impact of persistent AF on activity and mortality in patients with dual-chamber ICDs using the deidentified Discovery Link database.

METHODS

A retrospective analysis was performed using deidentified data from the Discovery Link database (6). Device data was available from centers that had agreed to allow data to be used for research purposes in accordance with Health Insurance Portability and Accountability Act regulations. Patient identification information was removed to protect patient privacy. Stored and programmed data is transferred from Medtronic (Minneapolis, Minnesota) devices to the Medtronic CareLink data server via remote telemetry. The Discovery Link database, a subset of the Medtronic CareLink database, represents all deidentified data obtained from devices implanted in the United States along with a few patient parameters from the device registration database (e.g., age, gender). The following parameters were retrieved from the Discovery Link database: age, gender, date of death, daily-device cumulative AF duration, mean ventricular rate during AF, patient activity, and daily device transthoracic impedance.

STUDY PATIENTS. Persistent AF was defined as AF ≥23 h/day for at least 7 consecutive days (6), which is consistent with the clinical definition recommended by guidelines (7). This study included patients with a persistent AF episode lasting more than 4 weeks. The first persistent AF episode lasting more than 4 weeks after at least 6 months post-implant was considered for analysis. The 6-month period was chosen to exclude any patients who had AF prior to the device implant.

Patients were included in this study if they met the following criteria: 1) persistent AF with duration of ≥28 consecutive days and ≥23 h of AF per day; 2) dual-chamber ICDs capable of monitoring daily activity and AF burden; 3) no AF between months 1 and 6 post-implant; and 4) ≥1 year of data. The flowchart in **Figure 1** illustrates the derivation of the study population.

ICD PROGRAMMING AND DIAGNOSTICS. ICD programming and the frequency of data transmission were at the discretion of physicians involved with the care of the respective patients. AF detection and episode quantification were performed using previously validated device algorithms (Online Figure 1A) (5). Device diagnosed AF includes any atrial tachyarrhythmias with an atrio-ventricular ratio >1:1 for >32 ventricular events and a fast median atrial rate (nominally >171 beats/min) as previously described (6).

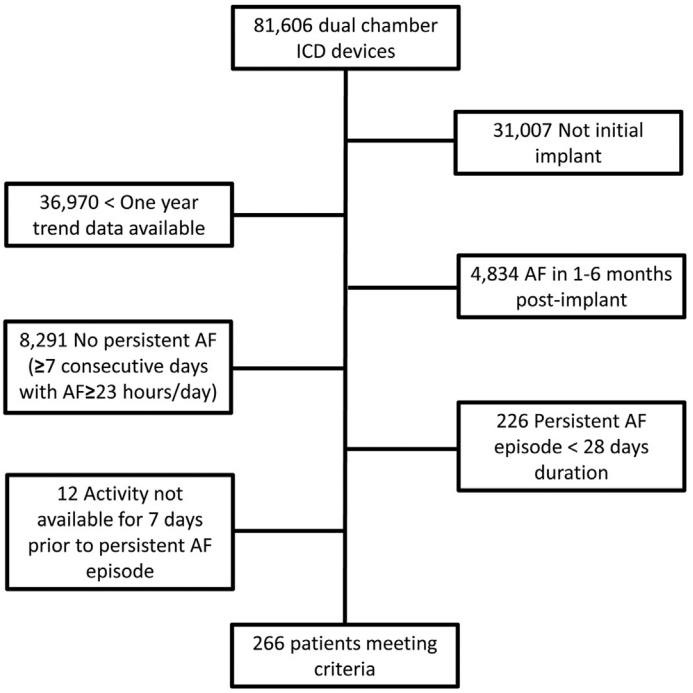
Modern ICD technology incorporates single-axis accelerometers designed to measure patient activity in daily number of minutes (Online Figure 1B) (11). An active minute corresponds to approximately 70 steps/min (12) and was validated with external 3-axis accelerometers (13).

The average (with standard error) daily activity was calculated over 7 consecutive day windows (Online Figure 1B). The baseline activity was calculated the week prior to the first persistent AF episode and compared to the following 4 weeks during the AF episode. The return to the baseline activity level after the persistent AF episode termination was evaluated as the percent of patients returning to within 10% of

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
ICD = implantable cardioverter-defibrillator
QoL = quality of life
SR = sinus rhythm

FIGURE 1 Flowchart Illustrating the Derivation of the ICD Study Population



AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator.

TABLE 1 Implantable Cardioverter-Defibrillator Patients With Persistent AF Characteristics (N = 266)

Age (n = 259), yrs	69 ± 10.2
Sex (n = 260)	87.7% male; 12.3% female
Persistent AF (100%)	
Time to first episode, days	980 ± 534
Duration, days	87 (interquartile range: 49-161)

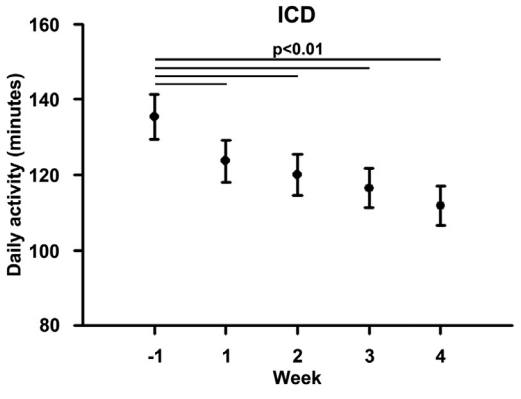
AF = atrial fibrillation.

their baseline daily activity for each week following termination.

Mortality data were obtained by cross-referencing the device registry with the Social Security Death Index. Mortality was compared between the patients with persistent AF and patients with no persistent AF. Patients with a persistent AF episode were randomly matched for gender, age, and time of onset of the first episode of persistent AF to a group with no persistent AF.

STATISTICAL ANALYSIS. Categorical variables were described using frequencies while continuous variables were described by means/medians with standard deviations/interquartile ranges. Weekly activity during AF was compared to the baseline weekly activity using an analysis of variance model and the Dunnett method to adjust for multiple comparisons. Time to return to baseline activity level was computed using the Kaplan-Meier method. For the patients that remained in AF for the duration of follow-up, weekly activity from the last 4 weeks of follow-up along with weekly activity from baseline and the first week of AF were compared using an analysis of variance model and the Tukey method to adjust for multiple comparisons. The Kaplan-Meier method was used to plot survival time. A log-rank test was used to compare survival between the persistent AF and no persistent AF groups. Differences were considered significant for a p value <0.05. The statistical software used was SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

FIGURE 2 Decline in Patient Activity After Onset of AF in Patients With ICDs



Decline in patient activity with each week of persistent atrial fibrillation atrial fibrillation (AF) lasting at least 4 weeks compared to the week prior (Week -1) to the persistent AF episode (n = 266 patients; p < 0.001 Week -1 vs. Week 1, Week 2, Week 3, Week 4).

RESULTS

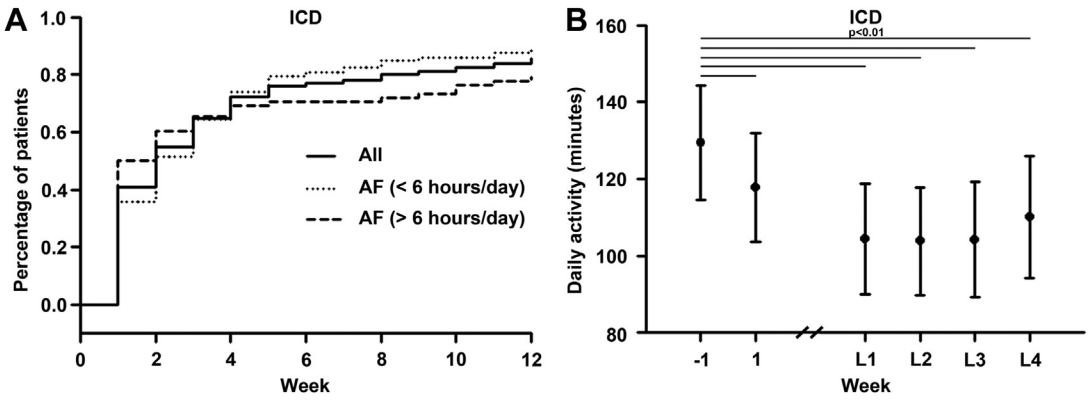
PATIENT CHARACTERISTICS. A total of 266 of 81,606 patients with dual-chamber ICDs satisfied the data requirements (see flowchart in Figure 1). There were 88% male patients averaging 69 ± 10 years of age. The first episode of AF occurred at 980 ± 534 days from implant and lasted a median 87 days (interquartile range: 49 to 161 days). The patients had device data for an average 4.3 ± 1.5 years from implant (Table 1).

PERSISTENT AF AND PATIENT ACTIVITY. There was a significant decrease in average daily activity (Figure 2) from the baseline week (135 min/day) compared to each of the 4 consecutive weeks after AF onset (8%, 11%, 14%, and 17% decrease, p < 0.001).

Upon termination of persistent AF, 85% of the patients returned to within 10% of baseline activity by week 12 (Figure 3A). Patients that had little AF (<6 h/day; n = 132) returned to baseline activity faster than patients that continued to have significant AF burden (>6 h/day; n = 80) after termination of persistent AF episode (Figure 3A). By week 6, 81% of patients with little AF (<6 h/day) compared to 71% patients with significant AF burden (>6 h/day) returned to baseline activity (Figure 3A). By contrast, patients that remained in AF never returned to the baseline activity level (Figure 3B). For these patients that remained in persistent AF, patient activity remained 15% to 19% lower in the final 4 weeks of available follow up data than in the week prior to the persistent AF episode (Figure 3B).

PERSISTENT AF AND MORTALITY. Patients with a persistent AF episode were matched for gender, age, and time to onset of the first episode of persistent AF to a group with no persistent AF (101 [38%] patients with no AF and 165 [62%] patients with paroxysmal AF). The group of patients with persistent AF had a significantly higher mortality at 4 years compared

FIGURE 3 Timeline to Baseline Activity Recovery in ICD Patients With a Persistent AF Episode Lasting at Least 4 Weeks



(A) Percentage of patients that returned to within 10% of baseline activity each week after the termination of an episode of a persistent AF (all: patients with at least 1 day with AF <23 h; n = 212). The less AF burden after termination of the persistent AF episode the faster the recovery. **(B)** Patients remaining in persistent AF never returned to baseline activity (Week -1) (n = 51 patients; $p < 0.01$; Week -1 vs. L 1, L 2, L 3, L 4). L 1 to 4 represent the final 4 weeks of available follow-up for each patient. Abbreviations as in Figure 1.

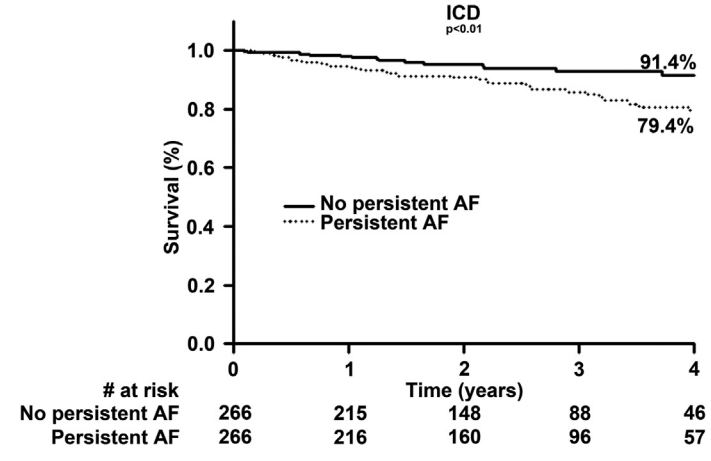
to patients with no persistent AF (20.6% vs. 8.6%, $p < 0.01$) (Figure 4).

DISCUSSION

There is significant interaction between cardiovascular disease and patient activity. Maximal exercise capacity is decreased during stress test in patients in AF but the impact of persistent AF on "spontaneous" patient activity has not been explored. Modern devices allow AF detection and quantification with high accuracy (5,6) and have accelerometers that can provide an objective measure of patient daily activity (11). In this study, we sought to determine the variations in patient activity with changes in rhythm in patients with persistent AF. Each patient served as his/her own control and measurements of patient activity were collected before, during, and after an episode of persistent AF lasting at least 4 weeks. Because patient activity varies by day of the week, we elected to perform our analysis in daily activity averages over weekly periods. Furthermore, since there was no clinical data available to us, patients with at least a 4-week persistent AF episode were selected to provide a sufficient sampling data and minimize the potential impact of a hospitalization on patient activity. Hospitalization for an episode of AF can potentially affect patient activity through bed rest but it is unlikely that a patient would be hospitalized for an extended period of 4 weeks.

This study demonstrated that onset of persistent AF coincided with a significant decline in patient activity in patients with devices but the impact varied with the type of device (see Online Appendix for patients with dual-chamber pacemakers [Online Figure 4A] and with cardiac resynchronization therapy defibrillator [Online Figure 4B]). In an ICD population, we found a continuous and gradual decline in patient activity with duration of AF. The profound decline of patient activity after onset of persistent AF likely reflects the small cardiovascular reserve that

FIGURE 4 Mortality in Patients With ICDs With and Without Persistent AF



Kaplan-Meier survival plot in ICD patients with persistent AF lasting at least 4 weeks (n = 266) compared to a matched group of patients without persistent AF (n = 266; $p < 0.01$). Abbreviations as in Figure 1.

the typical ICD patient manifests (left ventricular ejection fraction <35%) (14).

Observations on the trends of patient activity after termination of a persistent AF episode provide further insights. Most patients with restoration of SR return to baseline activity. However, this can be a lengthy process again underlining the profound impact of persistent AF on patient activity in patients with ICDs. Patient activity returned to within 10% of baseline activity by 12 weeks in 85% patients after termination of a persistent AF episode. The degree and duration of decline in patient activity is determined by the burden of AF after the conclusion of an episode of persistent AF. Patients with a low burden of AF (<6 h/day) recover their baseline activity faster than patients with a significant AF burden. AF maintains a profound and long lasting impact on patient activity in patients that remain in AF: they never return to their baseline activity levels. This finding is of particular importance as patients with long standing persistent AF frequently report no or very few symptoms (15). Patient activity data measurements from devices could provide objective measurements of decline in activity that may not be perceived by patients. In fact, assessment of symptoms using health-related quality of life (QoL) (16) surveys do suggest symptom underreporting or patient adjustment to AF. Asymptomatic to minimally symptomatic AF patients do experience QoL improvement after rate or rhythm control therapy (17). QoL was reported to improve in most measures in patients with asymptomatic long-standing persistent AF after successful ablation with restoration of SR (15). Patient activity measurement is easily available in all devices and could provide an additional and objective tool in determining the impact of AF on the QoL of these patients.

Persistent AF appeared to have a significant impact on mortality in our study. There was significantly higher mortality in the persistent AF group when compared to a group matched for age, gender, and time to detection of no persistent AF.

The number of patients included in this study is relatively small due to the stringent conditions imposed on the cohort. We imposed a period of 6 months of no AF after the implant in an attempt to eliminate any patients with a prior history of AF and to capture the first episode of persistent AF.

STUDY LIMITATIONS. This is a retrospective study that investigated the impact of persistent AF on patient activity and mortality in an ICD cohort. The generality of the conclusions is limited by the absence of clinical data regarding left ventricular ejection fraction, heart failure class, medication use, or procedures such as cardioversions/ablations to restore SR. Due to limitations in the algorithm to distinguish between AF and other atrial arrhythmias, the latter may be included in the measurement of AF duration. The study population does not allow us to dissect the role of worsening heart failure independently or as a consequence of AF in the decline or recovery of patient activity. Similarly, it does not allow us to determine if persistent AF is a consequence of worsening heart failure. Matching for mortality analysis was performed only for age and gender, due to limited clinical information. Other clinical conditions not accounted for in this study may affect the mortality. Nevertheless this cohort reflects the clinical practice in the United States and provides useful insights on the impact of AF on patient activity and mortality that could be used as a starting point to design further studies. The current study drew on a very large national sample of over 81,000 patients but the ultimate sample reflected <1% of that number. This strong selectivity allows for more a precise examination of the variables of interest from an empirical standpoint. As a result, the generalizability of these findings is limited to this selected sample (e.g., patients with an ICD).

CONCLUSIONS

Persistent AF is associated with a significant reduction in activity and a significant increase in mortality in patients with ICDs. Measurements of activity may provide an additional and accessible tool in patients with devices to assess the impact of AF on patient activity and guide SR restoration strategies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Device-based patient activity measurements may provide an objective assessment of patient activity decline associated with AF, particularly in patients that report no or few symptoms.

TRANSLATIONAL OUTLOOK: Additional studies in populations with different cardiovascular reserve are needed to assess patient activity changes with onset of atrial fibrillation.

REFERENCES

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285:2370–5.

2. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. Circ Cardiovasc Qual Outcomes 2011;4:313–20.

3. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation 2014;129:e28–292.

4. Botto GL, Luzi M, Ruffa F, Russo G, Ferrari G. Atrial tachyarrhythmias in primary and secondary prevention ICD recipients: clinical and prognostic data. Pacing Clin Electrophysiol 2006;29:S48–53.

5. Swerdlow CD, Schsls W, Dijkman B, et al. Detection of atrial fibrillation and flutter by a dual-chamber implantable cardioverter-defibrillator. For the Worldwide Jewel AF Investigators. Circulation 2000;101:878–85.

6. Ousdigian KT, Borek PP, Koehler JL, Heywood JT, Ziegler PD, Wilkoff BL. The epidemic of inadequate biventricular pacing in patients with persistent or permanent atrial fibrillation and its association with mortality. Circulation Arrhythm Electrophysiol 2014;7:370–6.

7. January CT, Wann LS, Alpert JS, et al. 2014 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.

8. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–429.

9. Gillis AM, Verma A, Talajic M, Nattel S, Dorian P, Committee CCSAFG. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: rate and rhythm management. Can J Cardiol 2011;27: 47–59.

10. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm 2012;9:632–696.e21.

11. Adamson PB, Smith AL, Abraham WT, et al. Continuous autonomic assessment in patients with symptomatic heart failure: prognostic value of heart rate variability measured by an implanted cardiac resynchronization device. Circulation 2004;110:2389–94.

12. Sears SF, Whited A, Koehler J, Gunderson B. Examination of the differential impacts of antitachycardia pacing vs. shock on patient activity in the EMPIRIC study. Europace 2015;17: 417–23.

13. Pressler A, Danner M, Esefeld K, et al. Validity of cardiac implantable electronic devices in assessing daily physical activity. Int J Cardiol 2013; 168:1127–30.

14. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6–75.

15. Mohanty S, Santangeli P, Mohanty P, et al. Catheter ablation of asymptomatic longstanding persistent atrial fibrillation: impact on quality of life, exercise performance, arrhythmia perception, and arrhythmia-free survival. J Cardiovasc Electrophysiol 2014;25:1057–64.

16. Zhang L, Gallagher R, Neubeck L. Health-related quality of life in atrial fibrillation patients over 65 years: a review. Eur J Prevent Cardiol 2015;22:987–1002.

17. King DR, Mehta ND, Gehi AK, et al. Minimally symptomatic atrial fibrillation patients derive significant symptom relief following rate control or rhythm control therapy. J Clin Med Res 2015;7:690–3.

KEY WORDS activity, atrial fibrillation, implantable cardioverter-defibrillator, mortality

APPENDIX For expanded Methods, Results, Discussion, and References sections, as well as supplemental tables and figures, please see the online version of this article.