Atrial Fibrillation Is an Independent Risk Factor for Ventricular Fibrillation
A Large-Scale Population-Based Case-Control Study

Abdennasser Bardai, MD; Marieke T. Blom, MA; Daniel A. van Hoeijen, MSc; Hanneke W.M. van Deutekom, PhD; Henk J. Brouwer, MSc; Hanno L. Tan, MD, PhD

Background—Atrial fibrillation (AF) is associated with sudden cardiac death. We aimed to study whether AF is associated with ventricular fibrillation (VF), the most common cause of sudden cardiac death and whether this association is independent of confounders, ie, concomitant disease, use of antiarrhythmic or QT-prolonging drugs, and acute myocardial infarction.

Methods and Results—We performed a community-based case-control study. Cases were patients with out-of-hospital cardiac arrest because of ECG-documented VF. Controls were age-/sex-matched non-VF subjects from the community. VF risk in AF patients was studied by means of (conditional) logistic regression, adjusting for all available confounders. We studied 1397 VF cases and 3474 controls. AF occurred in 215 cases (15.4%) and 90 controls (2.6%). AF was associated with a 3-fold increased risk of VF (adjusted odds ratio, 3.1 [2.1–4.5]). VF risk in AF cases was increased to the same extent across all age/sex groups and in AF cases who had no comorbidity (adjusted odds ratio 3.0 [1.6–5.1]) or used no confounding drugs (antiarrhythmics, 2.4 [1.4–4.3]; QT-prolonging drugs, 3.1 [1.8–5.4]). VF risk was similarly increased in AF cases with acute myocardial infarction–related VF (adjusted odds ratio 2.6 [1.4–4.8]), and those with non-acute myocardial infarction–related VF (adjusted odds ratio 4.3 [1.9–10.1]).

Conclusions—AF is independently associated with a 3-fold increased risk of VF. Comorbidity, use of antiarrhythmic or QT-prolonging drugs, or acute myocardial infarction does not fully account for this increased risk. (Circ Arrhythm Electrophysiol. 2014;7:1033-1039.)

Key Words: arrhythmias, cardiac — atrial fibrillation — death, sudden, cardiac — ventricular fibrillation

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is associated with increased rates of mortality.1–3 The causes of death in AF are noncardiac (eg, stroke) in a minority.2 How cardiac causes contribute to mortality in AF remains unresolved. Sudden cardiac death (SCD) emerged as an important mode of death in AF patients from 2 recent combined population-based studies.4 Given that SCD in the general population is caused by ventricular fibrillation (VF) in most patients,5 this finding raises the question whether AF and VF are associated. In both studies, SCD diagnosis was based on clinical information, while ECG documentation of VF was lacking, leaving this question unanswered.

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An association between AF and VF may exist in 3 ways. First, AF may intrinsically increase VF risk. For instance, AF and VF may have a shared (inherited) molecular basis as ion channel–encoding genes may be expressed both in atria and in ventricles. Mutations in these genes have been associated with both AF and VF.6,7 In addition, the continuous exposure to short-long-short R-R intervals, present in AF, may be proarrhythmic and trigger VF, even in nondiseased hearts.8 Second, AF may act as partner in crime with concomitant cardiac pathology that triggers VF. For example, rapid heart rates caused by AF may reduce coronary perfusion in patients with coronary artery disease and trigger acute myocardial infarction (AMI). Indeed, AF is associated with increased AMI risk, and AMI is a common cause of VF.5,9 Although VF in the general population is frequently preceded by AMI, studies in nonischemic VF are needed to clarify whether increased VF risk in AF is explained by increased AMI risk. Third, it may be noncausal. AF often coexists with risk factors for VF (eg, ischemic heart disease, heart failure) and may act as confounder.10 Likewise, antiarrhythmic drugs for AF treatment may increase VF risk; this applies to both QT-prolonging drugs (sotalol, amiodarone)11 and non-QT–prolonging drugs (flecainide).12 This confounder may be accounted for by studying AF patients not using such drugs.

Thus, the suggestion that AF and VF are associated awaits confirmation. Furthermore, it is unknown whether this association is explained by intrinsic VF-provoking effects of AF, AF acting as trigger in the face of underlying pathology or confounding. Answering these questions may have immediate clinical implications, given the high incidence of AF and the often-lethal outcome of VF. Therefore, the primary goal of this study was to study whether AF is an independent
risk factor for VF in the general population. The second goal was to study whether the association between AF and VF is explained by comorbidity (in particular, AMI), use of (antiarrhythmic) drugs, or both.

Methods

Setting

In this community-based case-control study, cases were patients with out-of-hospital cardiac arrest (OHCA) with ECG-documented VF in the Amsterdam Resuscitation Studies (ARREST) registry in the study period July 1, 2007, to December 31, 2011. Controls were randomly drawn non-OHCA subjects from the Huisartsen Netwerk Academisch Medisch Centrum (HAG-net-AMC). ARREST and HAG-net-AMC are ongoing, prospective, community-based studies.13–15

ARREST is designed to study the clinical, pharmacological, and genetic determinants and outcome of OHCA in the community.13 The ARREST research group prospectively collects data of all cardio-pulmonary resuscitation efforts for OHCA from cardiac causes in a contiguous region of the Netherlands (population >2.4 million) in collaboration with all Emergency Medical Services in this study region, using a mandatory multiple-source notification system (consisting of dispatch centers, ambulance services, and all 14 area hospitals). This ensures inclusion of >95% of all resuscitation efforts. Of the included patients with VF, additional information is gathered from the hospital of admission (cause of OHCA), general practitioner (GP) (medical history, risk factors), and community pharmacy (drug use).

HAG-net-AMC contains the complete medical records (medical history, risk factors) of >600000 patients from a large group of GPs in the same study region as ARREST.14,15 Data in HAG-net-AMC are representative for the community because, in the Netherlands, every citizen has a GP, and GPs have a complete overview of all diagnoses made by medical specialists.

This study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all subjects with aborted SCD. The Ethics Committee of the Academic Medical Center Amsterdam approved the use of data from patients who did not survive a cardiac arrest and approved this study.

Definitions

For all patients, AF status (AF diagnosed by GP or specialist) was retrieved from GP records, as were known risk factors for heart disease and VF. GP records contain diagnoses from GPs and specialists according to accepted guidelines and recorded according to the International Classification of Primary Care system.16 The following risk factors were included in this study: ischemic heart disease, cerebrovascular accident or transient ischemic attack, hypertension, diabetes mellitus, dyslipidemia, and heart failure.

In a subanalysis of patients in whom medication was retrieved (647 cases), prescriptions of antiarrhythmic drugs used for AF (sotalol, amiodarone, flecainide) or QT-prolonging drugs (class 1 or 2 according to Arizona-CERT [Arizona Center for Education and Research on Therapeutics] classification)15 were identified from computerized databases of community pharmacists. We studied the current use of medication, defined as VF date falling within the prescription duration or ≤10% after prescription duration (to account for carryover effects). Medication use could not be retrieved in controls.

Statistical Analysis

The association between AF and VF was estimated by calculation of the adjusted odds ratio (OR) using conditional logistic regression analysis. Risk factors that were individually associated with VF (at a P<0.1 level) were included in the regression analyses if they changed the point estimate of the association between AF and VF by >10%. In a second model, the OR was calculated by including all risk factors that were individually associated with VF (at a P<0.1 level) in the multivariable analysis. Age and sex were adjusted for in all analyses. We investigated the potential effect modification by age, sex, presence/absence of a single risk factor, and presence/absence of all risk factors, by calculating interaction on a multiplicative scale and subsequent stratifications according to possibly confounding factors. Effect modification by AMI was studied in patients in whom AMI status was established and their matched controls. To exclude a possible confounding/mediating effect of antiarrhythmic or QT-prolonging drugs, we performed a subanalysis excluding users of such drugs and their matched controls. Subanalyses were all performed using multivariable logistic regression, adjusting for age, sex, and all risk factors. All analyses were performed using SPSS for Mac version 20.0.

Results

Association Between AF and VF

A diagnosis of AF was found in 215 cases (15.4%) and 90 controls (2.6%). AF was associated with a 3-fold increased risk of VF after correction for confounding risk factors in both models (ORadjusted, 3.1 [95% confidence interval (CI), 2.1–4.5]; Table 2). This risk was increased across all age groups and did not differ significantly between groups (45–64 years: ORadjusted, 5.1 [95% CI, 2.2–12.0]; 65–84 years: ORadjusted, 2.1 [95% CI, 1.3–3.2]; >85 years: ORadjusted, 8.5 [95% CI, 2.7–27.1]; P for interaction age groups=1.0; Table 2). VF risk was increased in women and men with AF and did not differ significantly between sexes (ORadjusted= 4.6 [95% CI, 2.3–8.6] and 2.6 [95% CI, 1.7–4.0], respectively; P for sex interaction=0.17; Table 2).

![Flowchart of case inclusion](http://circep.ahajournals.org/ Downloaded from)
Association Between AF and VF Is Not Explained by Concomitant Diseases
The studied risk factors for heart disease and VF did not modify the risk of VF in AF patients, eg, VF risk was similarly increased in AF patients with heart failure (OR adjusted, 2.7 [95% CI, 1.1–6.7]; Table 3) and those without (OR adjusted, 2.8 [95% CI, 2.0–4.0]; Table 3). Moreover, VF risk was still increased 3-fold in apparently healthy cases, ie, those without any of the studied risk factors (OR adjusted, 3.0 [95% CI, 1.6–5.5]; Table 4).

Association Between AF and VF Is Not Explained by Concomitant Use of Antiarrhythmic or QT-Prolonging Drugs
In 647 VF cases of whom medication use was retrieved, 105 (16.2%) had a diagnosis of AF.

The proportion of AF in this sample was similar to the proportion in the total study cohort (15.4%). Of the 105 AF cases, 17 used an antiarrhythmic drug for AF. To study whether the association between AF and VF still existed in the absence of antiarrhythmic drug use, we performed a subanalysis in which we excluded these 17 cases. We found that VF risk among AF cases who used no antiarrhythmic drugs (n=88) was similar to VF risk in the total study cohort with known medication use (OR adjusted, 2.4 [95% CI, 1.4–4.3]; Table 5). A similar subanalysis excluding cases who used QT-prolonging drugs (n=15) showed that VF risk was also similar to the total cohort (OR adjusted, 3.1 [95% CI, 1.8–5.4]; Table 5). Stratified analysis to sex in both subanalyses showed no substantial difference in VF risk.

Association Between AF and VF Is Not Explained by AMI
To study whether the association between AF and VF was explained by AMI, we retrieved from hospital records, available of 970 cases (the remaining cases died before a diagnosis was made), whether AMI was the immediate cause for VF; this was so in 617 cases (64%). Of these 617 AMI-VF cases, 54 (8.8%) had AF compared with 31 (2.0%) among their matched controls (OR adjusted, 2.6 [95% CI, 1.4–4.8]; Table 6). Among the 353 (36%) non-AMI-VF cases, 79 (22.4%) had AF compared with 19 (2.0%) among their matched controls (OR adjusted, 4.3 [95% CI, 1.9–10.1]; Table 6). The increases in the proportions of AF patients were not significantly different between the AMI-VF group and the non-AMI-VF group.

Discussion
Main Findings
We provide systematically collected evidence that AF in the general population is an independent risk factor for VF. The
risk for VF in AF patients was increased to the same extent in men and women and across various age categories. Comorbidities, use of antiarrhythmic or QT-prolonging drugs, or AMI does not account for this increased risk.

**AF Is Associated With VF**

The pathophysiologic mechanisms underlying the association between AF and higher all-cause mortality rates remain incompletely understood. One study found that noncardiac causes account for a minority of deaths in AF patients (stroke 15%, heart failure 16%).

More studies have associated AF with cardiovascular death. Antiarrhythmic drugs used in AF treatment have been associated with SCD. Antiarrhythmic drugs and QT-prolonging drugs have been associated with SCD.

Concomitant Diseases Do Not Mediate the Association Between AF and VF

To date, most studies on cause-specific mortality in AF were confounded by concomitant disease; limiting conclusions on a causal link between AF and cause-specific mortality. The Women’s Health Study circumvented this problem by studying apparently healthy women.

Furthermore, the Atrial Fibrillation and Congestive Heart Failure study found evidence against the notion that AF causes death by promoting heart failure. In this study, terminating AF in heart failure patients did not affect heart failure severity or reduce its mortality rate. In the present study, we assessed comorbidity in 3 ways. First, we corrected for all available confounding factors. Second, to study the contribution of each risk factor to VF risk, we compared VF risk between cases with the risk factor and those without. Heart failure, for example, did not influence VF risk in AF patients, as we found that VF risk was similarly increased in AF patients with heart failure and those without. The same was found for remaining risk factors.

Third, we studied VF risk in AF patients without known comorbidities and found the same increased risk. Therefore, our observations support the hypothesis that SCD risk in AF patients is not explained by comorbidity.

### Table 2. Atrial Fibrillation (AF) and Risk for Ventricular Fibrillation Stratified to Sex and Age

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=1397)</th>
<th>Controls (n=3474)</th>
<th>OR* (95% CI)</th>
<th>OR† (95% CI)</th>
<th>OR‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AF</td>
<td>1182 (84.6)</td>
<td>3384 (97.4)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>AF</td>
<td>215 (15.4)</td>
<td>90 (2.6)</td>
<td>5.4 (4.1–7.2)</td>
<td>3.0 (2.1–4.4)</td>
<td>3.1 (2.1–4.5)</td>
</tr>
</tbody>
</table>

**Stratification by sex**

- **Male**:
  - Cases: 150 (14.0)
  - Controls: 55 (2.5)
  - OR: 4.3 (3.1–6.1) (95% CI)
  - OR: 2.5 (1.6–3.9) (95% CI)
  - OR: 2.6 (1.7–4.2) (95% CI)

- **Female**:
  - Cases: 65 (20.0)
  - Controls: 35 (2.7)
  - OR: 8.5 (5.1–14.2) (95% CI)
  - OR: 4.7 (2.4–8.9) (95% CI)
  - OR: 4.5 (2.3–8.6) (95% CI)

**Interaction**

- OR: 0.57 (0.3–1.3) (95% CI)
- P: 0.17

**Stratification by age, y**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>OR† (95% CI)</th>
<th>OR‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–64</td>
<td>52 (8.9)</td>
<td>16 (1.0)</td>
<td>8.2 (4.5–15.0) (95% CI)</td>
<td>5.6 (2.5–12.2) (95% CI)</td>
<td>5.1 (2.2–12.0) (95% CI)</td>
</tr>
<tr>
<td>65–84</td>
<td>131 (21.4)</td>
<td>59 (5.3)</td>
<td>4.3 (3.1–6.1) (95% CI)</td>
<td>2.0 (1.3–3.1) (95% CI)</td>
<td>2.1 (1.3–3.2) (95% CI)</td>
</tr>
<tr>
<td>&gt;85</td>
<td>30 (36.1)</td>
<td>15 (8.9)</td>
<td>6.5 (2.9–14.6) (95% CI)</td>
<td>8.3 (2.6–26.2) (95% CI)</td>
<td>8.5 (2.7–27.1) (95% CI)</td>
</tr>
</tbody>
</table>

**Interaction**

- OR: 1.0 (0.5–1.9) (95% CI)
- P: 1.0

Data are number (%) unless otherwise indicated. Percentages do not add up, as they are stratified to sex and age. Included risk factors in the model: heart failure (31%), cardiac ischemia (17%), and hypertension (11%). CI indicates confidence interval; and OR: odds ratio.

*Odds ratios adjusted and matched for age and sex.

†Odds ratios adjusted and matched for age and sex and adjusted for risk factors changing the point estimate of association between AF and ventricular fibrillation >10%.

‡Odds ratios adjusted and matched for age and sex and adjusted for all risk factors included in Table 1.

§Number and percentages of cases and controls [(cases (%)/controls (%)) without AF per stratum: males: 923 (86.0)/2130 (97.5); females: 259 (80.0)/1254 (97.3)].

║Number and percentages of cases and controls [(cases (%)/controls (%)) without AF per stratum: 45–64 y: 526 (91.1)/1589 (99.0); 65–84 y: 480 (76.6)/1048 (94.7); >85 y: 53 (63.9)/154 (91.1)].
In the present study, we performed a subanalysis in cases who did not use such drugs and found increased VF risk even in these patients. Therefore, we conclude that the use of such drugs does not underlie the association between AF and VF in this study. However, we were unable to study whether these drugs interact with AF or increase VF risk in patients using these drugs because drug use could not be retrieved in controls. Thus, an additional VF risk in these patients cannot be excluded.

A recent study associated AF with AMI, suggesting that AF may cause AMI.9 Because AMI is strongly related to VF,5 we examined whether AMI explained our results. We found that the proportion of AF patients was similarly increased among cases in whom VF was related to AMI and in those where it was not. This observation further supports the notion that AF independently underlies increase in VF risk.

**AF May Intrinsically Increase VF Risk**

Our study was not designed to study the pathophysiologic basis for the observed association between AF and VF, and we can only speculate about them. First, shortened ventricular refractoriness during rapid heart rates in AF may predispose to VF.22 Second, irregular ventricular rates during AF expose the ventricle to short-long-short R-R interval sequences, which may favor the development of ventricular arrhythmias.8 Third, atrial tachyarrhythmias may increase sympathetic tone and decrease parasympathetic tone because of their hemodynamic effects and favor VF development.23 Last, AF and VF may have the same inherited basis. Mutations in ion channel–encoding genes have been associated with both AF and VF.6,7

### Strengths and Limitations of the Study

The major strength of our study is its population-based design, minimizing selection bias. This enabled us to study symptomatic and asymptomatic AF patients. We also collected extensive information on concomitant diseases and potential confounders, while ECG documentation of VF minimized misclassification of nonarrhythmic and noncardiac death causes. Use of a wider SCD definition, as done in previous studies, might be a concern if used to study death causes in AF patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=1397)</th>
<th>Controls (n=3474)</th>
<th>OR* (95% CI)</th>
<th>OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac ischemia Present</td>
<td>122 (23.4)</td>
<td>19 (10.9)</td>
<td>2.1 (1.2–3.8)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>93 (10.6)</td>
<td>71 (2.2)</td>
<td>3.2 (2.2–4.7)</td>
<td></td>
</tr>
<tr>
<td>Heart failure Present</td>
<td>97 (41.6)</td>
<td>10 (25.7)</td>
<td>2.7 (1.1–6.7)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>118 (10.1)</td>
<td>80 (2.3)</td>
<td>2.8 (2.0–4.0)</td>
<td></td>
</tr>
<tr>
<td>Hypertension Present</td>
<td>136 (21.6)</td>
<td>25 (4.8)</td>
<td>3.9 (2.3–6.4)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>79 (5.7)</td>
<td>65 (2.2)</td>
<td>2.2 (1.4–3.4)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus Present</td>
<td>69 (25.2)</td>
<td>20 (6.8)</td>
<td>3.8 (2.0–7.4)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>146 (13.0)</td>
<td>70 (2.2)</td>
<td>2.6 (1.8–3.7)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia Present</td>
<td>76 (17.0)</td>
<td>9 (4.8)</td>
<td>2.8 (1.3–6.1)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>139 (10.0)</td>
<td>81 (2.5)</td>
<td>2.8 (1.9–3.8)</td>
<td></td>
</tr>
<tr>
<td>CVA or TIA Present</td>
<td>32 (23.2)</td>
<td>5 (4.4)</td>
<td>5.4 (1.7–17.9)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>183 (14.5)</td>
<td>85 (2.5)</td>
<td>2.7 (1.9–3.8)</td>
<td></td>
</tr>
</tbody>
</table>

Data are number (%) unless otherwise indicated. Percentages do not add up, as they are stratified by comorbidity. CI indicates confidence interval; CVA, cerebrovascular accident; SD, standard deviation; and TIA, transient ischemic attack.

*Odds ratios for interaction between absence and presence of the studied risk factor, adjusted for age and sex, and remaining risk factors included in Table 1.

†Odds ratios adjusted for age and sex and remaining risk factors included in Table 1.

Table 4. Atrial Fibrillation and Risk for Ventricular Fibrillation in Cases and Controls With or Without Comorbidities in Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=1397)</th>
<th>Controls (n=3474)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No comorbidities</td>
<td>n=389</td>
<td>n=2600</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>No atrial fibrillation</td>
<td>372 (95.6)</td>
<td>2565 (98.7)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>17 (4.4)</td>
<td>35 (1.3)</td>
<td>3.0 (1.6–5.5)*</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>n=1008</td>
<td>n=874</td>
<td>1.0 (95% CI)</td>
</tr>
<tr>
<td>No atrial fibrillation</td>
<td>810 (80.4)</td>
<td>819 (93.7)</td>
<td>1.0 (95% CI)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>198 (19.6)</td>
<td>55 (6.3)</td>
<td>4.5 (3.2–6.2)†</td>
</tr>
</tbody>
</table>

Data are number (%) unless otherwise indicated. CI indicates confidence interval; and OR, odds ratio.

*Odds ratios adjusted for age and sex.

†Odds ratios adjusted for age and sex and remaining risk factors included in Table 1.
patients. For example, stroke is a well-known cause of death in AF, but the SCD definition is largely based on (presumed and mostly unwitnessed) death circumstances. Consequently, an AF patient who is unexpectedly found dead within several hours after being in apparent stable condition is classified as SCD, while a fatal stroke might have been the true cause of death.

Our study has some limitations, which are typical for observational studies in the general population. First, AF ascertainment was based on GPs’ medical records and prevalence of (paroxysmal) AF might have been underestimated. Also, the interval between incident AF and VF occurrence remains unknown. Last, residual bias may remain from risk factors unavailable for analysis in this study.

Conclusions
AF is associated with 3-fold increased risk of VF. Comorbidity, antiarrhythmic/QT-prolonging drugs, or AMI do not fully account for this increased risk.

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References
Atrial Fibrillation (AF) is associated with sudden cardiac death in the general population. In this study, we aimed to establish whether AF is associated with ventricular fibrillation (VF), the most common cause of sudden cardiac death, and whether this association is independent of confounders, ie, concomitant disease, use of antiarrhythmic or QT-prolonging drugs, and acute myocardial infarction. To this end, we performed a community-based case-control study among 1397 out-of-hospital cardiac arrest cases with ECG-documented VF, and 3474 age-/sex-matched non-VF controls. VF risk in AF patients was studied by means of (conditional) logistic regression, adjusting for all available confounders. AF occurred in 15.4% of the cases and in 2.6% of the controls; AF was associated with a 3-fold increased risk of VF. VF risk in AF cases was increased to the same extent across all age/sex groups and in AF cases without prespecified comorbidities or antiarrhythmic or QT-prolonging drugs. Also, VF risk was similarly increased in AF cases with acute myocardial infarction–related VF and in those with non-acute myocardial infarction–related VF. We therefore conclude that AF is independently associated with a 3-fold increased risk of VF. Further studies to better define the mechanisms of this association are warranted.
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