Atrial fibrillation (AF) is a major public health problem owing to its increasing prevalence and strong association with morbidity and mortality.\(^1\)\(^2\) Patients with AF have 4 to 5 times the risk of stroke and about double the risk of mortality compared with those without AF.\(^3\)\(^\text{6}\)

Myocardial infarction (MI) is an established risk factor for AF,\(^7\) with AF occurring in 6\% to 21\% of patients with MI.\(^8\) Conversely, sporadic cases of thromboembolic acute MI also have been reported in patients with AF,\(^9\)\(^\text{10}\) and presence of AF during acute MI has been associated with increased risk of developing in-hospital reinfarction.\(^\text{11}\) These findings suggest that AF could also be a risk factor for MI. However, evidence from population studies to support this assertion is lacking. Therefore, we examined the association between AF and risk of incident MI in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study,\(^17\) a large biracial population-based cohort study.

**Methods**

The study protocol was reviewed and approved by the participating institutions’ institutional review boards. We examined the association between AF and risk of MI in REGARDS. Participants were free of coronary heart disease (CHD) at baseline. We excluded patients with previous MI and stroke and those who were lost to follow-up. We obtained demographic, clinical, and laboratory data at baseline. Incident MI was defined as a primary diagnosis of MI based on International Classification of Diseases–10 codes. AF was defined as having a diagnosis of AF or atrial flutter. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95\% confidence intervals (CIs) for MI in participants with and without AF after adjusting for age, sex, race, body mass index, diabetes, smoking status, hypertension, and total cholesterol. We further adjusted for diabetes, body mass index, systolic blood pressure, and estimated glomerular filtration rate. We also adjusted for congestive heart failure, history of stroke, history of vascular disease, and albumin-to-creatinine ratio.

**Results**

Over 6.9 years of follow-up (median 4.5 years), 648 incident MI events occurred. In a sociodemographic-adjusted model, AF was associated with about 2-fold increased risk of MI (HR, 1.96 [95\% CI, 1.52–2.52]). This association remained significant (HR, 1.70 [95\% CI, 1.26–2.30]) after further adjustment for total cholesterol, high-density lipoprotein cholesterol, smoking status, systolic blood pressure, blood pressure–lowering drugs, body mass index, diabetes, warfarin use, aspirin use, statin use, history of stroke and vascular disease, estimated glomerular filtration rate, albumin to creatinine ratio, and C-reactive protein level. In subgroup analysis, the risk of MI associated with AF was significantly higher in women (HR, 2.16 [95\% CI, 1.41–3.31]) than in men (HR, 1.39 [95\% CI, 0.91–2.10]) and in blacks (HR, 2.53 [95\% CI, 1.67–3.86]) than in whites (HR, 1.26 [95\% CI, 0.83–1.93]); for interactions, P = .03 and P = .02, respectively. On the other hand, there were no significant differences in the risk of MI associated with AF in older (\(\geq\)75 years) vs younger (<75 years) participants (HR, 2.00 [95\% CI, 1.16–3.35] and HR, 1.60 [95\% CI, 1.11–2.30], respectively); for interaction, P = .44.

**Conclusions and Relevance**

AF is independently associated with an increased risk of incident MI, especially in women and blacks. These findings add to the growing concerns of the seriousness of AF as a public health burden: in addition to being a well-known risk factor for stroke, AF is also associated with increased risk of MI.
Ascertaining MI Events

All CHD events were adjudicated by a team of experts following published guidelines. Details of the CHD adjudication have been described elsewhere.18 For MI, medical records were examined for the presence of signs or symptoms of myocardial ischemia; a rising and/or falling pattern in cardiac troponin or creatine phosphokinase-MB level over 6 hours or longer with a peak value twice the upper limit of normal or higher (diagnostic cardiac enzymes); and ECG changes consistent with myocardial ischemia or MI, guided by the Minnesota code and classified as evolving diagnostic, positive, nonspecific, or not consistent with ischemia.19 Definite MIs were those with diagnostic enzyme levels or ECG. Probable MIs (about 3% of MI cases) were those cases with elevated but not diagnostic (ie, equivocal) enzyme levels with a positive but not diagnostic ECG or cases where enzyme data were missing with a positive ECG in the presence of ischemic signs or symptoms. Fatal and nonfatal definite and probable MIs were included as events in this study.

Ascertaining AF

Details of ascertainment of AF have been published elsewhere.20 Briefly, AF was identified at baseline from 2 sources: (1) a study-scheduled ECG recorded during the in-home visit that was centrally read by electrocardiographers blinded to clinical data; and (2) a history of physician diagnosis of AF reported by the participants during the computer-assisted telephone surveys assessing medical history and health status. These 2 AF ascertainment methods have been equally predictive of stroke in the REGARDS study.20

Covariates

Age, sex, race, income, education, and smoking status were self-reported. Annual income was dichotomized at $20,000, and education was dichotomized at high school diploma. Smokers were defined as having smoked at least 100 cigarettes in their lifetime and smoking now, even occasionally. Data on blood pressure-lowering drugs and regular aspirin use were based on self-report, while use of digoxin, warfarin, and statin were based on pill-bottle review. Body mass index (BMI) was calculated from height and weight measured during in-home visit using a standardized protocol. Blood pressure was measured using an aneroid sphygmomanometer after a seated rest of 5 minutes with both feet on the floor. Two measures were obtained following a standardized protocol and averaged. Blood and urine markers included levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, fasting glucose, high-sensitivity C-reactive protein (CRP), serum creatinine, and urinary albumin and creatinine from a spot urine specimen. Diabetes was classified as present if the fasting glucose level was 126 mg/dL or higher (non-fasting glucose, ≥200 mg/dL [n = 229]) or if participant was taking diabetes medications. (To convert glucose to millimoles per liter, multiply by 0.0555.) We used current use of digoxin at baseline as a proxy for heart failure diagnosis similar to previous reports from REGARDS.21 CHADS2 score (congestive heart failure; hypertension; age, ≥75 years; diabetes mellitus; and prior stroke) was calculated using 1 point for each category except for prior stroke, which was given 2 points.22 Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration).23 Urinary albumin and creatinine were used to define the albumin to creatinine ratio (ACR).

Statistical Analysis

Characteristics of the analysis population were tabulated by AF status at baseline. Age-adjusted incidence rates of MI per 1000 person-years in participants with and those without baseline AF were calculated in the entire study population and in prespecified age, sex, and race subgroups. Cox proportional hazards analysis was used to examine the association between baseline AF with incident MI in a series of models with incremental adjustments as follows: model 1 adjusted for age, sex, race, region of residence, education level, and income; model 2 adjusted for model 1 covariates plus total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, BMI, diabetes, use of antihypertensive medications, warfarin, aspirin, or statin, and history of noncardiac vascular disease (stroke, peripheral vascular disease, and aortic aneurysm); model 3 adjusted for model 2 covariates plus eGFR lower than 60 mL/min/1.73m², log-transformed CRP, and log-transformed ACR.

In a sensitivity analysis, we used AF ascertained by more restricted methods such as “ECG only” and by “ECG and/or history of a physician diagnosis plus warfarin use.” Other analyses included further adjustment for baseline heart failure as well as stroke events and chest pain hospitalizations that occurred during follow-up (included in the model as time-updated variables), separately. We also examined whether using death as a competing risk affected the results.

Models with identical incremental adjustment for the main analysis were examined in subgroups of participants strati-
fied by age (using 75 years as a cut point in the main analysis and 65 years in additional analysis), sex, and race. Interaction between AF and each of these variables was examined in the full model. Because we observed significant interaction by sex and race, we also examined the age-adjusted risk of MI associated with AF in black men, black women, white men and white women, separately.

To investigate whether warfarin and aspirin modified the risk of MI associated with AF, we conducted subgroup analysis stratified by warfarin and aspirin use. We also examined the risk of MI in participants with AF and a CHADS2 score of 1 or lower; AF and a CHADS2 score higher than 1; and no AF (reference group).

The assumptions of proportionality were met. Individuals were censored at the time of their event, death, or the end of follow-up. Statistical significance for all analyses was considered as \( P < .05 \). Analyses were conducted using SAS 9.3 (SAS Institute) except for competing risk Cox proportional hazards regression models, which were fitted using STATA version 12 (STATA Inc).

## Results

After excluding participants with no follow-up data (n = 569), prevalent CHD at baseline (n = 5227), or missing data on AF status (n = 515), we found that 23,928 participants remained, and all of these were included in the analysis. At baseline, AF was present in 1631 participants; 268 AF cases were detected from the study baseline ECG, and the rest from medical history; 168 AF cases were detected by both methods. Table 1 lists the baseline characteristics of the study population stratified by AF status. Compared with those without AF, participants with AF were older, were less likely to be black and men, had more CHD risk factors such as diabetes and hypertension, and had worse kidney function.

Over 6.9 years of follow-up (median 4.5 years), 648 MI events occurred. The age-adjusted incidence rate of MI in participants with AF (12.0 [95%CI, 9.6-14.9] per 1000 person-years) was double the rate in those without AF (6.0 [95%CI, 5.6-6.6] per 1000 person-years) \( (P < .001) \). Figure 1 shows the

### Table 1. Baseline Characteristics of REGARDS Study Participants Stratified by Atrial Fibrillation Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atrial Fibrillation (n = 1631)</th>
<th>No Atrial Fibrillation (n = 22,297)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>66.5 (9.7)</td>
<td>63.9 (9.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Men, %</td>
<td>38.4</td>
<td>42.0</td>
<td>.01</td>
</tr>
<tr>
<td>African American, %</td>
<td>37.9</td>
<td>42.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education high school, %</td>
<td>39.4</td>
<td>36.6</td>
<td>.001</td>
</tr>
<tr>
<td>Annual income &lt;$20,000, %</td>
<td>24.5</td>
<td>19.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>29.6 (6.8)</td>
<td>29.3 (6.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>12.8</td>
<td>14.3</td>
<td>.08</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>22.8</td>
<td>19.1</td>
<td>.003</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>65.2</td>
<td>55.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of noncardiac vascular disease, %</td>
<td>11.1</td>
<td>6.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antihypertensive medication use, %</td>
<td>59.3</td>
<td>47.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>127 (17)</td>
<td>127 (16)</td>
<td>.37</td>
</tr>
<tr>
<td>Total Cholesterol, mean (SD), mg/dL</td>
<td>191 (40)</td>
<td>196 (39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL-Cholesterol, mean (SD), mg/dL</td>
<td>52 (17)</td>
<td>53 (16)</td>
<td>.06</td>
</tr>
<tr>
<td>LDL-Cholesterol, mean (SD), mg/dL</td>
<td>112 (34)</td>
<td>117 (40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglycerides, median (25th-75th percentile), mg/dL</td>
<td>112 (83-161)</td>
<td>109 (80-155)</td>
<td>.004</td>
</tr>
<tr>
<td>Statin use, %</td>
<td>33.1</td>
<td>27.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Warfarin use, %</td>
<td>19.9</td>
<td>1.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aspirin use, %</td>
<td>41.2</td>
<td>37.5</td>
<td>.003</td>
</tr>
<tr>
<td>C-reactive protein, median (25th-75th percentile), mg/L</td>
<td>2.6 (1.1-6.1)</td>
<td>2.2 (0.9-4.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate &lt;60 ml/min/1.73 m², %</td>
<td>13.7</td>
<td>9.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Albumin to creatinine ratio, median (25th-75th percentile), mg/g</td>
<td>8.9 (5.2-21.7)</td>
<td>7.0 (4.5-14.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

SI Conversions: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*Noncardiac vascular disease included stroke, peripheral artery disease, or aortic aneurism.*
In subgroup analysis, no statistically significant interaction by participant age (≥75 years vs <75 years) was detected (P = .44 for interaction) (Table 2). Similar results were obtained when we used 65 years as a cut point, comparing age 65 years or older (HR, 1.68 [95% CI, 1.14-2.48]) with younger than 65 years (HR, 1.28 [95% CI, 0.74-2.21]) (P = .45 for interaction). On the other hand, significant differences were observed in the sex and race subgroups. As summarized in Table 2, in a multivariable-adjusted model, the association was stronger in women than in men (P = .03 for interaction) and stronger in blacks than in whites (P = .02 for interaction). A similar direction of associations among these subgroups was observed when we used a more restricted method for ascertainment of AF such as AF by ECG and/or history of a physician diagnosis plus warfarin use and AF by ECG only (See eTable 1 in the Supplement) or by ECG only (See eTable 2 in the Supplement).

In sex-race stratified analyses, the MI association with AF was strongest in black men, followed by white women, then black women, but nonsignificant in white men (multivariable-adjusted HRs and 95% CIs, 2.91 [95% CI, 1.62-5.23]) for black men; 2.33 [1.27-4.28] for white women; 2.17 [1.19-3.98] for black women; and 0.86 [0.58-1.56] for white men (Figure 2).
In a multivariable model similar to model 3 summarized in Table 2, the risk of MI associated with AF in warfarin users was significantly less than that in nonusers (HR, 0.76 [95% CI, 0.29-1.94]) vs (HR, 1.92 [95% CI, 1.42-2.60]) (P = .02 for interaction). On the other hand, no statistically significant difference in the risk of MI associated with AF was observed between aspirin users and nonusers (HR, 2.13 [95% CI, 1.44-3.15] in aspirin users vs HR, 1.36 [95% CI 0.86-2.15] in nonusers) (P = .15 for interaction).

Atrial fibrillation with higher CHADS2 score was associated with higher risk of MI. As summarized in Table 3, compared with no AF, AF in the setting of a CHADS2 score higher than 1 was associated with a 95% increased risk of MI (HR, 1.95 [95% CI, 1.33-2.86]). This compares with only a 40% increased risk if the CHADS2 score was 1 or lower (HR, 1.40 [95% CI, 0.91-2.17]).

**Table 3. Risk of Incident MI Associated With Baseline AF Stratified by the Level of CHADS2 Score**

<table>
<thead>
<tr>
<th>CHADS2 Level</th>
<th>Participants, No.</th>
<th>MI Events, No.</th>
<th>HR (95% CI)</th>
<th>Modela</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AF</td>
<td>22 297</td>
<td>570</td>
<td>1 [Reference]</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>AF and CHADS2 score ≤1</td>
<td>983</td>
<td>30</td>
<td>1.40 (0.91-2.17)</td>
<td>.13</td>
<td></td>
</tr>
<tr>
<td>AF and CHADS2 score &gt;1</td>
<td>648</td>
<td>48</td>
<td>1.95 (1.33-2.86)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; CHADS2, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke (calculated using 1 point for each category except 2 points for prior stroke)22; HR, hazard ratio; MI, myocardial infarction; NA, not applicable.

a Model adjusted for age, sex, race, region of residence, education level, income, total cholesterol, high density lipoprotein cholesterol, smoking status, systolic blood pressure, body mass index, warfarin use, aspirin use, and statin use.

In a stratified analysis by warfarin use, the risk of MI associated with AF was lower in warfarin users than in nonusers, suggesting an effect modification by warfarin use. This accords with previous reports showing that warfarin might provide a protective effect against MI after acute coronary syndromes23 and in patients with AF who are prescribed anticoagulation for stroke prevention.26 A risk-benefit analysis is needed for routine use of anticoagulation in prevention of MI in patients with AF at high risk, such as those with higher CHADS2 scores. As we showed, AF plus higher CHADS2 score was associated with higher risk of MI.

**Possible Explanations**

Our results of increased risk of MI in AF and the known increased risk of AF in MI2 suggest a bidirectional relationship between these 2 conditions, with each leading to the other. Similar bidirectional relationships between AF and chronic kidney disease27,28 and between AF and heart failure29 have been reported.

A bidirectional relationship between AF and MI could be partially explained by the fact that AF and MI share similar risk factors, and therefore, common pathophysiologic processes might drive both outcomes. That is, in susceptible individuals, both AF and MI may eventually occur, and it is just a matter of which comes first. Similarly, it is also possible that subclinical CHD is associated with higher prevalence of AF and also associated with higher risk for the development of incident MI. That is, AF may not be a risk factor for incident MI but rather a marker of prevalent CHD that in turn places individuals at higher risk for MI events. These explanations, however, ignore the potential impact of AF on the risk profile that could lead to MI. For example, higher levels of inflammatory markers are associated with increased risk of both AF and MI, suggesting a role of inflammation in developing both conditions.30-34 When AF occurs, however, it creates and sustains an inflammatory and prothrombotic environment (ie, AF-induced inflammation),35 which subsequently can increase the risk of MI. An AF-induced increase in peripheral prothrombotic risk through systemic platelet activation, thrombin generation, and endothelial dysfunction as well as inflammation have been shown in several studies.36-38

Coronary thromboembolism with subsequent MI could be another potential explanation for the increased risk of MI in patients with AF. Although the actual incidence of coronary embolism is unknown, it is generally considered rare. The rarity of coronary embolization has been attributed to differ-

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ences between the caliber of the aorta and the coronary arteries, location of the coronary vessels at the root of the aorta, emergence of the coronary arteries at a right angle, the bulk and swiftness of the blood current in this portion of the aorta, and the fact that the major part of coronary filling occurs in diastole. Nevertheless, several sporadic cases of MI due to coronary embolism have been reported, suggesting that occurrence of coronary embolism could be higher than it is thought to be. Furthermore, in a postmortem study of 419 patients with MI, coronary embolization accounted for as many as 55 (13%) of these cases. A coronary lesion was considered to be embolic in that study if at autopsy a source was apparent and the occluded artery demonstrated no evidence of mural disease including arteritis or significant atherosclerosis with an essentially normal intima at the site of occlusion. Atrial fibrillation was the underlying disease predisposing to coronary embolism in 24% of these cases. These findings suggest that coronary embolization, which may not be as rare as we think, could be one of the mechanisms explaining our findings.

Another potential explanation for the increased risk of MI in patients with AF could be derived from the notion that some patients with AF present with episodes of poorly controlled ventricular response resulting in demand infarction, referred to as type 2 MI. In a cohort of unselected hospital patients, one-fourth of all MIs were type 2 MIs, and about half of those patients had no significant coronary artery disease, with tachyarrhythmias being one of the most frequent mechanisms.

Limitations

Our results should be read in the context of a number of limitations. Although we used 2 methods for AF ascertainment (study-scheduled ECG and history of a physician diagnosis), it remains possible that some paroxysmal and/or intermittent AF cases were not detected. This would misclassify some participants and put them in the “no AF” group. Nevertheless, this misclassification would likely attenuate the association between AF and MI, and therefore, our results should be considered as conservative.

Heart failure was not systematically assessed in the REGARDS study. Hence, we used current digoxin use as a proxy for heart failure similar to previous REGARDS articles. It has been reported that digoxin use has a specificity of about 99% and a sensitivity of about 28% for the diagnosis of heart failure.

Data on the actual onset of AF were not available, and therefore we could not adjust for the time between AF onset and baseline visit. Also, we could not conduct analysis of AF as a time-updated predictor because only prevalent AF is available in the REGARDS cohort at this stage.

Finally, REGARDS by design included only whites and blacks; hence, our results may not be applicable to other racial or ethnic groups. Similar to other studies using a similar observational design, residual confounding is always a possibility. However, we adjusted for several risk factors and potential confounders, thus lessening this concern.

Despite these limitations, this is the first report to our knowledge from a large biracial population-based study showing an increased risk of MI associated with AF in the general population. Other strengths include the substantial accumulating number of events, rigorous physician adjudication of study end points, and long follow-up time.

In conclusion, we showed that AF was independently associated with an increased risk of incident MI in the REGARDS study. This risk was stronger in women and blacks than in men and whites.

ARTICLE INFORMATION

Accepted for Publication: August 26, 2013.

Author Contributions: Drs Khodneva and Safford had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Soliman, Safford, Dawood, Zakai, Cushman.

Acquisition of data: Soliman, Safford, Judd, V. J. Howard, G. Howard, Cushman.

Analysis and interpretation of data: Soliman, Safford, Muntner, Khodneva, Zakai, Thacker, Judd, Herrington.

Drafting of the manuscript: Soliman, Khodneva, Dawood, G. Howard.

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Obtained funding: Safford, V. J. Howard, G. Howard, Cushman.

Administrative, technical, or material support: Soliman, Safford, Zakai, Judd, V. J. Howard, G. Howard, Cushman.

Study supervision: Safford, Muntner, Zakai, V. J. Howard.

Conflict of Interest Disclosures: None reported.

Funding/Support: The REGARDS study is supported by cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Services. Additional funding is provided by grant RO1 HL80477 from the National Heart, Lung, and Blood Institute.

Role of the Sponsor: Funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

Previous Presentation: An abstract of this article (No. 1151-49) was presented at the American College of Cardiology Annual 2013 Meeting; March 9, 2013; San Francisco, California.

Additional Contributions: The authors thank the investigators, staff, and participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org.

Correction: This article was corrected on January 6, 2014, to correct the number of all participants with no AF in Table 2.

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