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Atrial Fibrillation and Risk of ST-Segment Elevation versus Non-ST Segment Elevation Myocardial Infarction: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—It has recently been reported that atrial fibrillation [AF] is associated with an increased risk of myocardial infarction [MI]. However, the mechanism underlying this association is currently unknown. Further study of the relationship of AF with type of MI [ST elevation MI (STEMI) vs. non-ST elevation MI [NSTEMI] might shed light on the potential mechanisms.

Methods and Results—We examined the association between AF and incident MI in 14,462 participants [mean age 54 years, 56% women, 26% African Americans] from the Atherosclerosis Risk in Communities study who were free of coronary heart disease at baseline [1987–1989] with follow-up through December 31, 2010. AF cases were identified from study visits electrocardiogram and by review of hospital discharge records. Incident MI and its types were ascertained by an independent adjudication committee. Over a median follow up of 21.6 years, 1374 MI events occurred [829 NSTEMI, 249 STEMI, 296 unclassifiable]. In a multivariable adjusted model, AF [n=1545] as a time-varying variable was associated with a 63% increased risk

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of MI [HR (95% CI):1.63(1.32–2.02)]. However, AF was associated with NSTEMI [HR (95% CI): 1.80(1.39–2.31)] but not STEMI [HR (95% CI): 0.49(0.18–1.34)]; p-value for hazard ratios comparison=0.004. Combining the unclassifiable MI group with either STEMI or NSTEMI did not change this conclusion. The association between AF and MI, total and NSTEMI, was stronger in women than in men [interaction p-value<0.01 for both].

Conclusions—AF is associated with an increased risk of incident MI, especially in women. However, this association is limited to NSTEMI.

Keywords

Atrial Fibrillation; Myocardial Infarction; STEMI; NSTEMI

Introduction

The significance of atrial fibrillation [AF] as a major public health problem stems from its increasing prevalence and strong association with poor outcomes. Currently, the number of individuals with AF in the United States is estimated as ≈2.7 to 6.1 million, and this is expected to double by 2050.[1–3] In addition to being an established risk factor for stroke [4, 5], a recent study showed that AF is a risk factor for myocardial infarction [MI].[6] In the Reasons for Geographic and Racial Differences in Stroke [REGARDS] study, AF was associated with a 70% increased risk of incident MI after adjustment for several cardiovascular risk factors and potential confounders, and the risk was significantly higher in women than in men and in blacks than in whites.[6] These results are yet to be validated in an independent cohort, and the mechanism explaining this association is currently unknown. Further study of the relationship of AF with type of MI [ST elevation MI (STEMI) vs. non-ST elevation MI (NSTEMI] might shed light on the underlying mechanisms. Thus, we examined the association between AF and MI [overall and by type] in the Atherosclerosis Risk in Communities [ARIC] Study.

Methods

Study Population

The ARIC study is a community-based population study designed to investigate the causes of atherosclerosis and its clinical outcomes as well as variation in cardiovascular risk factors, medical care, and disease by race and sex.[7] From 1987 to 1989 [ARIC study baseline], 15,792 adults [55.2% women, 45–64 years of age] from four US communities [Washington County, MD; suburbs of Minneapolis, MN; Jackson, MS; and Forsyth County, NC] were enrolled and underwent a home interview and clinic visit. Additional exams were conducted in 1990–1992, 1993–1995, 1996–1998, and 2011–2013. Participants were mostly white in the Washington County and Minneapolis sites, exclusively African American in Jackson, and a mix of both in Forsyth County.

For the purpose of this study, we excluded participants with missing or poor quality baseline electrocardiograms [ECG] [n=242], missing data on baseline covariates [n=241], race other than white or black as well as non-white in the Minneapolis and Washington County sites [n=103], and those with prevalent coronary heart disease [history of MI, baseline ECG-

evidence of MI, or history of coronary bypass or angioplasty] [n=744]. After all exclusions, 14,462 participants remained and were included in this analysis. The ARIC study was approved by the institutional review boards at each participating center, and written informed consent was obtained from all participants.

Ascertainment of AF

AF cases were identified from study visit ECGs and by review of hospital discharge records.[8,9] At each study exam, a standard supine 12-lead resting ECG was recorded with a MAC PC Personal Cardiograph [Marquette Electronics, Milwaukee, Wisconsin, USA] and transmitted to the ARIC ECG Reading Center [EPICARE Center, Wake Forest School of Medicine, Winston Salem, NC] for automatic coding. A cardiologist visually confirmed all AF cases automatically detected from the study ECG. Information on hospitalizations during follow-up was obtained from annual follow-up calls and surveillance of local hospitals, with hospital discharge diagnoses codes collected by trained abstractors. AF during follow-up was defined as International Classification of Disease 9th revision, Clinical Modification [ICD-9-CM] 427.31 or 427.32 diagnosis codes. AF cases detected in the same hospitalization with open cardiac surgery were not included in the AF cases. Hospital diagnosis codes for AF ascertainment have been shown to have good positive predictive value reaching 98.6%.[8, 10, 11]

Ascertainment of MI events

MI events were identified by contacting participants annually, identifying hospitalizations during the previous year, and by review of all discharge records from all hospitals serving the four ARIC field centers.[12] Trained ARIC staff members abstracted medical records for all hospitalizations. Information obtained from medical records included presence of chest pain, history of MI or other cardiovascular-related conditions, and measures of cardiac biomarkers [total creatinine phosphokinase (CK), CK-MB, lactate dehydrogenase, and troponin]. Elevated cardiac enzymes were considered abnormal if the values are at least twice the upper limits of normal, while considered equivocal if they are between the upper limit of normal and twice that limit. Copies of up to three ECGs were obtained and sent to the University of Minnesota Electrocardiographic Reading Center [Minneapolis, MN] for classification according to the Minnesota code.[13] A standardized computerized algorithm was applied to data on chest pain, cardiac biomarkers, and ECG evidence to determine each participant's computer-based MI diagnosis.[14] Cases with disagreements between the computer-based diagnosis and discharge diagnosis codes were reviewed by physicians of the ARIC Mortality and Morbidity Classification Committee for final classification. All eligible hospitalized events were classified as definite, probable, possible or not present. Definite or probable MI defined MI event in our analysis. The diagnosis of definite MI was made if one or more of the following criteria were met: 1) Evolving diagnostic ECG pattern; 2) Diagnostic ECG pattern plus abnormal enzymes; or 3) Cardiac pain and abnormal enzymes plus evolving ST-T pattern or equivocal ECG pattern. On the other hand, the diagnosis of probable MI must meet one or more of the following criteria in the absence of sufficient evidence for definite MI: 1) Cardiac pain and abnormal enzymes; 2) Cardiac pain and equivocal enzymes plus either evolving ST-T pattern or diagnostic ECG pattern; or 3) Abnormal enzymes and evolving ST-T pattern. MI events were further classified as

NSTEMI or STEMI on the basis of the coded ECGs. MI events with missing or equivocal ECGs were considered as unclassifiable. For fatal MI events, documentation of MI was based on information obtained from the next of kin and other informants including the certifying physician, coroner, or medical examiner, or from medical records for any eligible hospitalization within 28 days before death. Detailed definition of on MI ascertainment in ARIC including details on the definitions of different ECG patterns involved in the diagnosis as well as the cut-points for cardiac enzymes could be found at the publically available manual of operation of surveillance components procedures in ARIC.[15]

In this analysis, incident MI event was defined as first occurrence of a fatal or non-fatal MI in a participant without evidence of prior MI. Follow-up time was stopped at the time of MI occurrence. Therefore, AF events occurring after MI incidence were not included, and those MI events were assigned to the non-AF follow-up.

Covariates

Baseline age, sex, race, education level, income and smoking status were determined by self-report. Body mass index [BMI] at baseline was calculated as weight [in kilograms] divided by height [in meters] squared. Blood samples were obtained after an 8-hour fasting period. Diabetes was defined as a fasting glucose level ≥126 mg/dL [or non-fasting glucose ≥200 mg/dL], a self-reported physician diagnosis of diabetes, or use of diabetes medications. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of blood pressure lowering medications. Estimated glomerular filtration rate (eGFR) based on creatinine (eGFRcreat) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation for creatinine.[16] At each study visit, medication history was obtained by self-report of medication intake during last two weeks and by reviewing medications brought by the participants to their visit. Each medication was coded by trained and certified interviewers with the use of a computerized medication classification system. Prevalent stroke and peripheral arterial disease were identified by self-reported history of a previous physician diagnosis. Prevalent heart failure was identified by the Gothenburg criteria and/or self-reported history of heart failure medication use in the past two weeks.[17]

Statistical analysis

Baseline characteristics of the analysis population were tabulated by AF status. Age-adjusted incidence rates of MI per 1000 person-years in participants with and without AF were calculated in the entire analysis population and in sex and race subgroups. In the AF group, person-time for the incidence rates was calculated from AF diagnosis to occurrence of MI or censoring, while in the non-AF group, person-time was calculated from baseline, AF occurrence, MI occurrence, or censoring. Event-free survival probability was estimated using Kaplan Meier method and compared using log-rank test by AF status.

Cox proportional hazards regression was used to examine the association between AF as a time-varying variable with incident MI [overall, and by MI type] in a series of models with incremental adjustments as follows: Model 1 adjusted for age, sex, race, field center, education, income; Model 2 adjusted for Model 1 plus baseline BMI, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering drugs,

diabetes, eGFR, heart failure, prevalent stroke, and prevalent peripheral arterial disease; Model 3 adjusted for Model 2 covariates plus time-varying use of statins, warfarin and aspirin ascertained at ARIC examinations. We examined the assumption of proportional hazards by computation of Schoenfeld residuals, and inspection of log(−log[survival function]) curves, and they were met. Individuals were censored at the time of MI, death or December 31, 2010, whichever occurred earlier. We compared the association of incident AF with STEMI and NSTEMI applying the competing risk approach proposed by Lunn and McNeil to an augmented data set. Differences in the association were tested including an interaction term between AF incidence and MI type in a stratified Cox model ran in this augmented data set.[18]

Because of the previously reported significant interaction by sex and race,[6] models with identical incremental adjustment as those described above for the main analysis were examined in subgroups by sex and race. Additionally, we examined interaction by age, using the median age (≥55 years) at the time of enrollment as a cut-point. Interactions were tested including multiplicative terms in the models.

In the analysis by MI type, we excluded the unclassifiable MIs. However, to examine the effect of the unclassifiable MIs on the association between AF and type of MI, we conducted sensitivity analyses in which we considered the unclassifiable MIs as STEMI in one set of analysis and as NSTEMI in another set of analysis. Also, to ensure temporality (i.e. occurrence of MI after AF), we conducted another sensitivity analysis in which we excluded participants with an MI event occurring within a short period (within a week) after a documented AF. Other additional analyses included: 1) Examining the association between AF and MI [overall and by type] using Cox proportional models adjusted for variables in model 3 plus other possible confounders [heart rate, beta blocker use, angiotensin converting enzyme inhibitors use, interim revascularization] all included in the models as time-varying covariates; 2) Comparing the association between AF and MI at different times of follow up; 3) Plotting the cumulative incidence of AF from baseline [1987–1989] to the end of follow up [2010]. The results of these additional analyses are provided in the Online-Only Data Supplement.

Statistical significance for all analyses was $p<0.05$ (two-sided). Analyses were conducted using SAS 9.2 [SAS Institute, Cary, NC].

Results

This analysis included 14,462 participants [mean age 54 years, 56% women, 26% African Americans] free of coronary heart disease at the time of enrollment, of whom 1,545 had AF either at baseline (n= 31) or during follow up (n=1514) before occurrence of an MI event. Supplemental Figure 1 shows the cumulative incidence of AF from baseline [1987–1989] to the end of follow up [2010], and Supplemental Table 1 shows the incidence rate of AF by 5-year time interval since baseline.

Table 1 shows the baseline characteristics of the study population at the study baseline [1987–1989] stratified by AF status detected at baseline and follow up through 2010.

Compared with those without AF by the end of follow up, participants with AF were more likely to be older, white, and men with higher prevalence of diabetes, hypertension, and prior cardiovascular disease [heart failure, stroke, peripheral arterial disease] at baseline.

Over a median follow up of 21.6 [25th and 75th percentiles = 16.9 and 22.6] years, 1374 incident MI events occurred. The mean ± SD time from AF diagnosis to MI in those with AF was 4.82±4.58 [median 3.35] years. The age adjusted incidence rate of MI was almost three-fold higher in those with AF than those without AF [event rate (95%CI): 11.60 (10.49–12.83) vs. 3.96 (3.71–4.22) per 1000 person-years respectively; incidence rate ratio (95%CI): 2.93 (2.61–3.30)]. Figure 1 shows the event (total MI) free survival curves by AF status. In subgroup analyses by sex and race, the highest age-adjusted MI incidence rate ratios [IRR] by AF status were observed in women [IRR (95%CI): 3.75 (3.14–4.47)] and blacks [IRR (95%CI): 3.26 (2.57–4.14)], which compare to IRR (95%CI) of 2.88 (2.52–3.30) in whites and 2.27 (1.94–2.66) in men (Figure 2). In a socio-demographic adjusted Cox proportional hazards model, AF, compared with no AF, was associated with a 92% increase in MI risk [p<0.001]. This association remained significant [63% increased risk, p<0.001] after further adjustment for traditional cardiovascular risk factors and other potential confounders (Table 2). Also, the results were similar when the variables in model 3 plus other possible confounders/mediators were used in the models as time-varying covariates (Supplemental Table 2)

In subgroup analysis, the association between AF and risk of MI was stronger in women than in men [interaction p<0.001; Table 2]. Quantitatively, the risk of MI associated with AF was stronger in blacks [multivariable HR (95%CI): 2.05 (1.32–3.18)] than in whites [multivariable HR (95%CI): 1.52 (1.19–1.94)] but the interaction p-value did not reach statistical significance [p=0.16] (Table 2). No significant differences in the association between AF and MI stratified by median age [55 years] were observed in Model 3 [HR (95%CI): 1.72 (1.17–2.53) for age <55 years and 1.59 (1.23–2.06) for age > 55years; interaction p=0.51].

Of 1374 incident MIs that occurred during follow up, 249 were STEMI and 829 were NSTEMI. There was no significant difference in the mean time from AF to STEMI [4.29± 4.58 (median 3.75) years] and NSTEMI [5.07± 4.56 (median 3.59) years]; p-value=0.74. Supplemental Figure 2 and Supplemental Figure 3 show the event free survival curves by AF status stratified by type of MI. Table 3 shows the relative HR for MI type by AF status. As shown, AF was associated with an increased risk of NSTEMI [multivariable HR (95%CI): 1.80 (1.39–2.31)] but not STEMI [multivariable HR (95%CI): 0.49, (0.18–1.34)]; p-value for comparison of HRs =0.004 using the Lunn-McNeil method. Similar patterns were observed in subgroup analysis stratified by sex and race (Table 4). Also, the results were similar when the variables in Model 3 plus other possible confounders/mediators were used in the models as time-varying covariates (Supplemental Table 3)

In a sensitivity analysis in which unclassifiable MIs (n= 296) were considered as either NSTEMI or STEMI, separately, the association between AF with NSTEMI remained statistically significant [p<0.001], and with STEMI remained non-significant [p=0.11]. Also, the magnitude and direction of the associations between AF with STEMI and NSTEMI in

the early years of ARIC [1987–2002] were similar to the associations observed in the later years of ARIC follow up [2003–2010]; interaction p-value by period of follow up =0.42 for STEMI and 0.44 for NSTEMI (Supplemental Table 4).

Excluding participants [n=72] with an MI event occurring within a week after a documented AF did not change our conclusions and only strengthened our results [multivariable adjusted HR (95%CI): 1.74 (1.40–2.16), p<0.001 for total MI, 1.91 (1.48–2.47), p<0.001 for NSTEMI; and 0.51 (0.18–1.38), p=0.18 for STEMI].

Discussion

In this analysis from the ARIC study, AF was associated with a significantly increased risk of incident MI after adjustment for cardiovascular and other risk factors. The association was stronger in women than in men. These results accord with the recently reported findings from the REGARDS study showing that AF is a risk factor for MI.[6] More importantly, however, our results from this analysis fill knowledge gaps and address several unanswered questions including the effect of MI type and methods of AF ascertainment on the AF and MI association. Our results show that the association between AF and MI is limited to NSTEMI. This finding may shed light on the underlying mechanism by which AF is linked to MI. Although STEMI and NSTEMI have similar long-term prognosis, their pathophysiology and treatment differ significantly.[19, 20] These different treatment strategies stem from the fact that in STEMI the culprit artery usually is occluded completely by a thrombus, whereas in NSTEMI the culprit artery is usually patent with a non-occlusive thrombus. With that in mind and given our finding that AF is associated with NSTEMI and not STEMI suggests that direct coronary thromboembolization is less likely to be the primary mechanism by which AF leads to MI. This suggestion accords with the common belief that direct coronary thromboembolization is less common because of the anatomical obstacles that minimize the possibility of direct coronary embolization e.g. differences 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, and the fact that the major part of coronary filling occurs in diastole.[21]

The association between AF and NSTEMI also suggests that factors that lead to partial occlusion of the coronary arteries or increased oxygen demand are more likely to explain the observed association between AF and MI. Hence, AF-induced increase in peripheral prothrombotic risk through systemic platelet activation, thrombin generation, endothelial dysfunction and inflammation [22–33] are more plausible explanations for the increased risk of MI with AF. Episodes of poorly controlled fast AF with uncontrolled ventricular response resulting in demand infarction, referred to as type-2 MI which typically occurs without ST elevation, could be another mechanism.

AF is an elusive rhythm that is hard to ascertain completely, especially in large population-based studies. Moreover, different methods of AF ascertainment can lead to different prevalence estimates.[34] Despite differences in the methods of AF ascertainment, the results in our ARIC analysis and REGARDS[6] reached similar conclusions; AF is associated with increased risk of MI with potential sex and race differences in the magnitude of association.

This consistency in results across studies provides assurance that the association between AF and MI is not dependent on the method of AF ascertainment. Notably, the hazard ratios for MI associated with AF were similar in both ARIC and REGARDS.

Our observation that AF is associated with increased risk of MI in women more than men and possibly in blacks more than whites adds to the accumulating evidence of the sex and racial differences in CVD outcomes and the potential differences in the impact of risk factors among sexes and races. Since we adjusted for several potential confounders, it is less likely that our observed sex and racial differences were confounded by differences in AF associated morbidities. Future investigation should assess whether genetic background, emerging risk factors, access to healthcare, awareness and adherence to medications contribute to sex and racial differences. In the REGARDS study, we have previously shown that blacks and women are less likely to be aware of having AF or to be treated with warfarin.[35] The excess risk of MI coupled with the tendency to under treat AF may magnify the risk of poor outcomes in these two groups.

Clinical and public health implications

The prevalence of AF doubles with each additional decade of life,[36] and so we should expect the prevalence of AF-associated morbidity/mortality including MI also to grow according to our results. In an increasingly older population, such as the United States population, this may incur a substantial burden on the healthcare system. Efforts to increase awareness and detection of AF, especially in blacks and women, and the development of risk stratification tools to identify AF patients who are high risk for developing MI are needed.

From the prevention perspective, our results raise the question of whether anticoagulants could be effective in prevention of MI as they are for stroke. Results from different meta-analyses among patients who had coronary artery disease suggest a potential reduction of MI risk in individuals receiving warfarin.[37–41] In our study, however, the risk of MI was only attenuated by 3% after adjustment for warfarin, aspirin and statin use [i.e. HR reduced from 1.66 in model 3 to 1.63 in model 4; Table 2]. Nevertheless, the relation between these medications and outcomes in our study should be interpreted with caution not only because they were self-reported which is subject to recall bias but also because they were only ascertained during study visits, introducing the potential for nonrandom misclassification. Also, whether the new generation of oral anticoagulants could have a role or will perform better than warfarin in prevention of MI in the setting of AF needs to be determined. The notion that AF potentiates thrombogenic risk through endothelial dysfunction and inflammation may highlight the potential importance of other therapeutic modalities that improve endothelial function and blunt the inflammatory response.

Strengths and limitations

Our results should be read in the context of certain limitations. Although we used two methods for AF ascertainment, study scheduled ECG and hospital discharge ICD codes, it remains possible that some paroxysmal/intermittent AF cases were not detected. However, this misclassification would likely attenuate the association between AF and MI and

subsequently our results should be considered as conservative. Also, most of AF cases in our study were detected through hospital discharge ICD codes. Thus, individuals with asymptomatic AF or those managed in an outpatient setting were more likely to remain unidentified. Nonetheless, the validity of hospital discharge codes for identifying incident AF in epidemiologic studies has previously been demonstrated.[8, 10, 11]

The number of blacks in the ARIC study may not be sufficient to examine black/white differences in the association between AF and MI. Hence, the non-significant interaction by race may be due to lack of statistical power.

Release of cardiac enzymes could be the result of non-ischemic causes (e.g. heart failure, myocarditis, etc.) or even non-cardiac causes (e.g. muscle trauma, rhabdomyolysis, etc.). Also, data on the timing of revascularization or thrombolysis during hospitalization for MI were not available to us which could have provided further insights into the unclassified MI cases. This could lead to misclassification of some cases of STEMI and non-STEMI. Nevertheless, as part of the standard procedures of MI ascertainment in ARIC,[15] information on non-ischemic or non-cardiac causes for elevated cardiac enzymes during hospital admission for an MI is routinely abstracted from the discharge summary on the ARIC participants. This information is considered in the interpretation of the cardiac enzymes as part of the MI diagnosis. Therefore, it is unlikely that non-cardiac causes of elevated cardiac enzymes have resulted in significant misclassification of MI.

On a related note, the growing use of highly sensitive troponin in recent years has led to an increase in the rates of detection of MI compared to before. This raises the possibility of differences in the association between AF with MI in the early years compared to the later years of ARIC follow up. However, changes in the ability to diagnose MI over time would be more relevant for the study of trends, which requires assessment of absolute incidence rates of MI over time. In our case, this is less important unless we think that the changes in sensitivity to identify MI are going to be different in those with vs those without AF, which is unlikely, as supported by our results of the association between AF and MI at different periods of follow up (Supplemental Table 4)

Finally, similar to other studies, residual confounding and misclassification of the outcome always remain a possibility. For example, we could not adjust for left ventricular ejection fraction or valvular heart disease, which could confound our results. Nevertheless, we adjusted for heart failure, minimizing the concern of confounding by left ventricular function. Also events triggering AF or the follow-up of AF patients may further confound or increase the suspicion for MI diagnosis, which could also lead to an association of AF with MI.

Despite these limitations, our study, with its robust methodology, provides further evidence for a link between AF and MI and highlights the role of MI type in this association. Key strengths of our study include a large community-based cohort, long-term follow up, substantial number of MI events identified by rigorous physician adjudication, and the ability to use AF as time-updated variable.

Conclusions

AF was associated with an increased risk of incident MI in the ARIC study. This association differed by MI type; AF was associated with an increased risk of NSTEMI but not STEMI. Sex differences in the association between AF and MI were also observed, with a stronger risk of MI associated with AF in women compared to men. While it is currently unknown whether AF prevention or use of anticoagulants will reduce MI risk, our findings extend AF complications beyond stroke and total mortality to include MI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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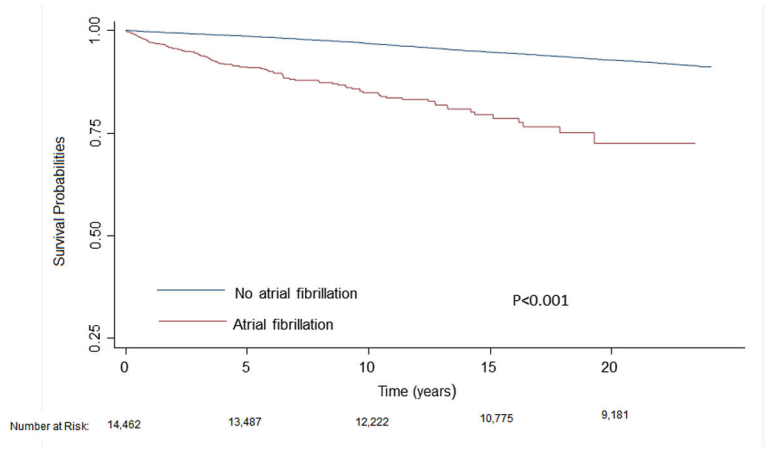

Figure 1.

Unadjusted Kaplan Meier myocardial infarction free survival curves by atrial fibrillation status. *Time to event in the AF group is the time from detection of AF not the cohort inception.

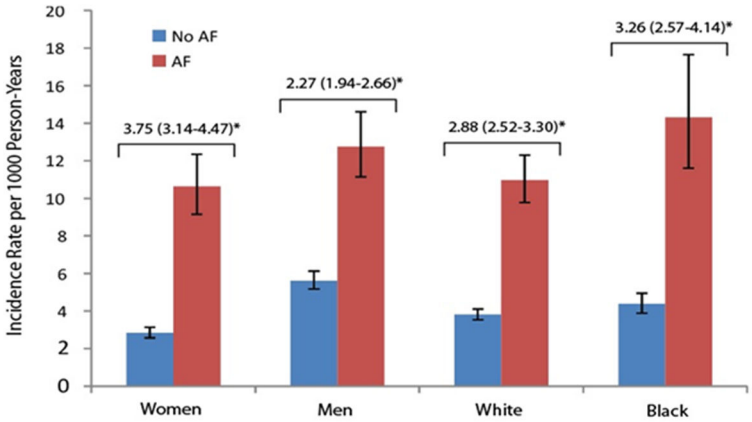

Figure 2.

Sex and race stratified age-adjusted incidence rates and incidence rate ratios of MI by AF status. MI= Myocardial infarction, AF= Atrial fibrillation. *Age-adjusted incidence rate ratio and incidence rates were based on the average age of the cohort (54 years). †Time to event in the AF group is the time from detection of AF not the cohort inception.

Table 1

Baseline (1987–1989) characteristics by atrial fibrillation status occurring through 2010

Characteristic*	No Atrial Fibrillation (N=12,917)	Atrial Fibrillation (N= 1545)
Age, years, mean, (SD)	53.7 (5.7)	56.6 (5.5)
Men, %	42.7	50.1
African American, %	26.6	18.7
Education ≥ high school, (%)	77.8	72.5
Annual income < $16,000, (%)	20.5	23.6
Body mass index, kg/m^2 mean,(SD)	27.5 (5.2)	28.9 (6.0)
Current smoking, %	25.8	28.0
Diabetes, %	10.6	14.3
Hypertension, %	32.1	44.2
Antihypertensive medication use, %	26.9	40.1
Systolic blood pressure, mmHg mean, (SD)	121 (19)	125 (19)
Diastolic blood pressure, mmHg mean, (SD)	74 (11)	73.7 (11)
Total cholesterol mg/dL mean,(SD)	215 (42)	213 (41)
HDL-cholesterol mg/dl mean,(SD)	52 (17)	49 (16)
Peripheral arterial disease, %	3.3	4.3
Heart failure, %	3.5	7.7
Stroke, %	1.7	1.9
Estimated glomerular filtration rate ml/min/1.73 m^2	103 (16)	99 (16)
Statin use, %	0.4	0.9
Warfarin use, %	0.3	1.3
Aspirin use,%	44.9	48.4

* Characteristics are measured at baseline (1987–1989) while the number of atrial fibrillation cases are from baseline and follow up (until 2010).

Table 2

Association between atrial fibrillation and incident myocardial infarction [ARIC, 1987–2010]

	Participants without AF		Participants with AF		Model 1†	Model 2*	Model 3 ‡	*Interaction p-value#*
	Participants (n)	***Events (n)***	***Participants (n)***	***Events(n)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	
All population	12,917	1267	1545	107	1.92 (1.56–2.35)	1.66 (1.35–2.04)	1.63 (1.32–2.02)	N/A
Women	7399	541	771	64	3.10 (2.37–4.06)	2.54 (1.94–3.32)	2.47 (1.87–3.25)	<0.0001
Men	5518	726	774	43	1.21 (0.88–1.65)	1.09 (0.80–1.50)	1.08 (0.78–1.50)	
White	9480	927	1256	84	1.76 (1.40–2.21)	1.56 (1.24–1.97)	1.52 (1.19–1.94)	0.16
Black	3437	340	289	23	2.59 (1.68–4.00)	2.02 (1.31–3.14)	2.05 (1.32–3.18)	

*Model 1, adjusted for age, sex, race, study field center, education level and income

†Model 2, Model 1 covariates plus, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, body mass index, diabetes, blood pressure lowering drugs, estimated glomerular filtration rate, heart failure, stroke, peripheral arterial disease.

‡Model 3, Model 2 plus time-varying use of statins, warfarin and aspirin ascertained at ARIC examinations

#Interaction tested in Model 3

Table 3

Association between AF and incident STEMI and NSTEMI [ARIC, 1987–2010]

	STEMI (n=249)		NSTEMI (n=829)		p-value for hazard ratios comparison
	Hazard ratio (95% CI)	*p-value*	*Hazard ratio (95% CI)*	*p-value*	
Model 1[*]	0.49 (0.18–1.33)	0.16	2.21 (1.74–2.82)	<0.0001	0.005
Model 2[†]	0.44 (0.16–1.20)	0.11	1.85 (1.47–2.36)	<0.0001	0.004
Model 3[‡]	0.49 (0.18–1.34)	0.17	1.80 (1.39–2.31)	<0.0001	0.004

AF= atrial fibrillation; MI=myocardial infarction; STEMI= ST elevation MI; NSTEMI= non-ST elevation MI

[*]Model 1, adjusted for age, sex, race, study field center, education level and income

[†]Model 2, Model 1 covariates plus, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, body mass index, diabetes, blood pressure lowering drugs, estimated glomerular filtration rate, heart failure, stroke, peripheral arterial disease.

[‡]Model 3, Model 2 plus time-varying use of statins, warfarin and aspirin ascertained at ARIC examinations.

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Table 4

Association between AF and incident STEMI and NSTEMI, stratified by race and sex [ARIC, 1987–2010]

Outcome	**Women (n=8170)**			**Men (n=6292)**			*Interaction p-value*
	Events (n)	*HR (95%CI)**	*p-value*	*Events (n)*	*HR (95%CI)**	*p-value*	
STEMI	90	0.29 (0.04–2.13)	0.22	159	0.53 (0.17–1.69)	0.28	0.86
NSTEMI	392	2.72 (1.98–3.74)	<0.0001	437	1.21 (0.82–1.78)	0.34	0.0002

Outcome	**White (n=10736)**			**Black (n=3777)**			*Interaction p-value*
	Events (n)	*HR (95%CI)**	*p-value*	*Events (n)*	*HR (95%CI)**	*p-value*	
STEMI	*178*	*0.38 (0.12–1.20)*	*0.10*	*72*	*0.72 (0.10–5.30)*	*0.74*	0.68
NSTEMI	584	1.67 (1.26–2.22)	0.0004	245	2.40 (1.49–3.88)	0.0003	0.13

AF= atrial fibrillation; MI=myocardial infarction; STEMI= ST elevation MI; NSTEMI= none ST elevation MI

*Adjusted for age, sex, race, study field center, education level and income total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, body mass index, diabetes, blood pressure lowering drugs, estimated glomerular filtration rate, heart failure, stroke, peripheral arterial disease and time-varying use of statins, warfarin and aspirin ascertained at ARIC examinations.