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Silent Myocardial Infarction and Long-Term Risk of Heart Failure in the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Although silent myocardial infarction (SMI) accounts for about half of the total number of MIs, the risk of HF among patients with SMI is not well established.

Objectives—To examine the association between SMI and clinically manifested MI (CMI), compared to no MI, with HF.

Methods—This analysis included 9,243 participants from the Atherosclerosis Risk in Communities (ARIC) study who were free of cardiovascular disease at baseline (ARIC visit-1, 1987–1989). SMI was defined as electrocardiographic evidence of MI without CMI after the baseline until ARIC visit-4 (1996–1998). HF events were ascertained starting from ARIC visit-4 until 2010 in individuals free of HF before that visit.

Results—Between ARIC visit-1 and visit-4, 305 SMI and 331 CMI occurred. After ARIC visit-4 and during a median follow-up of 13.0 years, 976 HF events occurred. The incidence rate of HF

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was higher in both CMI and SMI than those without MI (incidence rate per 1000 person-years were 30.4, 16.2 and 7.8, respectively; p-value <.001). In a model adjusted for demographics and HF risk factors, both SMI (HR (95% CI): 1.35 (1.02–1.78) and CMI (HR (95% CI): 2.85 (2.31–3.51), compared to no MI, were associated with increased risk of HF. These associations were consistent in subgroups of participants stratified by several HF risk predictors. However, the risk of HF associated with SMI was stronger in those younger than vs. those at or older the median age (53 years) (HR (95%CI) 1.66 (1.00–2.75) vs. 1.19 (0.85–1.66), respectively; interaction p-value <.001).

Conclusions—SMI is associated with increased risk of HF. Future research is needed to examine the cost-effectiveness of screening for SMI as part of HF risk assessment, and to identify preventive therapies to improve the risk of HF among patients with SMI.

Keywords

Silent myocardial infarction; Electrocardiogram; Heart failure

Introduction

Heart failure (HF) is the final outcome of up to 15% of the patients who suffer from acute myocardial infarction (MI) (1–4). The proportion of this segment of the population is likely to increase as the survival of post-MI patients has significantly improved over the last decade (5). Up to one third of the million patients who are hospitalized for HF each year in the United States have a history of MI (6). Several factors, such as recurrent MI, ventricular remodeling, mechanical MI complications, and stunned or hibernating myocardium, lead to HF post-MI (7–8). These conditions might be clinically silent and go unnoticed for a long time.

Silent MI (SMI), defined as evidence of MI on the electrocardiogram (ECG) in the absence of history of MI, accounts for about half of the total number of MIs (9). Previous reports from different populations have shown that both clinical MI (CMI) and SMI are associated with poor prognosis (9–10). However, whether SMI is associated with HF similar to CMI is currently unclear. Furthermore, HF prevalence varies by sex and race, and hence it is possible that sex and race modify the relationship between SMI and HF (11–12). Therefore, the aims of this study were to examine and compare the associations between SMI and CMI, versus no MI, with HF, and to examine the consistency of these associations in subgroups stratified by sex and race as well as HF risk factors.

Methods

Study Design and Population

The Atherosclerosis Risk in Communities (ARIC) study is a community-based, predominantly biracial prospective cohort study that was designed to study atherosclerosis and its clinical outcomes, and variation in cardiovascular risk factors, medical care, and disease by race, gender, location, and date. Details of the ARIC study have been previously published (13). Briefly, from 1987 to 1989 (ARIC visit-1, baseline), 15,792 adults (age 45–64 years) from 4 US communities (Washington County, Maryland; suburbs of Minneapolis,

MN; Jackson, MS; and Forsyth County, North Carolina) were prospectively enrolled in the ARIC study. They underwent a phone interview and subsequent clinic visit. Additional examinations were performed in 1990 to 1992 (visit-2), 1993 to 1995 (visit-3), 1996 to 1998 (visit-4), and 2011 to 2013 (visit-5). Participants were mostly white in the Washington County and Minneapolis sites, exclusively black in Jackson, and a mix of both in Forsyth County. The study was approved by the institutional review board at each study site. All participants provided written informed consent.

For the purpose of this analysis, all ARIC participants with good quality and complete ECG data at visit-1 through visit-4 as well as outcome events after visit-4 were considred. The following partcipants were excluded: 47 with reported race neither African-American nor white, 565 participants with ECG data that were not interpretable for the diagnosis of MI due to poor quality or suppression codes by the Minnesota ECG classification, 3,775 with missing ECG in any of the ARIC first four visits including those who died during this period, 201 with missing baseline cardiovascular disease (CVD) risk factors utilized in the models, and 119 missing HF follow-up data. We also excluded 1,706 participants with history of prevalent CVD at baseline which was defined as the presence of ECG evidence of MI, or a self-reported history of physician-diagnosed MI, coronary artery bypass surgery, coronary angioplasty, HF, or stroke. Finally, we excluded 136 cases with HF occurring between ARIC visit-1 and visit-4. After all exclusions (n=6,549), a total of 9,243 participants remained and were included in the analysis.

Baseline Covariates

Baseline (visit-1) age, sex, race, and smoking status were determined by self-report. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood samples were obtained after a12-hour fast and were examined in a central laboratory. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dL (or non-fasting glucose ≥200 mg/dL), a self-reported physician diagnosis of diabetes mellitus, or the use of anti-diabetes medications. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of blood pressure lowering medications. Medication use was obtained by self-report of medication intake during last 2 weeks and by a review of 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. Heart rate data were obtained from the baseline ECG.

Silent MI and Clinical MI

SMI was defined as ECG-evidence of new MI at ARIC visit-2, -3, or -4 that was not present at the baseline visit (visit-1) in the absence of documented CMI. CMI was adjudicated by physician review based on chest pain, cardiac biomarkers/enzymes from hospitalizations, ECG evidence including a new pathological Q wave, coronary heart disease history, and other associated information. All hospitalized events were classified into definite, probable, suspect and no MI. Details of classification and specific criteria for adjudication have been described previously (14). Definite and probable MIs were combined to define CMI in this analysis. Definite hospitalized CMI met ≥1 of the following criteria: evolving diagnostic ECG pattern, diagnostic ECG pattern and abnormal enzymes, or cardiac pain and abnormal

enzymes plus evolving ST-T pattern or equivocal ECG pattern. Probable hospitalized MI met ≥1 of the following criteria in the absence of sufficient evidence for definite hospitalized MI: cardiac pain and abnormal enzymes, cardiac pain and equivocal enzymes and either evolving ST-T pattern or diagnostic ECG pattern, or abnormal enzymes and evolving ST-T pattern (10). Participants with both SMI and CMI between ARIC visits 1 and 4 were considered to have CMI.

Resting 10-second standard simultaneous 12-lead ECGs were performed in all participants using identical electrocardiograph (MAC PC, Marquette Electronics Inc, Milwaukee, WI) machines at all clinical sites by trained personnel. These ECGs were processed in a central ECG laboratory (initially at Dalhousie University, Halifax, NS, Canada, and later at the Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston-Salem, NC), where all ECGs were visually inspected for quality and technical errors. ECG-evidence of MI was defined using the Minnesota Code (MC) ECG classifications as new appearance of a major Q/QS wave abnormality (MC 1.1 or MC 1.2) or minor Q/QS wave abnormality (MC 1.3) plus major ST-T abnormality (MC 4.1, MC 4.2, MC 5.1, or MC 5.2) (15,16).

Ascertainment of Heart Failure

Incident HF was defined as the first occurrence of HF hospitalization according to the International Classification of Diseases, 9th Revision (ICD-9), code 428 (428.0–428.9) as a diagnosis in any position. These diagnostic codes were obtained during retrospective surveillance of hospital discharges or a death certificate with death from HF in any position or death certificate with an ICD-9 code of 428 or an ICD-10 code of I-50 among any of the diagnoses listed or underlying causes of death on the death certificate (17).

Statistical Analysis

Baseline characteristics were compared by MI status (CMI, SMI, and no MI). Statistical significance for categorical variables was tested using the χ^2-method and the analysis of variance or *t*-test for continuous variables.

Cumulative incidence rates of HF per 1000 person-years occurring after visit-4 were calculated among ARIC participants who had SMI and CMI (versus no MI) that occurred between visit-1 and visit-4. Kaplan-Meier estimates were used to compute the cumulative incidence of HF stratified by the MI status and the difference in estimates was compared using the log-rank procedure. Follow-up time was defined as the time from visit-4 to the diagnosis of HF, death, loss to follow-up, or end of follow-up (December 31, 2010).

After testing for proportional hazard assumptions, Cox proportional hazard analysis was used to examine the association between CMI and SMI (versus no MI) with HF, in models adjusted as follows: Model 1 adjusted for demographics (age, sex, race); Model 2 adjusted for variables in model 1 plus the clinical components of the ARIC study HF risk score (BMI, smoking status, heart rate, systolic blood pressure, use of blood pressure lowering medications, and diabetes mellitus) (18). Since we excluded participants with coronary heart disease, we did not adjust for coronary heart disease although it is a component of the ARIC

HF risk score (18). Individuals were censored at the time of HF, death or December 31, 2010, whichever occurred earlier.

Subgroup analysis in the study participants stratified by the clinical components of the ARIC study HF risk score were also examined in models adjusted in a similar fashion to model 2, and p-value for interactions were calculated in each subgroup. For the purpose of subgroup analysis, we used hypertension to replace systolic blood pressure and use of blood pressure lowering medications. We also used the median age (53 years), instead of 65 years which is suggested by the ARIC HF risk score because of the small number of participants with SMI in those above the age of 65 years. On the other hand, we used the BMI of 25 kg/m^2 and heart rate of 60 beats/minutes as cut-off points as suggested by ARIC HF risk score (18). All analyses were performed with SAS version 9.3 (SAS Institute Inc, Cary, NC). A 2-sided p-value of<0.05 was considered significant.

RESULTS

Overall, 9,243 (mean age 53.7± 5.7 years, 57.2% women, 20.4% black) participants were included in the analysis. Table 1 shows the baseline characteristics stratified by MI status. Compared with the CMI group, the SMI group had more women, blacks and non-smokers. CMI and SMI had expectedly higher prevalence of coronary heart disease risk factors than the no MI group.

During a median follow- up of 13.0 years (IQR: 12.2, 13.9 years), there were 976 cases of HF; 104 HF cases among CMI group, 54 among SMI group and 818 among the no MI group. The incidence rate of HF was higher in both CMI and SMI than those without MI (incidence rate per 1,000 person year were 30.4, 16.2 and 7.8, respectively; p-value <0.001). The Central Illustration shows the cumulative incidence of HF stratified by MI status.

In multivariable adjusted Cox proportional hazard models, both CMI and SMI, compared with no MI, were significantly associated with HF, independent of demographics and clinical risk factors (Table 2). However, the magnitude of risk of HF associated with CMI was larger than the risk associated with SMI.

Figure 1 and Supplemental Table 1 show subgroups analyses stratified by demographics and HF risk factors. As shown, the pattern of associations between MI status and HF was consistent among these subgroups i.e. no effect modification by race, diabetes, hypertension, heart rate or heart rate on the association between MI by type and HF. However, there was effect modification by age; the risk of HF associated with SMI was stronger in those younger than vs. those at or older the median age (interaction p-value <0.001). Also the risk of HF associated with SMI was slightly different stronger for women compared with men (interaction p-value = 0.093), and in overweight compared to normal weight (interaction p-value =0.093), and in never smokers (interaction p-value = 0.076).

DISCUSSION

In this analysis from the ARIC study, we showed that SMI is associated with increased risk of HF independent of HF risk factors (Central Illustration). CMI also was associated with

HF, and the association was stronger than that that of SMI. HF has been defined as global pandemic, since it affects around 26 million people worldwide (19). Currently 5.7 million people in the United States have HF, and it is expected that by 2030 >8 million people will have this condition (20). Therefore, identifying a new potential mechanism contributing to this pandemic is of enormous importance. While future research is needed to examine the cost-effectiveness of screening for SMI as part of HF risk assessment, we believe that our report provides novel insights into overlooked and potentially addressable contributor to the HF pandemic.

SMI was first described in 1949 and further characterized in the Framingham Heart Study in 1959 (21,22). Its prevalence in the general population ranges from 0.3–4.8% (23–29). Certain subgroups, such as the elderly, persons with diabetes and women are known to have higher prevalence of up to 15% (25,30,31). These subgroups are also uniquely at higher risk of adverse events. Among individuals with MI, SMI constitutes up to half of the total number of MIs, (30,32) and is associated with increased risk of re-infarction, (30) other coronary heart disease, sudden cardiac death and all-cause mortality (24). To our knowledge, this study is the first to provide evidence that SMI is associated with increased risk of HF as well. Our subgroup analysis shows that the risk of HF associated with SMI is stronger with young age; although they may be less exposed to SMI. Other subgroups of interest that showed borderline effect modification include overweight; stronger association of SMI with HF in overweight than those with normal weight. This could probably explained by the added risk of obesity to HF. On the other hand, there was there was borderline effect modification by smoking where the association was stronger in never smoker than current smoker and was in-between in former smokers. Whether this is due to survival bias or a by-chance finding requires further investigation.

Even though men have higher risk of HF than women, the association between different types of MI and HF did not significantly differ by sex in our study. As a matter of fact, there was tendency for more HF risk associated with SMI in women than men (interaction p-value = 0.093). In the Prevention of REnal and Vascular END-stage Disease (PREVEND) Study, men were more likely to develop HF than women, but women had higher risk of HF with preserved ejection fraction (HFpEF) (33). This finding and the notion that coronary heart disease (of which SMI is part) is an established risk factor for HFpEF (34,35) suggest that examining HF types along with MI types may shed more light on whether effect modification by sex on the association between SMI and HF exists or not. Similarly, Hebert et al. showed that black patients with HFpEF tend to have a lower prevalence of ECG-based MI than whites, although blacks are at a higher risk of HF overall (36). This may partially explain the non-significant slightly stronger association between SMI and HF in whites than blacks in our analysis. Further studies examining sex and race differences in the association between MI (clinical and silent) with different types of HF (HFpEF and HFrEF) might be in a better position to examine the effect modification of race and sex on the associations between SMI and HF.

Not surprisingly, CMI is associated with a stronger association with HF than SMI. ECG changes reflecting ischemic cascade in the myocardium could precede clinical symptoms (37). Therefore, it is possible that SMI represents milder or earlier changes prior to the

development of CMI or HF. Also, it is possible that CMI patients might have a larger infarct size than SMI, and thus SMI led to a smaller degree of insult to the myocardium. That is to say, SMI probably remained silent because of being small in size or subclinical, and hence did not significantly impact the myocardium as CMI did, which could explain the stronger risk of HF with CMI than SMI.

Recently, increased life expectancy and better care of post-MI patients in the United States resulted in an upsurge of HF (38). Early detection of HF prior to overt physiological and structural changes may lead to better outcomes (39). Hence, early detection of risk factors has the potential to minimize the burden of HF-related mortality, morbidity and health care costs. In this regard, our study provides evidence for a new risk factor that may be otherwise missed in routine care. Since ECG is a readily available tool with high inter-rater reliability, SMI, as a subclinical risk factor, could be identified with ease. Although guideline-directed therapy has a clear role in preventing future HF among CMI patients and therefore is a part of quality of care core measure (40, 41), it is not known whether such benefit exists for persons with SMI. Thus, SMI could be considered as a condition for American College of Cardiology/American Heart Association Stage-A HF (i.e., at risk for HF) (42). Future studies are needed to study the beneficial effects of screening for SMI and whether guideline-directed therapy in SMI patients have improved outcomes in the same way as among CMI patients.

Our results should be considered in the context of certain limitations. As in other studies with similar design, residual confounding despite adjustment of several confounders remains a possibility. The inability to detect significant interactions in the subgroups analyses could be related to lack of enough power due to the small sample size within the subgroups. Also, including only whites and blacks limits the generalizability of our study to other races/ethnicities. Since the diagnosis of CMI is not reliant on high sensitivity troponin assays, it is possible that the prevalence of CMI was underestimated in ARIC. However, troponin was not available until 1998, the date our ascertainment of SMI ended. Finally, HF was based on hospitalized cases using ICD-9 and ICD-10 codes and not validated by physician review for diagnosis of HF, which might have led to misclassification and underestimation of the true incidence of HF; however, use of inpatient HF events has a high diagnostic specificity in ARIC, as shown previously (17).

Despite these limitations, this is the first report from a large community-based study showing a link between SMI and HF, which provides an opportunity to identify a new risk factor contributing to a strongly emerging pandemic. Strengths of the study include a biracial population with good representation of women, long-term follow up, and well-ascertained variables and outcomes including ECG data evaluated at a central reading center.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SMI	Silent Myocardial Infarction
CMI	Clinically Manifested MI
HF	Heart failure
ARIC	Atherosclerosis Risk in Communities study
LVH	Left Ventricular Hypertrophy
BMI	Body Mass Index
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
ECG	Electrocardiogram

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CLINICAL PERSPECTIVES

Heart failure (HF) is a frequent complication of myocardial infarction (MI). Although silent MI (SMI) accounts for about half of the total number of MIs, the risk of HF among patients with SMI is not well established. In this analysis from the ARIC study, we showed that SMI is associated with increased risk of HF independent of HF predictors.

TRANSLATIONAL OUTLOOK

This study provides evidence that SMI is a risk factor for HF. Future studies are needed to examine the cost-effectiveness of screening for SMI as part of HF risk assessment, and to study preventive therapies to improve the risk of HF among patients with ECG-evidence of SMI.

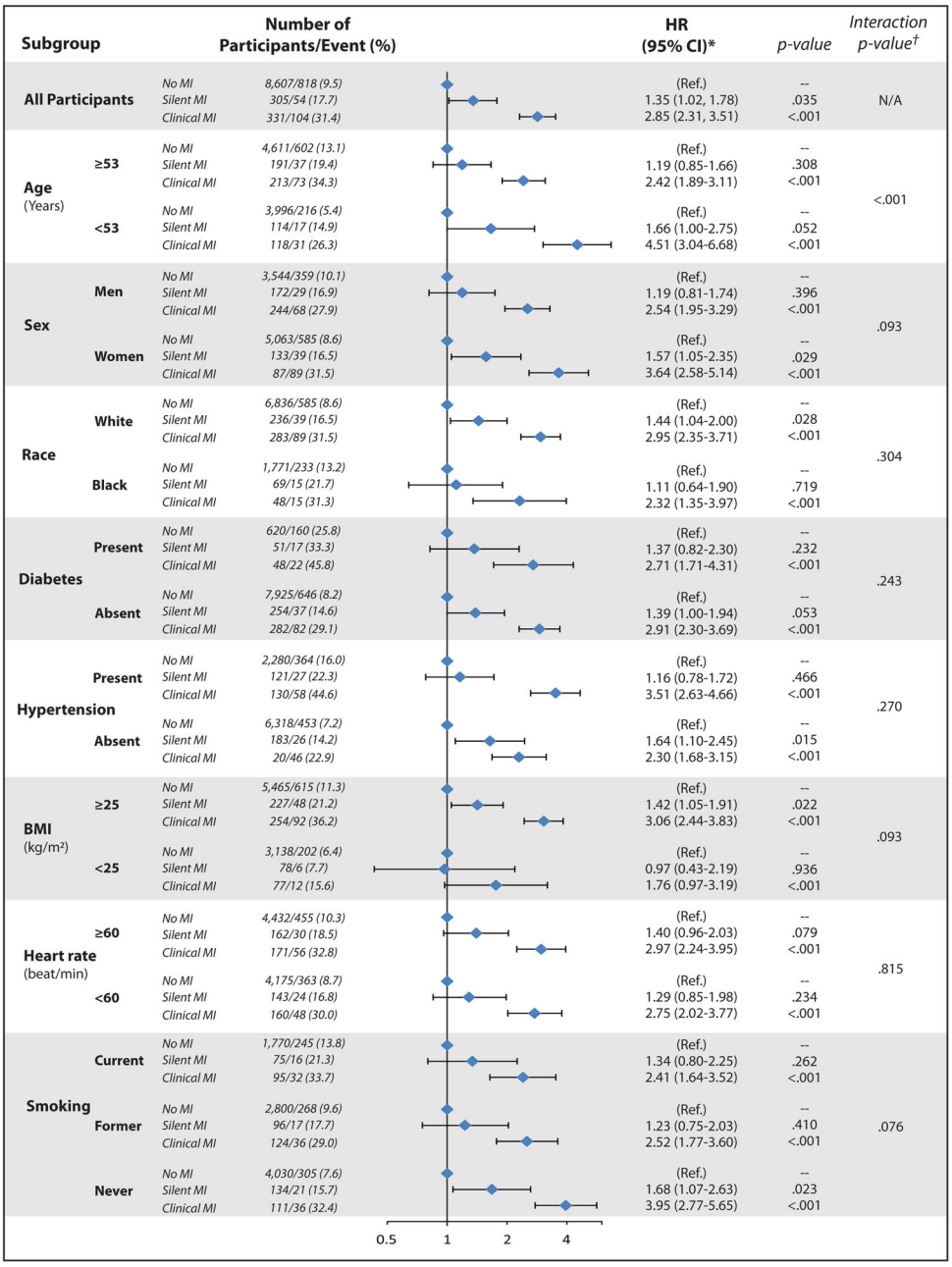
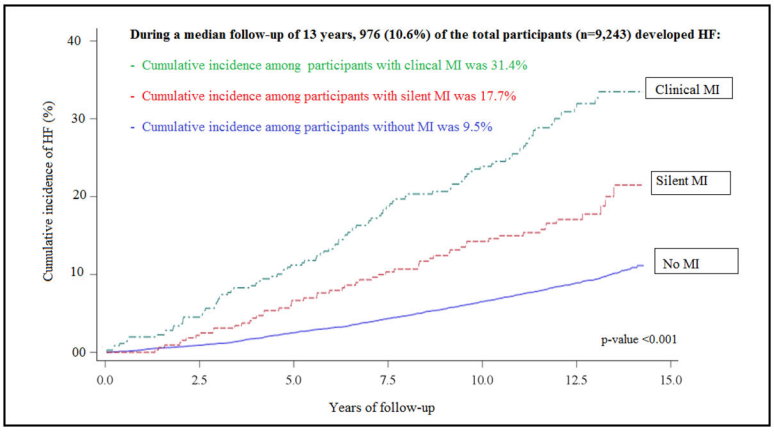


Figure 1. Associations between Type of Myocardial Infarction and Incident Heart Failure in Subgroups

HR=hazard ratio; CI=confidence interval; MI= myocardial infarction. Models adjusted for age, sex, race, plus body mass index, smoking status, heart rate, systolic blood pressure, blood pressure lowering medications, and diabetes mellitus (subgroup used in stratification is not included in the model).



Central Illustration. Risk of HF Associated with Different Patterns of MI

Cumulative Incidence of Heart Failure Stratified by Myocardial Infarction Status. MI= Myocardial Infraction; HF= Heart Failure.

Table 1

Baseline (ARIC visit-1, 1987–89) Participant Characteristics Stratified by Myocardial Infarction Status

Characteristics*	**No MI *(n=8607)***	**Silent MI *(n=305)***	**Clinical MI *(n=331)***	***p-value*†**
Age (years)	54 ±5.6	55 ±5.9	55 ±5.6	<.001
Women	5,063 (59%)	133 (44%)	87 (26%)	<.001
African-American	1,771 (21%)	69 (23%)	48 (15%)	.017
Heart rate (beats/minute)	65.6 ±9.6	66.9 ±10.5	65.3 ±9.6	.045
Smoking Status				<.001
Current	1,770 (21%)	75 (25%)	95 (29%)	
Past	2,800 (32%)	96 (31%)	124 (37%)	
Never	4,030 (47%)	134 (44%)	111 (34%)	
Body mass index (kg/m^2)	27 ±5.0	29 ±5.6	28 ±4.2	<.001
Systolic blood pressure (mmHg)	118 ±17	125 ±19	125±19	<.001
Hypertension	2,280 (27%)	121 (40%)	130 (39%)	<.001
BP lowering medication use	1,910 (22%)	102 (33%)	99 (30%)	<.001
Diabetes	620 (7.3%)	51 (17%)	48 (15%)	<.001

MI= myocardial infarction; BP= blood pressure

*Values expresses as mean± SD or n (%)

†p-value for comparison among the three groups using analysis of variance and $\chi^2$for continuous and categorical variables, respectively

Table 2

Associations between Type of Myocardial Infarction and Incident Heart Failure

	Participants	Events	Incidence Rate	Model 1*		Model2 †	
	n	*n*	*1000-person- year*	HR (95% CI)	p-value	HR (95% CI)	p-value
No MI	8,607	818	7.8	1 (ref.)		1 (ref.)	----
Silent MI	305	54	16.2	1.85 (1.40–2.44)	<.001	1.35 (1.02–1.78)	.035
Clinical MI	331	104	30.4	3.49 (2.83–4.30)	<.001	2.85 (2.31–3.51)	<.001

HR=hazard ratio; CI=confidence interval; MI= myocardial infarction

*Model 1 adjusted for age, sex, and race.

†Model 2 adjusted for variables in model 1 plus body mass index, smoking status, heart rate, systolic blood pressure, use of blood pressure lowering medications, and diabetes mellitus

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