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ORIGINAL RESEARCH

Coronary Artery Disease and Heart Failure With Preserved Ejection Fraction: The ARIC Study

Jenine E. John, MD; Brian Claggett, PhD; Hicham Skali, MD, MSc; Scott D. Solomon, MD; Jonathan W. Cunningham, MD; Kunihiro Matsushita, MD, PhD; Suma H. Konety, MD, MS; Dalane W. Kitzman, MD; Thomas H. Mosley, PhD; Donald Clark, III, MD; Patricia P. Chang, MD, MHS; Amil M. Shah, MD, MPH

BACKGROUND: Whether coronary artery disease (CAD) is a significant risk factor for heart failure (HF) with preserved ejection fraction (HFpEF) is unclear.

METHODS AND RESULTS: Among 9902 participants in the ARIC (Atherosclerosis Risk in Communities) study, we assessed the association of incident CAD with subsequent incident HFpEF (left ventricular ejection fraction [≥50%]) and HF with reduced ejection fraction (HFrEF; left ventricular ejection fraction <50%) using survival models with time-updated variables. We also assessed the extent to which echocardiographic correlates of prevalent CAD account for the relationship between CAD and incident HFpEF. Over 13-year follow-up, incident CAD developed in 892 participants and 178 subsequently developed HF (86 HFrEF, 71 HFpEF). Incident HFrEF and HFpEF risk were both greatest early after the CAD event. At >1 year post-CAD event, adjusted incidence of HFrEF and HFpEF were similar (7.2 [95% CI, 5.2–10.0] and 6.7 [4.8–9.2] per 1000 person-years, respectively) and CAD remained predictive of both (HFrEF: hazard ratio, 2.76 [95% CI, 1.99–3.84]; HFpEF: 1.85 [1.35–2.54]) after adjusting for demographics and common comorbidities. Among 4779 HF-free participants at Visit 5 (2011–2013), the 490 with prevalent CAD had lower left ventricular ejection fraction and higher left ventricular mass index, E/e', and left atrial volume index (all $P<0.01$). The association of prevalent CAD with incident HFpEF post-Visit 5 was not significant after adjusting for echocardiographic measures, with the greatest attenuation observed for left ventricular diastolic function.

CONCLUSIONS: CAD is a significant risk factor for incident HFpEF after adjustment for demographics and common comorbidities. This relationship is partially accounted for by echocardiographic alterations, particularly left ventricular diastolic function.

Key Words: atherosclerosis ■ coronary artery disease ■ diastolic function ■ echocardiography ■ heart failure with preserved ejection fraction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a major public health concern given its rising prevalence with the aging population.[1] Limited understanding of HFpEF pathobiology has hindered the development of efficacious treatments. While epicardial coronary artery disease (CAD) is an important risk factor for HF with reduced ejection fraction (HFrEF), and has been more strongly associated with HFrEF than with HFpEF, the prevalence of CAD in HFpEF is considerably higher than among people free of HF.[2–6] Prior epidemiologic studies have identified a history of myocardial infarction (MI) as a risk factor for HFpEF,[7–9] but these studies were generally limited by assessing CAD history at a single time-point, occurring at an undefined period prior to the HFpEF event and relative to the development of other HF risk factors.

Correspondence to: Amil M. Shah, MD, MPH, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.
Email: ashah11@rics.bwh.harvard.edu

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CLINICAL PERSPECTIVE

What Is New?

- Coronary artery disease (CAD) is a risk factor for both incident heart failure with reduced ejection fraction and heart failure with preserved ejection (HFpEF) after adjusting for common cardiovascular comorbidities, and this risk is partially accounted for by CAD-associated impairments in left ventricular diastolic function.
- The incidence of heart failure with reduced ejection fraction and of HFpEF are similar after 1 year following a CAD event.

What Are the Clinical Implications?

- Both heart failure with reduced ejection fraction and HFpEF should be in the differential diagnosis for patients with stable CAD and symptoms suspicious for heart failure.
- Further research is required to determine whether CAD contributes to HFpEF development, and whether therapies targeting ischemia can be beneficial in preventing or treating a subset of patients with HFpEF.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
FHS	Framingham Heart Study
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction

Limited data exist regarding the prognostic importance of CAD for the development of HFpEF after accounting for concurrent common shared cardiovascular comorbidities. Furthermore, there are limited data regarding the extent to which CAD-associated alterations in cardiac structure and function, including contemporary measures of left ventricular (LV) deformation and diastolic function, account for associations with subsequent HFpEF development.

Understanding the role of CAD as a risk factor for HFpEF could have significant implications for the diagnostic and therapeutic approach to HFpEF. We aimed to determine the longitudinal association of CAD, defined using MI or coronary revascularization, with subsequent incident HFpEF after adjusting for common comorbidities assessed in a time-updated manner. We also aimed to assess the extent to which CAD-associated alterations in cardiac structure and function may account for this relationship.

METHODS

Data and Analytic Methods Availability

Anonymized data from the ARIC (Atherosclerosis Risk in Communities) study have been made publicly available at the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) and can be accessed at https://biolincc.nhlbi.nih.gov/studies/aric/. The code used for statistical analyses in this study is available from the corresponding author upon reasonable request.

Study Population

The ARIC study is an ongoing prospective cohort study that enrolled 15 792 men and women aged 45 to 65 years in 1987 to1989 from 4 communities in the United States: Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD. Participants have completed 7 study visits, with comprehensive echocardiography performed at the fifth study visit (2011–2013). Evaluations including physical examination, questionnaires, ECG, and blood draws were performed at study visits, with information on interim medical events and medication use collected through additional annual and semi-annual questionnaires as previously described.[10] Participants who were free of CAD and HF as of 2005, the time at which adjudication for HF began, were included for the analysis of incident CAD as a risk factor for incident HF (Analysis 1; Figure 1). Prevalent HF was defined based on Gothenburg criteria at Visit 1, HF-related *International Classification of Diseases* (*ICD*) hospital discharge codes between Visit 1 and January 1, 2005, and physician survey response affirming the presence of HF in participants who self-reported HF between Visit 1 and January 1, 2005. Prevalent CAD as of 2005 was defined as a self-reported history of CAD at Visit 1, or an adjudicated MI or coronary revascularization event prior to January 1, 2005. Participants who were free of HF and underwent a standardized echocardiogram at Visit 5 were included for the analysis of echocardiographic parameters associated with prevalent CAD (Analysis 2; Figure 1). For this analysis, prevalent HF at Visit 5 was defined based on physician adjudication of hospitalizations with HF-related *ICD* discharge codes starting in 2005, HF-related *ICD* codes from hospitalizations before 2005, physician survey, and self-report on annual/semi-annual follow-up calls. Institutional review boards at each field center approved the study protocol, and all participants provided written informed consent.

Ascertainment of CAD

Surveillance of MI and coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery) was performed from study inception

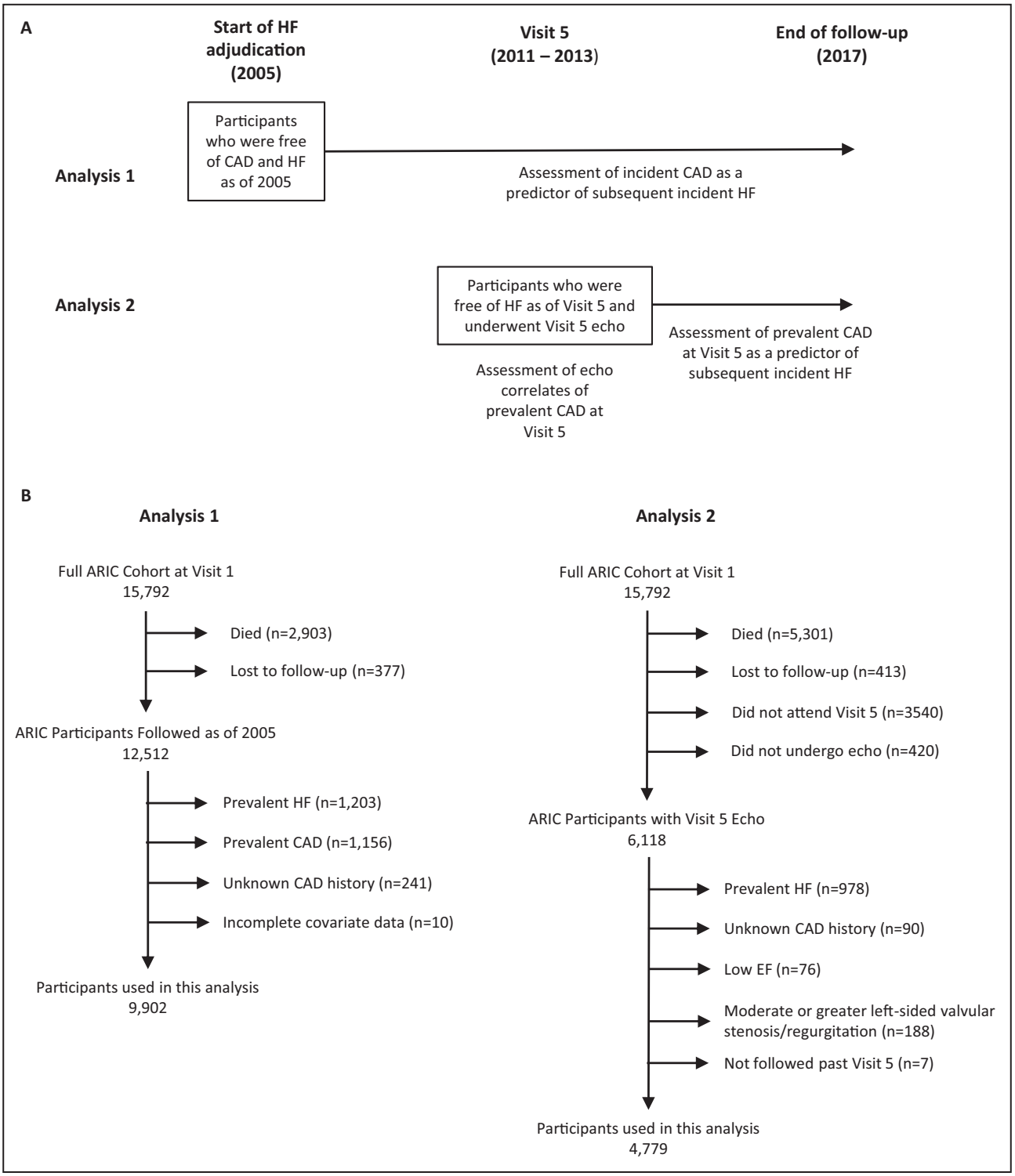

Figure 1. Study design.
A, Design of Analysis 1 (analysis of incident CAD as a risk factor for subsequent incident HF) and Analysis 2 (analysis of echocardiographic correlates of CAD). **B**, Derivation of study sample from overall ARIC cohort for Analysis 1 and 2. ARIC indicates Atherosclerosis Risk in Communities; CAD, coronary artery disease; echo, echocardiogram; EF, ejection fraction; and HF, heart failure.

through active surveillance of *ICD* hospital discharge codes and participant interview. Medical records were abstracted from all identified hospitalizations and were adjudicated by physicians as previously described.[11] For Analysis 1, incident CAD was defined using adjudicated MI and coronary revascularization. For Analysis 2,

prevalent CAD at visit 5 was defined as a self-reported history of CAD at Visit 1, an adjudicated MI or coronary revascularization event prior to Visit 5, or silent MI by serial ECG changes as of Visit 5. Deaths were ascertained by ARIC surveillance or the National Death Index.

Ascertainment of Heart Failure

Physician adjudication of HF in ARIC began in 2005 as previously described, so incident HF cases between 2005 and 2017 were assessed.[12] Surveillance of *ICD* codes related to HF, including dyspnea and acute lung edema, was performed to identify hospitalizations for adjudication. Incident heart failure was defined as the first hospitalization for HF. Hospitalizations that were adjudicated as both MI and HF hospitalizations were classified as MI-only hospitalizations, since HF signs and symptoms may occur as a manifestation of MI (eg, Killip class; n=72). LVEF abstracted from the first incident adjudicated HF hospitalization was used to classify HF as HFpEF (LVEF ≥50%) or HFrEF (LVEF <50%). A separate category for HF with midrange ejection fraction (HFmrEF) was not created given the absence of reliable numeric LVEF values in 33% of hospitalizations and resultant limitations in power to draw meaningful conclusions about this group. When LVEF was unavailable from this hospitalization, the most recent abstracted LVEF from a prior hospitalization—if available—was used. If the prior LVEF was normal, it was only used if it was from within 6 months before the HF hospitalization and without an interval MI. Of the incident HF cases between 2005 and 2017, 8% of the HFrEF cases and 3% of the HFpEF cases were defined using a prior LVEF. During this period, 14% of incident HF cases were unclassifiable with respect to LVEF.

Assessment of Clinical Covariates

Information on clinical covariates was obtained from measurements, medication lists, and self-reported data from study visits, as well as self-reported data from annual and semi-annual questionnaires. Hypertension and diabetes were assessed using measurements at study visits (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg for hypertension, fasting glucose ≥126 mg/dL or nonfasting glucose ≥200 md/dL for diabetes), self-report, and medication use. Atrial fibrillation was assessed using study visit ECGs, hospital discharge records, and self-report.[13] Stroke was assessed by self-report and adjudication of hospitalizations.[14] Smoking status was assessed by self-report. Laboratory values were obtained from blood drawn at study visits. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[15] Body mass index (BMI, kg/m^2) was determined using weight and height from study visits. Covariates at 2005 were determined using the most recently available values from prior visits or annual/semi-annual follow-up calls. For eGFR and BMI, these data were primarily carried forward from Visit 4 (1996–1999).

Echocardiography

Standardized comprehensive echocardiography was performed at Visit 5 (2011–2013) by certified study sonographers following a standardized image acquisition protocol using uniform imaging equipment as previously described (Data S1).[16] Blinded analysts at a dedicated core laboratory determined quantitative measures according to the recommendations of the American Society of Echocardiography.[17,18] Reproducibility metrics have been previously reported.[16]

Statistical Analysis

For the analysis of incident CAD as a risk factor for subsequent incident HF (Analysis 1), multivariable Cox proportional hazards models were employed to analyze the association of incident CAD with the outcome of subsequent incident HF and HF phenotype. Because patients are at high risk for several weeks immediately following a CAD event, and are generally considered to have stable CAD by 1 year after the CAD event,[19] CAD was modeled as a time-updated variable with separate categories for 0 to <90 days after the CAD event, 90 days to 1 year after the CAD event, and >1 year after the CAD event. Model covariates were selected based on a priori knowledge. Adjustment variables were age, race-sex category, hypertension, atrial fibrillation, stroke, eGFR, and BMI. Diabetes, current/prior smoking, and field center were included as stratification factors rather than covariates to address potential violations of proportional hazards assumptions. Participants were divided by self-reported race into Black and non-Black categories, and self-reported race and sex were combined to create a race-sex categorical variable. Hypertension, atrial fibrillation, stroke, diabetes, current/prior smoking, eGFR, and BMI were modeled as time-updated variables. eGFR and BMI were modeled quadratically.

Adjusted incidence rates of HF, HFpEF, and HFrEF were obtained using Poisson regression with adjustment for the same covariates as used in the Cox proportional hazards model. When assessing incident HFpEF as the primary outcome, participants experiencing incident HFrEF or incident HF with unknown EF were censored at the time of that event, and vice versa for incident HFrEF. A sensitivity analysis was also performed using the Fine-Gray subdistribution hazard modeling approach for competing risks.[20] Diabetes, smoking, and field center were included as covariates for these models. In order to determine whether sex or factors associated with the social construct of race affect the relationship between incident CAD and subsequent HF,

effect modification by sex and self-reported race on the relationship was assessed by multiplicative interaction terms. Participants reporting non-Black and non-White race were excluded from the assessment of effect modification by self-reported race (n=30). Additional sensitivity analyses were performed categorizing participants with incident HF with unknown EF as either HFpEF or HFrEF. The composite outcome of death and HF hospitalization was also assessed.

The analysis of the echocardiographic correlates of prevalent CAD at Visit 5 was performed among HF-free ARIC participants who underwent echocardiography at Visit 5 and had an LVEF ≥50% (Analysis 2). Participants with unknown CAD history (n=90) or moderate or greater left-sided valvular disease (n=188) on Visit 5 echocardiography were excluded. The association of prevalent CAD at Visit 5 with echocardiographic measures was performed using 2 multivariable linear regression models: Model 1 adjusted for age, sex, self-reported race, and field center; Model 2 additionally adjusted for diabetes, hypertension, atrial fibrillation, stroke, current/prior smoking, eGFR, BMI, hemoglobin A1c, and hemoglobin.

The association of prevalent CAD at Visit 5 with incident HFpEF was assessed in a multivariable Cox proportional hazards model. The model was adjusted only for demographic variables given that clinical HF risk factors may impact HF risk through effects on cardiac structure and function. The model was adjusted for age with sex, self-reported race, and field center as stratification factors to avoid potential overfitting given the limited number of events. The extent to which echocardiographic measures attenuated the association of prevalent CAD with incident HFpEF was then assessed by comparing models without or with echocardiographic measures as model covariates. Participants with an MI after Visit 5 were censored at the time of that event so that the predictive value of Visit 5 echo parameters on subsequent HFpEF could be assessed in the absence of intercurrent MI. Echocardiographic measures were grouped into those relating to structure (end-diastolic LV internal dimension, mean LV thickness, LV mass index), systolic function (ejection fraction, longitudinal strain), and diastolic function (left atrial volume index, peak E wave, septal e', E/e').

A *P* value of <0.05 was considered significant. Analyses were performed with Stata, version 14 (Statacorp, College Station, TX).

RESULTS

Incident CAD and Subsequent Incident HFpEF and HFrEF

Of the 12 512 ARIC participants followed as of 2005, 1203 had prevalent HF, 1156 had prevalent CAD, 241 had incomplete history of CAD, and 10 had missing covariate data, leaving 9902 CAD-free and HF-free participants included in the analysis (Figure 1). The average age was 70±6 years, 61% were female, and 26% were Black (Table 1). During median follow-up of 13 years, 892 participants (9%) developed incident CAD (560 MI and 332 coronary revascularization), of whom 178 developed subsequent HF (20% of patients with incident CAD; 86 HFrEF and 71 HFpEF). An additional 934 participants developed incident HF without antecedent incident MI/revascularization.

The risk of incident HF was time-dependent following the incident CAD event, with risk greatest in the first 90 days, intermediate in the period from 90 days to 1 year, and lowest at >1 year after the CAD event (Table 2). A similar temporal pattern was observed for incident HFrEF alone and HFpEF alone (Table 2, Figure 2), and for the composite of HF or death (Table S1). At >1 year after the CAD event, incident CAD remained predictive of both incident HFrEF (hazard ratio [HR], 2.76; 95% CI, 1.99–3.84) and HFpEF (HR, 1.85; 95% CI, 1.35–2.54), with no significant effect modification by sex or self-reported race (Figure 3, Tables S2 and S3). Similar risks for HFpEF were observed at >1 year following incident MI alone, and following incident revascularization alone (Table S4). The adjusted incidence rates of HFrEF and HFpEF were similar at >1 year following the CAD event ([7.2, 95% CI, 5.2–10.0]

Table 1. Baseline Characteristics for Participants Free of CAD and HF in 2005 (n=9902)

Charecteristic	Value (mean±SD or n (%))
Age, y	70±6
Female	6046 (61%)
Self-reported race	
Black	2542 (26%)
White	7340 (74%)
Asian	22 (<1%)
Native American	8 (<1%)
Diabetes	2381 (24%)
Hypertension	6865 (69%)
Atrial fibrillation	438 (4%)
Stroke	321 (3%)
Current/former smoker	6007 (61%)
eGFR, mL/min per 1.73 m^2	82.8±15.5
BMI, kg/m^2	28.5±5.5
Center	
Forsyth	2495 (25%)
Jackson	2276 (23%)
Minneapolis	2683 (27%)
Washington	2458 (25%)

BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; and HF, heart failure.

and [6.7, 95% CI, 4.8–9.2] per 1000 person-years, respectively; Table 2). Similar results were obtained in the following sensitivity analyses: (1) classifying all HF with unknown LVEF either as HFrEF or as HFpEF (Table S5); (2) censoring participants if they develop an MI after the initial CAD event (72 participants; Table S6); (3) censoring participants if the initial CAD hospitalization was also adjudicated as an HF hospitalization (Table S7); (4) including incident HF hospitalizations that were also adjudicated as an MI hospitalization (Table S8); (5) performing Fine-Gray modeling for competing risks[20] (Table S9); and (6) performing the analysis separately in the early portion of the study period (2005–2011) and late portion of the study period (2011–2017; Table S10).

Cardiac Structural and Functional Correlates of Prevalent CAD With Preserved LVEF

Of the 6118 ARIC participants undergoing echocardiography at Visit 5, 978 had prevalent HF, 90 had unknown CAD history, 76 had an LVEF <50%, 188 had at least moderate left-sided valvular disease, and 7 were not followed after Visit 5, leaving 4779 HF-free participants included in the analysis (Figure 1). Prevalent CAD was present in 490 (10%) of participants at Visit 5, and was associated with older age and higher prevalence of cardiovascular comorbidities (Table 3). Prevalent CAD was associated with lower LVEF, higher LV mass index related to both greater LV wall thickness and chamber dimension, and higher echocardiographic indices of LV filling pressure (E/e' ratio and left atrial volume index; Table 4). These associations persisted after adjustment for demographics and common cardiovascular comorbidities, including diabetes, hypertension, atrial fibrillation, stroke, and current/prior smoking, in addition to eGFR, BMI, hemoglobin A1c, and hemoglobin.

At a median follow-up of 5.5 years post-Visit 5, 214 participants developed incident HF (74 HFrEF, 109 HFpEF). Prevalent CAD at Visit 5 was a significant predictor both incident HFrEF (HR, 2.05; 95% CI, 1.13–3.75) and HFpEF (HR, 1.80; 95% CI, 1.07–3.02). The association with HFpEF was attenuated after further adjustment for echocardiographic measures, with the greatest attenuation observed with the addition of LV structural measures or diastolic function measures (Table 5).

DISCUSSION

CAD is an established—and powerful—risk factor for incident HF generally, and HFrEF in particular. Using a time-updated analysis in a community-based cohort, we report that incident CAD, as defined by MI and coronary

Table 2. Risk of Incident HF and HF Subtypes by CAD Status

	Incident HF				Incident HFrEF				Incident HFpEF			
	Events (n=1112)	Adjusted incidence rate	Hazard ratio	*P* value	Events (n=419)	Adjusted incidence rate	Hazard ratio	*P* value	Events (n=532)	Adjusted incidence rate	Hazard ratio	*P* value
No CAD event	934	7.1 (6.6–7.7)	Reference		333	2.5 (2.2–2.8)	Reference		461	3.3 (2.9–3.7)	Reference	
0 to <90 d after CAD event	41	134.5 (98.2–184.2)	20.02 (14.44–27.75)	<0.001	24	78.0 (51.4–118.3)	34.29 (22.09–53.23)	<0.001	15	45.6 (27.2–76.6)	13.63 (7.99–23.26)	<0.001
90 d to 1 y after CAD event	32	38.0 (26.6–54.1)	5.57 (3.90–7.97)	<0.001	18	21.2 (13.2–34.2)	8.63 (5.31–14.02)	<0.001	11	12.1 (6.6–22.0)	3.99 (2.18–7.32)	<0.001
>1 y after CAD event	105	17.0 (13.8–20.9)	2.20 (1.79–2.72)	<0.001	44	7.2 (5.2–10.0)	2.76 (1.99–3.84)	<0.001	45	6.7 (4.8–9.2)	1.85 (1.35–2.54)	<0.001

Models are adjusted for age, combined self-reported race and sex variable, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. Adjusted incidence rates are per 1000 person-years. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

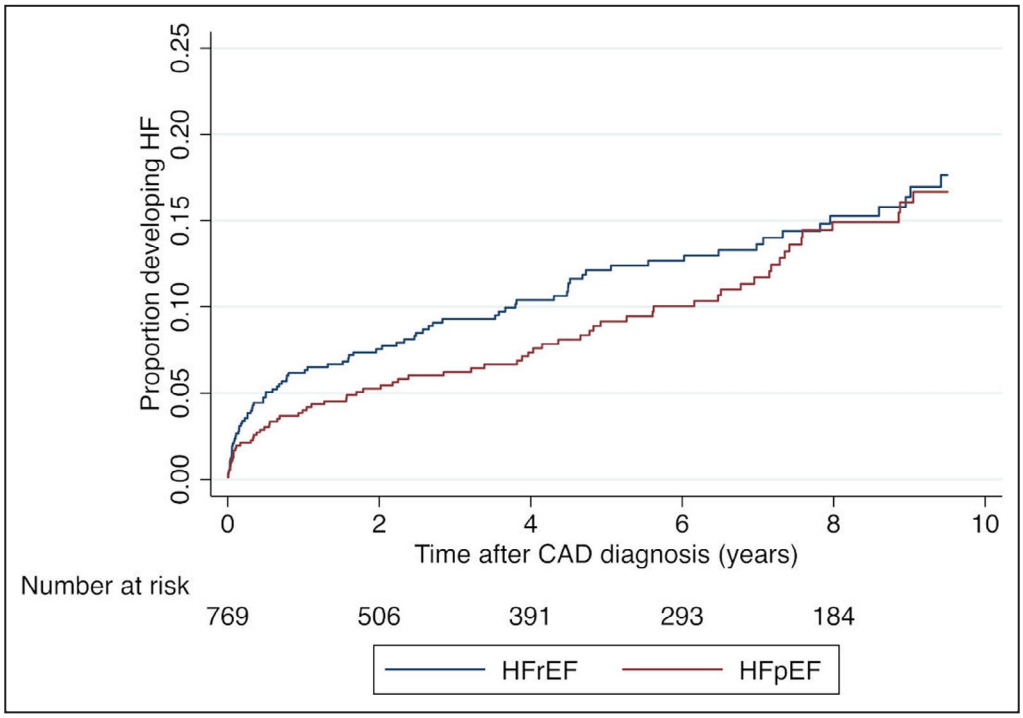

Figure 2. Incidence of HFrEF and HFpEF following CAD event.
Cumulative incidence of HFrEF (blue) and HFpEF (red) after CAD diagnosed by MI or revascularization. CAD indicates coronary artery disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and MI, myocardial infarction.

revascularization, is also a risk factor for subsequent incident HFpEF after adjusting for common comorbidities including hypertension, diabetes, atrial fibrillation, smoking, stroke, eGFR, and BMI. At >1 year after an incident CAD event, there was a similar likelihood of developing HFpEF and HFrEF. Even in the setting of a preserved LVEF, prevalent CAD was associated with greater LV mass index and higher LV filling pressure, as indicated by higher E/e' ratio and left atrial volume index, and these parameters partially accounted for the relationship between CAD and incident HFpEF.

Prior Research on CAD in HFpEF

Both HFrEF and HFpEF are characterized by a combination of systolic dysfunction (abnormal ejection fraction or abnormal longitudinal strain), and diastolic dysfunction.[2,21,22] Myocardial ischemia results in earlier and more prolonged impairment in LV diastolic compared to systolic function,[23–25] and revascularization rapidly improves diastolic function in patients with stable CAD and normal ejection fraction.[26,27] CAD may therefore be an important contributor to the development of HFpEF, as supported by previous studies demonstrating associations between prior MI and HFpEF and between extent of CAD and HFpEF risk in patients who are post-MI.[28] Prior MI was the one of the strongest risk factors for prevalent HF–the large majority HFpEF—in the CHS (Cardiovascular Health Study) .[7] In a cross-cohort evaluation of CHS, the FHS (Framingham Heart Study) , and the PREVEND (Prevention of Renal and Vascular Endstage Disease) study, history of MI at baseline was a predictor of incident HFpEF over a median follow-up of 12 years.[8] In the MESA (Multi-Ethnic Study of Atherosclerosis) , post-enrollment MI was a significant risk factor for incident HFpEF although adjustment covariates were assessed only at baseline.[9] Patients with MI represent one subset of CAD patients. Studies of participants with stable CAD and normal EF have found that most of those who later develop HF did not have an interval MI, and that prior revascularization is a risk factor for incident HF.[29,30]

CAD as a Risk Factor for HFpEF

We found both MI and revascularization without preceding MI to be a significant predictor of incident HFpEF after adjusting for demographics and common comorbidities. By analyzing CAD and the potential confounding covariates as time-updated variables, our analysis minimized residual confounding relative to prior analyses assessing predictors and confounders at a single time point. By accounting for the high HF risk early after a CAD event, we observed that CAD is a predictor of HFpEF beyond the acute functional and hemodynamic perturbations and increased monitoring occurring in the period surrounding a CAD event. We

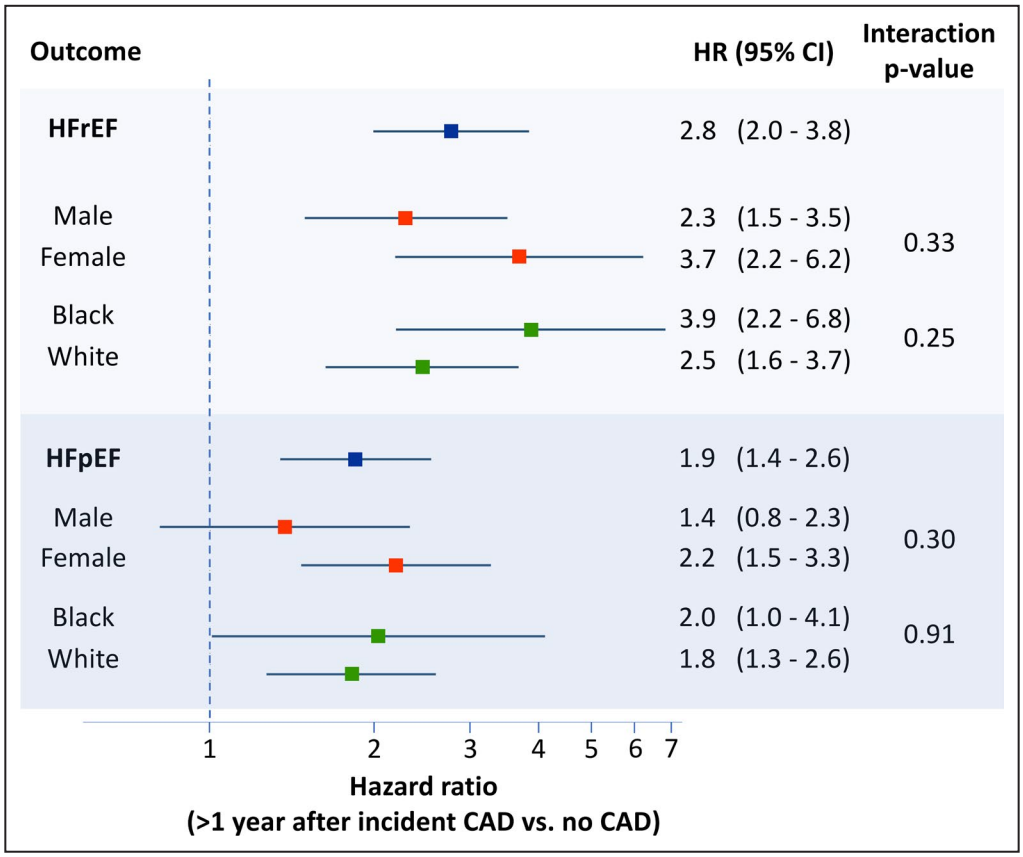

Figure 3. Risk of incident HFrEF and HFpEF associated with incident CAD compared to no CAD. Analysis 1 hazard ratios for incident CAD as a risk factor for incident HFrEF and HFpEF events occurring >1 year afterward. Models are adjusted for age, combined self-reported race and sex variable, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. Boxes represent the hazard ratios, and the horizontal lines indicate the 95% CIs. The vertical dashed line marks a hazard ratio of 1. Blue represents the hazard ratios for all HFrEF and HFpEF events. Red represents sex subgroups and green represents self-reported race subgroups. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

focused on the period of >1 year after the CAD event to evaluate stable CAD, but it is interesting to note that the risk for both HFpEF and HFrEF was higher at 90 days to 1 year after incident CAD compared with >1 year after incident CAD.

Prior small studies of patients with prevalent HFpEF have observed only subtle differences in echocardiographic measures between those with versus without prevalent CAD.[6,31] In our study of older people free of HF, prevalent CAD was associated with greater structural remodeling, higher LV filling pressure, and lower LVEF. Each of these partially accounted for the association of CAD with incident HFpEF. It is possible that the presence of structural remodeling or echocardiographic markers of elevated left atrial pressure may itself make a diagnosis of HFpEF more likely in a patient admitted with symptoms consistent with HF, so our findings merit future confirmation. Together these findings raise the possibility that CAD-associated ischemia, due either to epicardial CAD or concomitant coronary microvascular dysfunction, may lead to systolic and diastolic dysfunction and ultimately HFpEF. Consistent with this are prior studies that have implicated microvascular dysfunction in the development of HFpEF, and the finding that both obstructive and nonobstructive CAD may have associated coronary microvascular dysfunction.[32–35] These findings argue for an important, and potentially underappreciated, role of CAD in the development of HFpEF.

Future Directions

Our findings highlight that a promising group to target for HFpEF prevention is people with CAD. This is particularly important as CAD in HFpEF is likely underdiagnosed with current clinical approaches since coronary angiography is infrequently used to evaluate

Table 3. Baseline Characteristics for Participants Free of HF, LVEF <50%, and Moderate-or-Greater Left-Sided Valvular Dysfunction at Visit 5

Variable	No CAD (n=4289)	Prevalent CAD (n=490)	*P* value	Adj *P* value
Age, y	75.1±5.0	76.9±5.2	<0.001	<0.001*
Female	2679 (62.5%)	153 (31.2%)	<0.001	<0.001*
Black	907 (21.1%)	30 (6.1%)	<0.001	0.120*
Diabetes	1453 (33.9%)	205 (41.8%)	0.001	<0.001
Hypertension	3472 (81.0%)	462 (94.3%)	<0.001	<0.001
Atrial fibrillation	712 (16.6%)	138 (28.2%)	<0.001	<0.001
Stroke	109 (2.5%)	23 (4.7%)	0.012	0.025
Current/former smoker	2537 (59.2%)	354 (72.2%)	<0.001	0.001
eGFR, mL/min per 1.73 m^2	71±16	66±17	<0.001	<0.001
BMI, kg/m^2	28.5±5.5	27.9±4.2	0.017	0.57
Hemoglobin, g/dL	13.3±1.4	13.7±2.1	<0.001	0.162
Hemoglobin A1c, %	5.9±0.8	6.0±0.8	<0.001	<0.001
Center			<0.001	
Forsyth	1010 (23.5%)	136 (27.8%)		
Jackson	823 (19.2%)	24 (4.9%)		
Minneapolis	1316 (30.7%)	157 (32.0%)		
Washington	1140 (26.6%)	173 (35.3%)		

Adjusted *P* values are adjusted for age, sex, self-reported race, and field center. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; and LVEF, left ventricular ejection fraction.

*The adjusted *P* values for these variables are adjusted only for the remaining variables.

HFpEF.[36] Prior observational studies have found a prevalence of CAD of about 50% or less among individuals with HFpEF.[3,4] However, an autopsy-based study reported CAD in 65% of HFpEF patients compared with only 13% of age-matched controls,[5] and a study of systematic angiography in patients with acute decompensated HFpEF found obstructive coronary artery stenosis or a history of CAD in 79%.[6] Despite recent observational data suggesting less reduction in LVEF and improved survival among HFpEF patients with CAD undergoing complete revascularization versus not,[31,37] the lack of benefit with revascularization in prior observational studies make the potential benefit of routine revascularization of stable CAD for HFpEF prevention uncertain.[38,39] However, rigorous identification of CAD may allow the identification of a subset of HFpEF patients for whom certain medical therapies are effective, such as spironolactone,[40] interleukin-1

Table 4. Echocardiographic Correlates of Prevalent CAD at Visit 5

Variable	No CAD	CAD	*P* value	Model 1 *P* value	Model 2 *P* value
Structure					
LVEDD (cm)	4.35±0.47	4.51±0.49	<0.001	0.019	0.043
Mean LV wall thickness (cm)	0.97±0.13	1.02±0.15	<0.001	<0.001	0.014
LVMI (g/m^2)	77±17	85±21	<0.001	<0.001	<0.001
Systolic function					
Ejection fraction (%)	66.2±5.2	64.9±5.5	<0.001	0.001	0.006
Longitudinal strain (%)	–18.2±2.3	–17.7±2.6	<0.001	0.002	0.059
Diastolic function					
LAVi (mL/m^2)	25±8	28±10	<0.001	<0.001	<0.001
Peak E wave (cm/s)	66±17	68±20	0.010	<0.001	<0.001
Septal e' (cm/s)	5.8±1.5	5.6±1.3	0.031	0.011	0.081
E/e'	12.0±3.8	12.8±5.0	<0.001	<0.001	<0.001

Values are mean±SD, n (%), or median [25th–75th percentile]. Model 1: Adjusted for age, sex, self-reported race, field center. Model 2: Adjusted for age, sex, self-reported race, field center, diabetes, hypertension, atrial fibrillation, stroke, current/prior smoking, hemoglobin A1c, and hemoglobin. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; LAVi, left atrial volume index; LV, left ventricular, LVEDD, left ventricular end-diastolic dimension and LVMI, left ventricular mass index.

Table 5. Impact of Left Ventricular Structure and Function on the Association of Prevalent CAD at Visit 5 With Subsequent Incident HFpEF

	Model for HFpEF without echo parameters		Model for HFpEF with echo parameters	
	HR of CAD	*P* value	HR of CAD	*P* value
Structure	1.80 (1.07–3.03)	0.027	1.54 (0.91–2.62)	0.110
Systolic function	1.75 (1.03–2.98)	0.039	1.68 (0.98–2.87)	0.058
Diastolic function	1.73 (1.02–2.94)	0.043	1.35 (0.78–2.33)	0.277

Model is adjusted for age and stratified by sex, self-reported race, and field center. Structural parameters are end-diastolic LV internal dimension (cm) and mean LV thickness (cm); systolic function parameters are ejection fraction (%) and longitudinal strain (%); diastolic function parameters are left atrial volume index (mL/m^2), peak E wave (cm/s), septal e' (cm/s), and E/e'. CAD indicates coronary artery disease; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; and LV, left ventricular.

inhibitors[41] or sodium-glucose cotransporter-2 (SGLT2) inhibitors.[42]

Limitations

Several limitations of this study should be noted. There may be survival bias because of participant death, but the ARIC cohort is a community-based study of primarily older individuals, and therefore is roughly representative of the population at risk for HFpEF. Among ARIC participants alive and followed as of Visit 5, 61% chose to attend the visit and underwent echocardiography. Attrition bias due to visit nonattendance may therefore be an issue for Analysis 2 and may limit the generalizability of Analysis 2 findings. Analysis 1 is more robust to attrition bias as information from annual and semiannual follow-up telephone calls and surveillance of hospitalizations was used for this analysis. An additional limitation is that the large majority of Black participants are from the Jackson field center, and therefore race effects cannot be disentangled from effects related to the region or center of participants. Data on LVEF at the time of HF hospitalization were not available in a minority of hospitalizations, but sensitivity analyses found that this does not meaningfully impact the results. Baseline values for some characteristics such as eGFR and BMI had to be carried forward from prior time points and may have led to misclassification. The definition of HFpEF in the study was consistent with that used in prior epidemiologic studies.[43] However, recent consensus statements have proposed specific echocardiographic and biomarker criteria for diagnosing HFpEF. These recommendations were not available at the time of HF hospitalization, chart abstraction, or adjudication, and these measures were therefore not routinely available from the time of incident HF hospitalization. Additionally, as with the majority of epidemiology studies on HFpEF, only inpatient HF diagnoses were captured.[43] It is possible that some coronary revascularization procedures were performed for an outpatient HF diagnosis, but this is more likely for HFrEF than HFpEF. We used adjudicated MI events, rather than *ICD* codes, to mitigate the potential for misclassifying a type 2 MI related to decompensated HF exacerbation as an MI. Also, a sensitivity analysis showed that the results would not significantly change if we censored participants if their initial CAD hospitalization was also classified as an HF hospitalization. Finally, participants without an MI but with nonobstructive CAD or unrevascularized obstructive CAD would not be captured as CAD in this study, but we would expect this to bias results toward the null.

ARTICLE INFORMATION

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Affiliations

Noninvasive Cardiovascular Imaging Program, Departments of Medicine and Radiology (J.E.J., H.S., J.W.C.); Cardiovascular Division (J.E.J., B.C., H.S., S.D.S., J.W.C., A.M.S.); Johns Hopkins Bloomberg School of Public Health (K.M.); Division of Cardiovascular Medicine (S.H.K.); Cardiovascular Medicine Section, Wake Forest School of Medicine, Winston-Salem, NC (D.W.K.); Department of Medicine (T.H.M.); and Division of Cardiology (D.C.), University of Mississippi Medical Center, Jackson, MS; and Division of Cardiology, University of North Carolina at Chapel Hill, Chapel Hill, NC (P.P.C.).

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Supplemental Material

Data S1
Tables S1–S10

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Echocardiograms were obtained during Visit 5 by trained sonographers who used a pre-programmed acquisition protocol. The protocol included two-dimensional imaging of each view, along with color Doppler, continuous wave (CW) Doppler, pulsed wave (PW) Doppler, and tissue Doppler imaging (TDI) of certain views. At least three full cardiac cycles per view were recorded for patients in sinus rhythm, and at least five full cardiac cycles per view were recorded for patients in atrial fibrillation. Measurements were performed in accordance with American Society of Echocardiography guidelines by trained analysts at a dedicated core laboratory and were over-read by cardiologists.

Left ventricular (LV) dimensions were measured in the parasternal long axis view. The LV mass was determined from the LV linear dimensions and was indexed to the body surface area to obtain the LV mass index. LV volumes in the apical 4-chamber and apical 2-chamber views were calculated by the modified Simpson's method, and these volumes were used to determine the LV ejection fraction. The left atrial volume was calculated from the apical 4-chamber and apical 2-chamber views using the method of discs, and was indexed to obtain the left atrial volume index (LAVi). The peak E wave was measured using PW Doppler with the sample volume positioned at the tip of the mitral leaflets on the apical 4-chamber view. The peak septal mitral annular relaxation velocity (septal e') was assessed using TDI on the apical 4-chamber view. E/e' was calculated from these two values.

Table S1. Risk of the composite outcome of incident HF and death by CAD status

CAD Status	Incident HF + Death		
	Events	**Hazard ratio**	**P-value**
No CAD event	3137	Reference	
0 to <90 days after CAD event	109	16.01(13.14 – 19.51)	<0.001
90 days to 1 yr after CAD event	59	3.25(2.51 – 4.22)	<0.001
>1 yr after CAD event	210	1.43(1.24 – 1.65)	<0.001

Models are adjusted for age, race, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; and HF, heart failure.

Table S2. Risk of incident HF and HF subtypes by CAD status, separated by sex

		Incident HF			Incident HFrEF			Incident HFpEF		
		Events	Hazard ratio	P-value	Events	Hazard ratio	P-value	Events	Hazard ratio	P-value
Male participants (3865)	No CAD event	360	Reference		178	Reference		136	Reference	
	0 to <90 days after CAD event	15	16.27 (9.34 – 28.35)	<0.001	11	23.41 (11.97 – 45.78)	<0.001	3	8.40 (2.52 – 27.95)	0.001
	90 days to 1 yr after CAD event	14	4.88 (2.81 – 8.47)	<0.001	8	5.98 (2.86 – 12.47)	<0.001	5	4.10 (1.62 – 10.34)	0.003
	>1 yr after CAD event	52	1.85 (1.37 – 2.51)	<0.001	27	2.29 (1.50 – 3.51)	<0.001	17	1.36 (0.80 – 2.30)	0.251
Female participants (6037)	No CAD event	574	Reference		155	Reference		325	Reference	
	0 to <90 days after CAD event	26	24.34 (15.88 – 37.31)	<0.001	13	62.67 (32.83 – 119.65)	<0.001	12	16.58 (8.94 – 30.75)	<0.001
	90 days to 1 yr after CAD event	18	6.99 (4.32 – 11.32)	<0.001	10	15.56 (7.95 – 30.44)	<0.001	6	4.13 (1.81 – 9.38)	0.001
	>1 yr after CAD event	53	2.60 (1.94 – 3.48)	<0.001	17	3.71 (2.20 – 6.24)	<0.001	28	2.21 (1.48 – 3.30)	<0.001

Models are adjusted for age, race, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

Table S3. Risk of incident HF and HF subtypes by CAD status, separated by race

		Incident HF			Incident HFrEF			Incident HFpEF		
		Events	Hazard ratio	P-value	Events	Hazard ratio	P-value	Events	Hazard ratio	P-value
Black participants (2536)	No CAD event	309	Reference		132	Reference		142	Reference	
	0 to <90 days after CAD event	9	14.45 (7.24 – 28.85)	<0.001	5	17.00 (6.63 – 43.60)	<0.001	3	10.21 (3.14 – 33.18)	<0.001
	90 days to 1 yr after CAD event	8	4.86 (2.29 – 10.28)	<0.001	8	11.11 (5.05 – 24.43)	<0.001	0	-	-
	>1 yr after CAD event	30	3.21 (2.16 – 4.78)	<0.001	15	3.87 (2.19 – 6.81)	<0.001	9	2.03 (1.01 – 4.10)	0.047
White participants (7336)	No CAD event	622	Reference		201	Reference		316	Reference	
	0 to <90 days after CAD event	32	22.87 (15.74 – 33.25)	<0.001	19	44.36 (26.84 – 73.32)	<0.001	12	15.98 (8.74 – 29.24)	<0.001
	90 days to 1 yr after CAD event	24	5.53 (3.65 – 8.37)	<0.001	10	6.70 (3.51 – 12.79)	<0.001	11	5.31 (2.88 – 9.80)	<0.001
	>1 yr after CAD event	75	1.96 (1.53 – 2.51)	<0.001	29	2.45 (1.63 – 3.67)	<0.001	142	1.82 (1.27 – 2.59)	0.001

Models are adjusted for age, sex, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

Table S4. Risk of incident HF and HF subtypes by CAD status, with CAD separated into MI and revascularization

		Incident HF			Incident HFrEF			Incident HFpEF		
		Events	Hazard ratio	P-value	Events	Hazard ratio	P-value	Events	Hazard ratio	P-value
CAD defined as MI only (revascularization censored)	No CAD event	934	Reference		333	Reference		461	Reference	
	0 to <90 days after CAD event	33	23.86 (16.55 – 34.40)	<0.001	21	47.94 (29.72 – 77.33)	<0.001	11	14.11 (7.55 – 26.37)	<0.001
	90 days to 1 yr after CAD event	28	7.96 (5.42 – 11.69)	<0.001	18	14.49 (8.87 – 23.67)	<0.001	7	4.18 (1.96 – 8.90)	<0.001
	>1 yr after CAD event	63	2.88 (2.22 – 3.75)	<0.001	30	4.23 (2.88 – 6.22)	<0.001	23	1.99 (1.30 – 3.05)	0.002
CAD defined as revascularization only (MI censored)	No CAD event	934	Reference		333	Reference		461	Reference	
	0 to <90 days after CAD event	8	13.09 (6.41 – 26.76)	<0.001	3	11.31 (3.51 – 36.41)	<0.001	4	13.82 (5.01 – 38.10)	<0.001
	90 days to 1 yr after CAD event	4	1.95 (0.72 – 5.23)	0.187	0	-	-	4	4.06 (1.50 – 11.00)	0.006
	>1 yr after CAD event	42	1.74 (1.27 – 2.38)	<0.001	14	1.69 (0.98 – 2.93)	<0.001	22	1.87 (1.21 – 2.89)	0.005

Models are adjusted for age, combined race and sex variable, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and MI, myocardial infarction.

Table S5. Sensitivity analysis for risk of incident HF and HF subtypes by CAD status, with all unclassified incident HF cases added to HFrEF category and HFpEF category

		Incident HFrEF			Incident HFpEF		
		Events	Hazard ratio	P-value	Events	Hazard ratio	P-value
Unclassified HF reclassified as HFrEF	No CAD event	473	Reference				
	0 to <90 days after CAD event	26	26.33 (17.38 – 39.91)	<0.001			
	90 days to 1 yr after CAD event	21	7.08 (4.53 – 11.06)	<0.001			
	>1 yr after CAD event	60	2.56 (1.93 – 3.38)	<0.001			
Unclassified HF reclassified as HFpEF	No CAD event				601	Reference	
	0 to <90 days after CAD event				17	11.96 (7.26 – 19.70)	<0.001
	90 days to 1 yr after CAD event				14	3.84 (2.25 – 6.57)	<0.001
	>1 yr after CAD event				61	1.91 (1.46 – 2.52)	<0.001

Models are adjusted for age, combined race and sex variable, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

Table S6. Risk of incident HF and HF subtypes by CAD status, with censoring of participants who develop an MI after the incident CAD event

		Incident HF			Incident HFrEF			Incident HFpEF		
		Events	Hazard ratio	P-value	Events	Hazard ratio	P-value	Events	Hazard ratio	P-value
With censoring for MI after CAD	No CAD event	934	Reference		333	Reference		461	Reference	
	0 to <90 days after CAD event	39	19.33 (13.84 – 27.00)	<0.001	22	32.07 (20.31 – 50.65)	<0.001	15	13.85 (8.12 – 23.61)	<0.001
	90 days to 1 yr after CAD event	24	4.17 (2.77 – 6.29)	<0.001	10	4.75 (2.51 – 8.98)	<0.001	11	4.00 (2.18 – 7.33)	<0.001
	>1 yr after CAD event	90	1.88 (1.51 – 2.36)	<0.001	37	2.30 (1.61 – 3.27)	<0.001	39	1.61 (1.15 – 2.25)	0.006

Models are adjusted for age, combined race and sex variable, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and MI, myocardial infarction.

Table S7. Risk of incident HF and HF subtypes by CAD status, with censoring of participants for whom the hospitalization for incident CAD was also adjudicated as a HF hospitalization

		Incident HF			Incident HFrEF			Incident HFpEF		
		Events	Hazard ratio	P-value	Events	Hazard ratio	P-value	Events	Hazard ratio	P-value
With censoring if adjudicated HF at same hospitalization as initial CAD event	No CAD event	934	Reference		333	Reference		461	Reference	
	0 to <90 days after CAD event	21	12.22 (7.83 – 19.07)	<0.001	9	15.01 (7.58 – 29.76)	<0.001	10	10.71 (5.62 – 20.42)	<0.001
	90 days to 1 yr after CAD event	18	3.49 (2.18 – 5.59)	<0.001	7	3.57 (1.67 – 7.61)	0.001	8	3.34 (1.65 – 6.79)	0.001
	>1 yr after CAD event	81	1.77 (1.40 – 2.24)	<0.001	26	1.66 (1.10 – 2.51)	0.016	41	1.80 (1.29 – 2.51)	<0.001

Models are adjusted for age, combined race and sex variable, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

Table S8. Risk of incident HF and HF subtypes by CAD status, with incident HF defined as the first hospitalization that is adjudicated for HF, regardless of whether an MI was diagnosed in the same hospitalization (note- if a hospitalization is for both HF and MI, the incident HF event is included in the "No CAD event" category rather than in the "0 to <90 days after CAD event" category, since the HF date is determined by the admission date rather than the exact date of HF diagnosis during the hospitalization, which is unavailable)

		Incident HF			**Incident HFrEF**			**Incident HFpEF**		
		Events	Hazard ratio	P-value	Events	Hazard ratio	P-value	Events	Hazard ratio	P-value
With incident HF defined as first HF hospitalization, regardless of whether an MI diagnosed at the time	No CAD event	1051	Reference		421	Reference		490	Reference	
	0 to <90 days after CAD event	22	11.10 (7.20 – 17.12)	<0.001	10	12.47 (6.54 – 23.78)	<0.001	10	10.17 (5.35 – 19.37)	<0.001
	90 days to 1 yr after CAD event	20	3.51 (2.24 – 5.49)	<0.001	9	3.82 (1.96 – 7.45)	<0.001	8	3.14 (1.55 – 6.36)	0.002
	>1 yr after CAD event	91	1.79 (1.43 – 2.23)	<0.001	33	1.72 (1.19 – 2.48)	0.004	44	1.80 (1.31 – 2.48)	<0.001

Models are adjusted for age, combined race and sex variable, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated

glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and MI, myocardial infarction.

Table S9. Risk of incident HF and HF subtypes by CAD status, comparing main analysis with Fine-Gray modeling

	Incident HFrEF			**Incident HFpEF**		
	HR (main analysis)	SHR with HFpEF and unclassified HF as competing risks (Fine-Gray modeling)	SHR with HFpEF, unclassified HF, and death as competing risks (Fine-Gray modeling)	HR (main analysis)	SHR with HFpEF and unclassified HF as competing risks (Fine-Gray modeling)	SHR with HFpEF, unclassified HF, and death as competing risks (Fine-Gray modeling)
No CAD event	Reference	Reference	Reference	Reference	Reference	Reference
0 to <90 days after CAD event	34.29 (22.09 – 53.23) p <0.001	17.23 (10.11 – 29.36) p <0.001	8.01 (4.84 – 13.23) p <0.001	13.63 (7.99 – 23.26) p <0.001	5.78 (3.09 – 10.80) p <0.001	3.17 (1.76 – 5.71) p <0.001
90 days to 1 yr after CAD event	8.63 (5.31 – 14.02) p <0.001	7.83 (4.77 – 12.86) p <0.001	6.62 (3.91 – 11.19) p <0.001	3.99 (2.18 – 7.32) p <0.001	2.84 (1.51 – 5.33) p 0.001	2.56 (1.35 – 4.85) p 0.004
>1 yr after CAD event	2.76 (1.99 – 3.84) p <0.001	2.70 (1.93 – 3.76) p <0.001	2.84 (2.02 – 3.99) p <0.001	1.85 (1.35 – 2.54) p <0.001	1.76 (1.27 – 2.44) p 0.001	1.92 (1.38 – 2.66) p <0.001

Models are adjusted for age, combined race and sex variable, hypertension, atrial fibrillation, stroke, eGFR, BMI, current/prior smoking, diabetes, and field center.

BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; and SHR, sub-distribution hazard ratio.

Table S10. Risk of incident HF and HF subtypes by CAD status, with analysis performed separately for the early half (1/1/2005 to 7/2/2011) and the late half (7/3/2011 to 12/31/2017) of the study period

	Incident HFrEF						Incident HFpEF					
	Full study period		Early		Late		Full study period		Early		Late	
	Events	Hazard ratio	Events	Hazard ratio	Events	Hazard ratio	Events	Hazard ratio	Events	Hazard ratio	Events	Hazard ratio
No CAD event	333	Reference	162	Reference	160	Reference	461	Reference	184	Reference	265	Reference
0 to <90 days after CAD event	24	34.29 (22.09 – 53.23) p <0.001	10	21.91 (11.18 – 42.95) p <0.001	14	76.59 (41.36 – 141.85) p <0.001	15	13.63 (7.99 – 23.26) p <0.001	11	17.34 (9.12 – 32.96) p <0.001	4	9.68 (3.52 – 26.62) p <0.001
90 days to 1 yr after CAD event	18	8.63 (5.31 – 14.02) p <0.001	10	8.44 (4.37 – 16.30) p <0.001	5	6.97 (2.82 – 17.25) p <0.001	11	3.99 (2.18 – 7.32) p <0.001	7	4.92 (2.28 – 10.63) p <0.001	4	3.66 (1.35 – 9.93) p 0.011
>1 yr after CAD event	44	2.76 (1.99 – 3.84) p <0.001	13	3.22 (1.77 – 5.84) p <0.001	9	3.97 (2.00 – 7.89) p <0.001	45	1.85 (1.35 – 2.54) p <0.001	7	1.25 (0.58 – 2.71) p 0.574	13	3.40 (1.91 – 6.03) p <0.001

Models are adjusted for age, combined race and sex variable, hypertension, atrial fibrillation, stroke, eGFR, and BMI, with current/prior smoking, diabetes, and field center as stratification factors. BMI indicates body mass index; CAD, coronary artery disease; eGFR, estimated

glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.