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Implications of Coronary Artery Disease in Heart Failure With Preserved Ejection Fraction

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Objectives This study investigated the characteristics, evaluation, prognostic impact, and treatment of coronary artery disease (CAD) in patients with heart failure and preserved ejection fraction (HFpEF).

Background CAD is common in patients with HFpEF, but it remains unclear how CAD should be categorized, evaluated for, and treated in HFpEF.

Methods Clinical, hemodynamic, echocardiographic, treatment, and outcome characteristics were examined in consecutive patients with previous HFpEF hospitalizations who underwent coronary angiography.

Results Of the 376 HFpEF patients examined, 255 (68%) had angiographically-proven CAD. Compared with HFpEF patients without CAD, patients with CAD were more likely to be men, to have CAD risk factors, and to be treated with anti-ischemic medications. However, symptoms of angina and heart failure were similar in patients with and without CAD, as were measures of cardiovascular structure, function, and hemodynamics. Compared with patients without CAD, HFpEF patients with CAD displayed greater deterioration in ejection fraction and increased mortality, independent of other predictors (hazard ratio: 1.71, 95% confidence interval: 1.03 to 2.98; $p = 0.04$). Complete revascularization was associated with less deterioration in ejection fraction and lower mortality compared with patients who were not completely revascularized, independent of other predictors (hazard ratio: 0.56, 95% confidence interval: 0.33 to 0.93; $p = 0.03$).

Conclusions CAD is common in patients with HFpEF and is associated with increased mortality and greater deterioration in ventricular function. Revascularization may be associated with preservation of cardiac function and improved outcomes in patients with CAD. Given the paucity of effective treatments for HFpEF, prospective trials are urgently needed to determine the optimal evaluation and management of CAD in HFpEF. (J Am Coll Cardiol 2014;63:2817–27)

Approximately one-half of all patients with heart failure (HF) have heart failure with preserved ejection fraction (HFpEF) (1). In contrast to heart failure with reduced ejection fraction (HFrEF), there is no proven effective treatment for HFpEF (2). Accordingly, current studies and guidelines endorse treatment of commonly observed comorbidities (3–5). It has also recently been proposed that HFpEF represents a heterogeneous group of diseases that may respond differently to treatments (6). This heterogeneity may be minimized by subgrouping HFpEF patients according to the presence or absence of key comorbidities. Coronary artery disease (CAD) qualifies as a viable candidate for subclassification because it is common in HFpEF (1). CAD also plausibly explains the pathophysiology, because myocardial ischemia causes diastolic and systolic dysfunction (7–11), which are both common in patients with HFpEF (2,12).

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However, because CAD and HFpEF are associated with common risk factors, such as aging and hypertension, it is also possible that CAD and HFpEF simply coexist in many patients without any mechanistic relationship. As such, it remains unclear whether HFpEF patients with CAD should be diagnostically grouped separately from those without CAD, how and when to evaluate for CAD in patients presenting with HFpEF, and how to manage CAD once it is identified, at least in the absence of an acute coronary syndrome.

As a first step toward better understanding of the implications of CAD in patients with HFpEF, we investigated the clinical, structural, functional, hemodynamic, and outcome characteristics in a rigorously phenotyped group of patients who were previously hospitalized for HFpEF,

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
HR = hazard ratio
IQR = interquartile range
LV = left ventricular
LVEF = left ventricular ejection fraction
PASP = pulmonary artery systolic pressure

comparing those with angiographically-verified CAD with patients without significant CAD. To provide further insight into therapeutics, we then examined the associations of revascularization with survival and ventricular function in HFpEF patients with CAD.

Methods

Study population. All patients discharged from St. Mary's Hospital at the Mayo Clinic with the primary diagnosis of HF (International Classification of Diseases-9th revision code 428) between January 1, 2004, and December 31, 2012, were identified. From this group, individuals who had undergone echocardiography were identified and cross-checked with the Mayo Clinic catheterization laboratory database to identify all patients with coronary angiography within 1 year of hospital discharge and echocardiography within 6 months before angiography. Data from the first angiogram were used for patients with >1 examination. HFpEF was defined by clinical diagnosis of decompensated HF according to the admitting physician and left ventricular ejection fraction (LVEF) ≥50% within 6 months of hospitalization. In addition to HF hospitalization, all HF patients had to fulfill the Framingham criteria and/or demonstrate elevated left heart filling pressures at catheterization (pulmonary capillary wedge pressure or left ventricular [LV] end-diastolic pressure; >15 mm Hg at rest or ≥25 mm Hg with exercise) in studies performed specifically for the evaluation of dyspnea (13). Patients with significant valvular disease (more than moderate left-sided regurgitation or more than mild stenosis); severe pulmonary disease; acute coronary syndrome (defined by ≥2 of the following: increasing cardiac enzymes, ischemic electrocardiographic changes, typical chest pain); primary renal, hepatic, or pulmonary vascular disease; high output HF; chest radiation; severe anemia (≤9.0 g/dl); constrictive pericarditis; and infiltrative, restrictive, or hypertrophic cardiomyopathies were excluded.

Study design. HFpEF patients were divided into those with and without significant anatomic CAD, defined by angiographic stenosis of >50% in ≥1 epicardial coronary artery with a visual reference lumen diameter of ≥2.5 mm, previous infarction, or any previous revascularization. All angiograms were interpreted by a single experienced interventional cardiologist (S.J.H.). Syntax score was calculated as previously described (14,15). Clinical, hemodynamic, stress testing, and echocardiographic data were abstracted from detailed chart review and compared in HFpEF patients with and without CAD. Ischemia on noninvasive stress testing was defined as ST-segment depression >2 mm, new regional wall motion abnormalities on echocardiography, or reversible perfusion defects on myocardial nuclear imaging.

Complete revascularization was defined as treatment of all >50% coronary stenoses in epicardial vessels by percutaneous intervention and/or coronary bypass grafting. Incomplete revascularization was defined as intervention on ≥1 significant stenosis, but with residual lesion(s) of >50% stenosis. The impact of the presence or absence of CAD and the impact of revascularization in HFpEF patients with CAD was assessed by follow-up echocardiography performed no sooner than 6 months after angiography and by assessing vital status ascertained through chart review and the Social Security Death Index.

Assessment of cardiovascular structure, function, and hemodynamics. Two-dimensional and Doppler echocardiography were performed to assess LV morphology and systolic and diastolic function according to American Society of Echocardiography guidelines by experienced sonographers and echocardiologists (16). Right and left heart catheterization were performed in the supine position via the jugular or femoral veins and femoral or radial arteries using fluid-filled catheters (13). Hemodynamic parameters including right and left heart filling pressures, pulmonary artery pressures, cardiac output, pulmonary and systemic arterial resistance, compliance, and elastance were determined as described previously (17).

Statistical analysis. Continuous variables were reported as mean ± SD or median (interquartile range [IQR]) and compared by analysis of variance, paired *t* test, or Mann-Whitney *U* test. Categorical variables were expressed as number (percent) and were compared by chi-square or Fisher exact test. Regression was used to adjust for potential confounding, in which the dependent variable was the normally distributed continuous (linear least-squares regression) or categorical (logistic regression) outcome variable of interest. The impact of the presence of CAD on survival and impact of revascularization in patients with CAD were assessed by the Kaplan-Meier method with Cox regression analysis to adjust for other univariate predictors of death. Univariate predictors were selected based on previously-published studies that showed an association with increased mortality in HFpEF (18,19) and sufficient availability of data in the sample population. In the primary treatment analysis, "revascularization" was considered complete in patients who received complete revascularization, whereas patients who did not undergo revascularization or had "incomplete revascularization" were included together in the comparator group (20).

Results

During the 8-year study, there were 4,331 unique patients who were admitted with a primary diagnosis of HF who underwent both echocardiography and angiography within