Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 3, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.09.039

# Heart Failure With Preserved Ejection Fraction

## Comparison of Patients With and Without Angina Pectoris (From the Duke Databank for Cardiovascular Disease)

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**Objectives** This study investigated the characteristics and outcomes of patients with heart failure with preserved ejection fraction (HFpEF) and angina pectoris (AP).

**Background** AP is a predictor of adverse events in patients with heart failure with reduced EF. The implications of AP in HFpEF are unknown.

**Methods** We analyzed HFpEF patients (EF ≥50%) who underwent coronary angiography at Duke University Medical Center from 2000 through 2010 with and without AP in the previous 6 weeks. Time to first event was examined using Kaplan-Meier methods for the primary endpoint of death/myocardial infarction (MI)/revascularization/stroke (i.e., major adverse cardiac events [MACE]) and secondary endpoints of death/MI/revascularization, death/MI/stroke, death/MI, death, and cardiovascular death/cardiovascular hospitalization.

**Results** In the Duke Databank, 3,517 patients met criteria for inclusion and 1,402 (40%) had AP. Those with AP were older with more comorbidities and prior revascularization compared with non-AP patients. AP patients more often received beta-blockers, angiotensin-converting enzyme inhibitors, nitrates, and statins (all $p < 0.05$). In unadjusted analysis, AP patients had increased MACE and death/MI/revascularization (both $p < 0.001$), lower rates of death and death/MI (both $p < 0.05$), and similar rates of death/MI/stroke and cardiovascular death/cardiovascular hospitalization (both $p > 0.1$). After multivariable adjustment, those with AP remained at increased risk for MACE (hazard ratio [HR]: 1.30, 95% confidence interval [CI]: 1.17 to 1.45) and death/MI/revascularization (HR: 1.29, 95% CI: 1.15 to 1.43), but they were at similar risk for other endpoints ($p > 0.06$).

**Conclusions** AP in HFpEF patients with a history of coronary artery disease is common despite medical therapy and is independently associated with increased MACE due to revascularization with similar risk of death, MI, and hospitalization. (J Am Coll Cardiol 2014;63:251–8) © 2014 by the American College of Cardiology Foundation

Angina pectoris (AP) is the symptomatic condition related to ischemia and has different prognostic implications in various patient populations (1). We have previously shown that the presence of AP in patients with heart failure (HF) with reduced ejection fraction (EF) is common despite medical therapy and previous revascularization, and is associated with increased cardiovascular death or rehospitalization (2). Heart failure with preserved ejection fraction (HFpEF) accounts for upward of 50% of all patients with HF (3), and the evidence for therapies to reduce adverse events in this population is limited (4). The implications of AP in HFpEF are not well defined because these patients have generally been excluded from AP studies (5). We compared the clinical characteristics and the outcomes of patients with and without AP in a cohort of HFpEF patients.

## Methods

Patient data were obtained from the Duke Databank for Cardiovascular Disease (DDCD), an ongoing databank of all patients undergoing diagnostic cardiac catheterization at Duke University Medical Center. Patients were included in the study population if they underwent coronary angiography from January 2000 through December 2010, and if they had HFpEF and a history of ≥50% stenosis in at least 1 epicardial coronary vessel (only those patients with a history of significant coronary artery disease receive DDCD follow-up). Coronary stenoses were graded by visual consensus of at least 2 experienced observers. Patients were

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Manuscript received April 5, 2013; revised manuscript received September 22, 2013, accepted September 23, 2013.

**Abbreviations and Acronyms**

AP = angina pectoris
CI = confidence interval
DDCD = Duke Databank for Cardiovascular Disease
EF = ejection fraction
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HR = hazard ratio
IQR = interquartile range
KM = Kaplan-Meier
MACE = major adverse cardiac events
MI = myocardial infarction
NYHA = New York Heart Association

defined as having HFpEF if they had New York Heart Association (NYHA) functional class II to IV symptoms in the 2 weeks before index catheterization and EF ≥50% (6). Patients were excluded from analysis if they had EF <50%, unknown EF, unknown NYHA functional class, primary valvular heart disease (defined as moderate or severe aortic or mitral insufficiency, or severe stenosis of any heart valve), congenital heart disease, acquired immunodeficiency syndrome, or metastatic cancer.

Data from the index catheterization were prospectively collected as part of routine patient care. Baseline clinical variables for each patient were stored in the DDCD using methods previously described (7). Follow-up was obtained through self-administered questionnaires, with telephone follow-up to nonresponders. Patients not contacted through this mechanism had vital status determined through a search of the National Death Index (8).

AP classification was based on physician-obtained patient history just before cardiac catheterization and was defined as chest pain within the previous 6 weeks. Because many groups (e.g., women, elderly patients) present with atypical angina (9,10), we did not want to bias our results by using a classic angina definition alone. Given the prognostic value of angina characteristics, the severity, frequency, and pattern of occurrence were recorded at baseline. Revascularization was defined as treatment with percutaneous coronary intervention or coronary artery bypass graft. Death, myocardial infarction (MI), stroke, and cardiovascular rehospitalization were determined using methods previously described (7).

**Statistical analysis.** Baseline characteristics are described with medians and interquartile ranges (IQRs) for continuous variables and percentages for discrete variables in HFpEF patients with versus without AP. These characteristics were compared using the Wilcoxon rank sum test for continuous variables and chi-square tests for categorical variables unless otherwise noted. The primary endpoint was death/MI/revascularization/stroke (i.e., major adverse cardiac events [MACE]) and secondary endpoints were death/MI/revascularization, death/MI/stroke, death/MI, death, and cardiovascular death/cardiovascular hospitalization. Multivariable Cox proportional hazards regression analysis was used to adjust for baseline differences between groups. A comprehensive set of covariates was used for the adjustment analysis (see Table 3 footnote) based on clinical relevance and data from a previous investigation (2). With the large number of events in each analysis, there was no overfitting problem with adjustment variables. Adjusted time-to-event results were generated for the endpoints, and comparisons were made using the log-rank test. A p value of <0.05 was used to indicate statistical significance for all comparisons. Statistical analyses were performed by Duke Clinical Research Institute (Durham, North Carolina) using SAS (version 9.2, SAS Institute, Cary, North Carolina). The protocol was approved by the institutional review board at Duke University, and all patients voluntarily provided written informed consent.

## Results

A total of 3,517 patients met the criteria for the study (Fig. 1), and 1,402 (40%) had AP. In the AP cohort, 48% had typical angina and 49% had atypical angina in the previous 6 weeks. AP was described as stable, progressing, or unstable in 24%, 47%, and 27% of patients in the preceding 6 weeks, respectively. Using a modification of the Canadian Cardiovascular Society angina grade (11), the percentage of AP patients with Canadian Cardiovascular Society classes I (no symptoms with ordinary activity), II (symptoms with moderate exertion), III (symptoms with ordinary exertion), IV (symptoms with any exertion or at rest), and symptoms unrelated to exertion were 0.2%, 13.3%, 15.0%, 41.5%, and 30.1%, respectively. The median frequency per week of chest pain episodes was 4 (IQR: 3 to 7).

Baseline characteristics for the AP and non-AP groups are provided in Table 1. As expected, a number of baseline characteristics differed significantly between the cohorts, with AP patients tending to be older and more likely to have a prior history of hypertension, diabetes, hyperlipidemia, vascular disease, smoking, and coronary revascularization. Notably, those with AP tended to have less severe NYHA functional class symptoms and were less likely to have rales or an S3 gallop. Systolic blood pressure was significantly higher in the AP group. The basic laboratory parameters were similar between the 2 groups even though there were statistically significant differences in several of the laboratory parameters due to the large sample size. AP patients more often received beta-blockers, angiotensin-converting enzyme inhibitors, nitrates, and statins but were less likely to receive diuretics as compared with non-AP patients. In this HFpEF population, both groups had high baseline use of beta-blockers and angiotensin-converting enzyme inhibitors, but modest use of calcium channel blockers, nitrates, and hydralazine. In the AP group, 77% of patients received a beta-blocker, calcium channel blocker, or nitrate at baseline compared with 68% in the non-AP group.

The median follow-up time for all patients was 4.0 years (IQR: 1.6 to 7.6 years). Five-year unadjusted Kaplan-Meier (KM) survival for the study population was 66.3%. AP patients were observed to have a significantly increased event rate for the primary endpoint of MACE, as well as death/