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Original Article

Survival in Patients With Nonischemic Cardiomyopathy With Preserved vs Reduced Ejection Fraction

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ABSTRACT

Background: Prior studies suggest similar long-term mortality rates for patients with heart failure (HF) with preserved ejection fraction (HFpEF) vs reduced ejection fraction. However, although coronary heart disease (CHD) is associated with worse prognosis in HF, clinical outcomes are less well characterized for HF without CHD. We investigated the characteristics and 5-year mortality outcomes among patients with HF without significant CHD, stratified by EF.

Methods: Patients with clinical heart failure who underwent coronary angiography at Duke University Medical Center from 1996 through 2009 and had no significant CHD with EF ≤ 40% were compared with patients without significant CHD with EF > 40%. Survival was examined using Kaplan-Meier methods and multivariable Cox proportional hazards modeling. Analyses were repeated using EF ≥ 50%.

Results: Of 3154 patients with HF without significant CHD, 1530 (48.5%) had HFpEF (EF > 40%). These patients were older and more likely to have a Charlson Index ≥ 2 than patients with reduced EF.

RÉSUMÉ

Introduction : Des études antérieures indiquent des taux de mortalité à long terme similaires entre les patients atteints d'insuffisance cardiaque (IC) avec fraction d'éjection (FE) préservée (ICFEP) *vs* les patients atteints d'IC avec FE réduite (ICFER). Toutefois, bien que la coronaropathie soit associée à un plus mauvais pronostic de l'IC, les résultats cliniques sont moins bien définis que ceux de l'IC sans coronaropathie. Nous avons examiné les caractéristiques et les résultats des patients atteints d'IC sans coronaropathie importante, stratifiés selon la FE, sur la mortalité dans les cinq ans.

Méthodes : Nous avons comparé les patients montrant des signes cliniques d'IC qui avaient subi une angiographie coronarienne à la Duke University de 1996 à 2009 et n'avait pas de coronaropathie importante avec FE ≤ 40 % aux patients sans coronaropathie importante avec FE > 40 %. Nous avons examiné la survie à l'aide de la méthode de Kaplan-Meier et du modèle multivarié à risques proportionnels de Cox. Nous avons répété les analyses en fonction d'une FE ≥ 50 %.

The burden of disease in heart failure (HF) remains significant. By 2030, more than 8 million Americans are projected to have HF, with a growing proportion being diagnosed with HF with preserved ejection fraction (HFpEF).[1,2] Despite significant therapeutic advances in HF with reduced ejection fraction (HFrEF), HFpEF remains difficult to characterize clinically, with no medical therapy shown to clearly improve outcomes. Thus, understanding treatable comorbidities and underlying HF etiology (ie, ischemic or nonischemic origin) remains vital to prognostication and management.

Coronary heart disease (CHD) is a leading cause of HF. The presence of significant CHD portends worse outcomes in both HFrEF and HFpEF, yet research in this area has tended to focus on patients with HFrEF.[3-8] However, CHD is also extremely common in HFpEF and is associated with worsening of ventricular function over time, suggesting a potential subgroup of patients with HFpEF who share more characteristics with patients with HFrEF.[8] Even as outcomes have improved in HFrEF over time, outcomes in HFpEF may be worsening.[2] However, given the significant contribution of CHD to this population, few studies have specifically evaluated the outcomes of patients with HF without significant CHD. We studied the clinical characteristics and long-term survival trends of patients with angiographically confirmed nonischemic HF with preserved vs reduced EF.

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Ethics Statement: The Duke University Institutional Review Board approved this analysis.

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Patients with HFpEF had a lower risk of death than those with reduced EF (unadjusted hazard ratio [HR] 0.85; 95% confidence interval [CI] 0.74-0.99). From 1996 through 2009, the secular trend of death decreased among patients without CHD and with reduced EF (HR 0.92; 95% CI 0.88-0.97) but not among those with preserved EF (HR 0.99; 95% CI 0.93-1.05; *P* interaction 0.095). No finding was significant after multivariable risk adjustment. Results were consistent when defining preserved EF as EF $\geq$ 50%.

Conclusions: Among patients without significant CHD, those with HFpEF had similar risks of 5-year mortality as patients with HF with reduced ejection fraction.

Résultats : Parmi les 3 154 patients atteints d'IC sans coronaropathie importante, 1 530 (48,5 %) avaient une ICFEP (FE $>$ 40 %). Ces patients étaient plus âgés et plus susceptibles d'avoir un indice de Charlson $\geq$ 2 que les patients atteints d'ICFER. Les patients atteints d'ICFEP avaient un risque plus faible de mortalité que ceux atteints d'une ICFER (rapport de risque [RR] non ajusté 0,85; intervalle de confiance [IC] à 95 % 0,74-0,99). De 1996 à 2009, la tendance séculaire de la mortalité avait diminué chez les patients sans coronaropathie et qui avaient une FE réduite (RR 0,92; IC à 95 % 0,88-0,97), mais non chez ceux qui avaient une FE préservée (RR 0,99; IC à 95 % 0,93-1,05; valeur *P* de l'interaction 0,095). Aucun résultat n'était significatif après l'ajustement multivarié en fonction du risque. Les résultats étaient cohérents lorsque la FE préservée était définie par une FE $\geq$ 50 %.

Conclusions : Chez les patients sans coronaropathie importante, ceux atteints d'une ICFEP avaient des risques similaires de mortalité dans les cinq ans aux patients atteints d'ICFER.

Methods

Study population

Patient data were obtained from the Duke Databank for Cardiovascular Disease (DDCD), a registry of patients undergoing cardiac catheterization at Duke University Medical Center. Data collection and analysis methods in the DDCD have been published previously.[9,10] Patients were included in the study population if they had a documented history of HF, a known EF, and had undergone index coronary angiography at some point from January 1996 through December 2009. A review of patients in the DDCD prior to 1996 showed more missing baseline data, which precluded multivariable adjustment; therefore, these patients were excluded. Given that we were interested in long-term (ie, 5-year) follow-up of patients and that the DDCD follow-up ended in 2014, we defined our study cohort as being from 1996 through 2009. Patients were also excluded if they had an unknown EF, unknown coronary angiography data, primary valvular heart disease (defined as severe aortic or mitral insufficiency or severe stenosis of any heart valve), congenital heart disease, acquired immunodeficiency syndrome, or metastatic cancer.

Study definitions

Only patients with symptomatic HFpEF were included in this analysis. As in prior work with the DDCD, HFpEF was defined as an EF $>$ 40%, with New York Heart Association (NYHA) functional class II to IV symptoms in the 2 weeks prior to the index catheterization. Patients with HFrEF were defined as those having an EF $\leq$ 40% with any NYHA functional class symptoms. Recent clinical treatment guidelines assign patients with HF and a left ventricular EF of 40%-49% to an "intermediate" subgroup, and define HFpEF as an EF $\geq$ 50%.[11,12] Given these parameters, we conducted a sensitivity analysis in which HFpEF was defined as an EF $\geq$ 50%, *and HFrEF was defined as an EF $<$ 50%,* to assess consistency of results.

CHD was defined as $\geq$ 75% stenosis in $\geq$ 1 epicardial coronary vessels found at index catheterization, a history of previous coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention), or a history of myocardial infarction based on prior work.[3] Coronary angiography was reviewed and graded in a standardized fashion by 2 experienced operators at the time of catheterization. Patients without evidence of CHD were defined as having nonischemic HF.

Study data

Baseline clinical data from the index catheterization were prospectively collected as part of routine patient care and stored in the DDCD using methods previously described.[13] EF data were obtained from the most recent echocardiogram or nuclear perfusion study within 3 months prior or 1 month after catheterization, with no intervening myocardial infarction or percutaneous coronary intervention. Vital status was obtained through follow-up questionnaires or telephone interview, or it was determined through a search of the National Death Index and Social Security Death Master File.[14] The Duke University Institutional Review Board approved this analysis.

Statistical analysis

Patients with nonischemic HFpEF were compared with patients with nonischemic HFrEF. Baseline characteristics for the 2 groups were summarized with medians and interquartile ranges for continuous variables, and percentages for categorical variables. These characteristics were compared using the Wilcoxon rank-sum test for continuous variables, and χ^2 tests for categorical variables, unless otherwise noted. The primary endpoint was all-cause mortality at 5 years; data were truncated at 5 years of follow up. We estimated the overall survival by the Kaplan-Meier method and tested for differences in survival between groups using the log-rank test.

Multivariable Cox proportional hazards regression was used to adjust for baseline differences between groups, using only complete case analysis. Candidate variable selection was based on clinical relevance and prior analyses.[15] We included 25 patient covariates in the model: age, race, sex, hypertension, systolic blood pressure, heart rate, diabetes, hyperlipidemia, cerebrovascular disease, peripheral vascular disease,

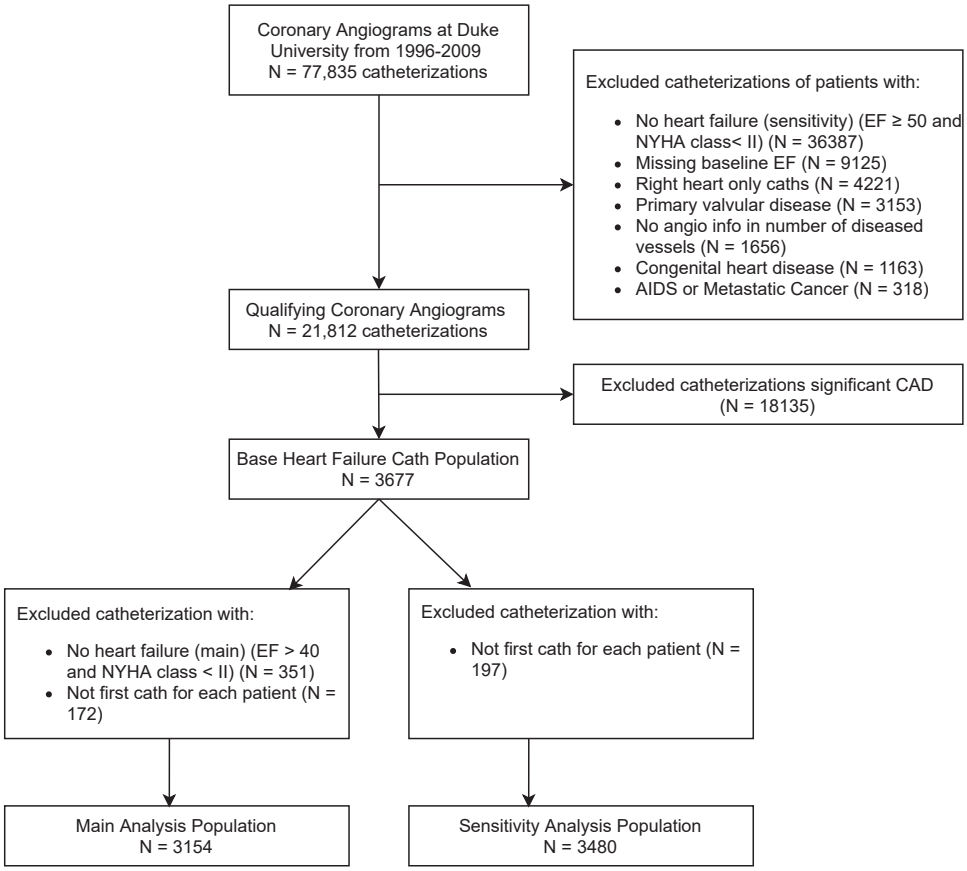

Figure 1. Flow diagram of the study design. This figure displays the initial study population, through exclusions, to the final study population. AIDS, acquired immunodeficiency syndrome; angio, angiography; CAD, coronary artery disease; cath, catheterization; EF, ejection fraction; info, information; NYHA, New York Heart Association.

history of smoking, Charlson comorbidity index, body mass index, beta-blocker use, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker use, hydralazine use, nitrates use, aspirin use, clopidogrel use, statin use, diuretic use, serum creatinine level, blood urea nitrogen level, hemoglobin level, and sodium level. Nonlinear relationships between continuous adjustment variables and 5-year mortality were accounted for in the model using restricted cubic spline transformations. The proportional hazards assumption for the comparator group was evaluated using weighted Schoenfeld residuals, and there was no evidence to suggest that the proportional hazards assumption was violated.

To evaluate time trends in 5-year mortality, the study population was divided into cohorts by 2-year increments by year of catheterization, giving a total of 7 cohorts. Cox proportional hazards modeling was used, including year of catheterization and EF group, assuming time trends were linear on the log hazard scale. Within each EF group, the interaction between year and EF was also included. Time trends in the adjusted hazard of mortality were also examined, with inclusion of the same adjustment variables. Additionally, the above analyses were repeated with HFpEF defined as an EF $\geq$ 50%. Statistical analyses were performed by the Duke Clinical Research Institute (Durham, NC) using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Between 1996 and 2009, there were 21,812 coronary angiograms in unique patients with HF. Of these, 18,135 patients (83.1%) were excluded for significant CHD. In the main analysis population, 3154 patients with nonischemic cardiomyopathy met criteria for the study (Fig. 1), of whom 1530 (48.5%) had HFpEF, and 1624 (51.5%) had HFrEF. Baseline characteristics for the study groups are provided in Table 1. Patients with preserved ejection fraction were older (59 vs 56 years), were more likely to be female (64% vs 42%) and White (64% vs 47%), and had a higher median body mass index (30 vs 28 kg/m^2). The HFpEF patients had a greater burden of cardiovascular disease and risk factors, including a higher proportion with hyperlipidemia (38% vs 29%), cerebrovascular disease (8% vs 6%), and peripheral vascular disease (6% vs 3%), and higher systolic blood pressure (median 142 mm Hg vs 132 mm Hg). The prevalence of diabetes was similar by group (25% vs 24%). Overall, the HFpEF group had a higher proportion of patients with a Charlson Index $\geq$ 2 (20% vs 15%). A Charlson comorbidity index $\geq$ 2 predicts a 10% or higher 10-year mortality.[16] Patients with HFrEF more often received beta-blockers (79% vs 63%) and angiotensin-converting enzyme inhibitors (80% vs 46%), but they also more often received diuretic (80% vs 67%), statin (47% vs 41%), and aspirin therapy (80% vs 69%). In this catheterization referral population, there was a fairly consistent

Table 1. Baseline characteristics of the nonischemic population by ejection fraction (EF) group

Characteristic	EF ≤ 40 n = 1624	EF > 40 n = 1530	*P*
Age (y)	56 (46, 66)	59 (50, 59)	< 0.001
Female	41.7	63.6	< 0.001
Race			< 0.001
White	47.3	64.2	
Black	48.5	30.8	
NYHA Class			N/a
Not available	25.1	Excluded	
I	3.8	Excluded	
II	16.0	37.4	
III	31.1	44.0	
IV	24.0	18.6	
Hypertension	60.5	62.4	0.29
Diabetes	24.1	24.7	0.71
Hyperlipidemia	28.7	38.4	< 0.001
Ejection fraction (%)	25 (20, 35)	55 (55, 56)	< 0.001
Cerebrovascular disease	6.3	8.4	0.03
Peripheral vascular disease	2.6	5.8	< 0.001
Previous smoking	44.3	38.0	< 0.001
Charlson Index ≥ 2	14.7	19.7	< 0.001
COPD	7.9	12.0	< 0.001
Renal disease	6.8	6.9	0.86
History of liver disease	0.7	1.4	0.05
Body mass index (kg/m^2)	28.1 (23.8, 33.4)	29.8 (35.4, 36.8)	< 0.001
Heart rate (beats/min)	83 (71, 96)	75 (65, 86)	< 0.001
Systolic blood pressure (mm Hg)	132 (116, 150)	142 (125, 162)	< 0.001
S3 Gallop	19.8	4.1	< 0.001
Serum sodium (mmol/L)	139 (137, 141)	140 (138, 141)	< 0.001
Blood urea nitrogen (mg/dL)	17 (13, 23)	16 (12, 22)	< 0.001
Serum creatinine (mg/dL)	1.1 (0.9, 1.3)	1.0 (0.8, 1.2)	< 0.001
Hemoglobin (g/dL)	13.3 (11.9, 14.5)	12.8 (11.3, 14.0)	< 0.001
Beta blocker use	79.1	63.1	< 0.001
ACE inhibitor use	80.3	46.0	< 0.001
ARB use	29.2	31.4	0.18
Hydralazine use	19.4	14.0	< 0.001
Nitrate use	36.9	31.2	< 0.001
Calcium channel blocker use	30.1	40.9	< 0.001
Diuretic use	80.0	67.1	< 0.001
Aspirin use	79.9	69.3	< 0.001
Clopidogrel use	7.5	7.3	0.78
Statin use	46.6	40.8	< 0.001

Values are expressed as %, or median (quartile 1, quartile 3), unless otherwise indicated.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disorder; N/a, not available; NYHA, New York Heart Association.

distribution of patients with HFrEF vs HFpEF over time, with each EF group representing approximately half of the cohort from 1996 through 2009 (Table 2).

Survival data through 5 years were available for all 3154 patients. The 5-year unadjusted Kaplan-Meier mortality for the study population was 24.6% (Fig. 2). Patients with nonischemic HFpEF had a lower risk of death than did those with HFrEF (unadjusted hazard ratio [HR] 0.85; 95% confidence interval [CI] 0.74, 0.99; $P = 0.03$). After adjustment for differences in baseline characteristics and stratification for year of catheterization, the mortality risk for patients with nonischemic HFpEF was similar to that for patients with HFrEF (adjusted HR 1.05; 95% CI 0.88, 1.26; $P = 0.58$).

Among patients with nonischemic HFrEF, the risk of death decreased over time from 1996 through 2009 (unadjusted HR 0.92 per year; 95% CI 0.88, 0.97). However, the likelihood of mortality among patients with preserved EF did not change over the study period (unadjusted HR 0.99 per year; 95% CI 0.93, 1.05). In consecutive catheterization year cohorts, the difference in mortality between patients with reduced EF vs preserved EF decreased over time (Table 2). The unadjusted interaction *P* value for catheterization year and EF group was 0.095, providing weak evidence that time trends differed between the EF groups. After adjustment for baseline characteristics, there was no evidence of a significant difference in mortality over time within the EF groups (adjusted HR for reduced EF: 1.06; 95% CI 0.99, 1.12, and for preserved EF: 1.02; 95% CI 0.96, 1.09) or between the EF groups (adjusted interaction *P* value 0.43; Table 2). Figure 3 shows the event rates over time for patients with reduced vs preserved ejection fraction from 1996 through 2009.

Sensitivity analysis

We repeated the above analyses with HFpEF defined as an EF ≥ 50%, and HFrEF defined as an EF < 50%.[11,12] This combined HF population was larger in size, with N = 3480

Table 2. Distribution of patients by ejection fraction (EF) group and 5-year Kaplan-Meier (KM) mortality event rate comparing heart failure with reduced vs preserved EF and changes over time

Cohort	EF ≤ 40% (ref)	EF > 40%
1996-1997		
KM rate	35.2 (29.0, 42.3)	25.8 (20.1, 32.7)
n = 382	51.3% (196)	48.7% (186)
HR	0.72 (0.56, 0.93)	
1998-1999		
KM rate	29.5 (24.0, 35.9)	23.5 (18.4, 29.7)
n = 449	49% (220)	51% (229)
HR	0.77 (0.63, 0.94)	
2000-2001		
KM rate	27.8 (22.5, 34.2)	23.4 (18.9, 28.7)
n = 534	44.2% (236)	55.8% (298)
HR	0.82 (0.71, 0.96)	
2002-2003		
KM rate	19.9 (15.7, 24.9)	21.5 (16.8, 27.3)
n = 560	55.0% (308)	45.0% (252)
HR	0.88 (0.76, 1.02)	
2004-2005		
KM rate	26.0 (21.1, 31.7)	19.6 (14.8, 25.7)
n = 500	54.6% (274)	45.5% (227)
HR	0.94 (0.79, 1.13)	
2006-2007		
KM rate	22.6 (17.3, 29.3)	21.1 (15.3, 28.7)
n = 365	55.8% (203)	44.2% (161)
HR	1.01 (0.80, 1.27)	
2008-2009		
KM rate	23.0 (17.2, 30.4)	27.5 (21.0, 35.5)
n = 365	49.0% (179)	51.0% (186)
HR	1.08 (0.80, 1.45)	

	Time trends		
	EF ≤ 40% (ref)	EF > 40%	*P* for interaction
Unadjusted HR over time (compared to year prior)	0.92 (0.88, 0.97)	0.99 (0.93, 1.05)	0.095
Adjusted* HR over time (compared to year prior)	1.06 (0.99, 1.12)	1.02 (0.96, 1.09)	0.43

KM rates and hazard ratios (HR) are given with 95% confidence intervals.
ref, referent.
*Adjusted for age, race, gender, hypertension, systolic blood pressure, heart rate, diabetes, hyperlipidemia, cerebrovascular disease, peripheral vascular disease, history of smoking, Charlson comorbidity index, body mass index, beta-blocker use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, hydralazine use, nitrate use, aspirin use, clopidogrel use, statin use, diuretic use, serum creatinine level, blood urea nitrogen level, hemoglobin level, and sodium level.

patients, owing to inclusion of patients with a mid-range EF of 40%-50% who had NYHA class I symptoms. Their baseline characteristics are included in Supplemental Tables S1 and S2 and largely mirrored the differences seen in the primary cohort. Trends in outcomes also emulated patterns seen in the primary cohort, with key differences. In the unadjusted model, there was no difference in mortality among patients with a preserved EF, compared with patients with a reduced EF (HR 0.89; 95% CI 0.77, 1.03; $P = 0.12$). There was no difference between groups after adjustment for baseline characteristics (adjusted HR 1.03; 95% CI 0.86, 1.23; $P = 0.76$). Trends in mortality risk from 1996 through 2009 also were consistent with the primary analysis.

Discussion

We found that in a catheterization referral database of 3154 patients with angiographically confirmed nonischemic cardiomyopathy, patients with HFpEF represented about half of the cohort. Patients with HFpEF had a 5-year mortality of approximately 25%, and after adjustment for baseline differences, their risk was similar compared to that of patients with HFrEF. Although the secular trend for survival improved during the study period among patients with nonischemic cardiomyopathy and a reduced ejection fraction, it did not improve among patients with nonischemic cardiomyopathy and a preserved ejection fraction. These findings were consistent when defining preserved EF as > 50% vs > 40%. In a cohort that excluded the population at higher risk with CHD, we found that patients with nonischemic HFpEF remain at significant risk for future mortality.

In our study, 5-year mortality was approximately 25%. Two large community-based studies have previously suggested a relatively similar long-term mortality rate in patients with HFrEF vs HFpEF.[2,17] Bhatia et al.[17] reported in a single-province Canadian study that the 1-year mortality rate was 22% for patients with HFpEF, and 26% for patients with HFrEF. In the Olmsted County, Minnesota study, Owan et al.[2] found a similar 5-year mortality rate after hospitalization—65% in patients with HFpEF, and 68% in patients with HFrEF. However, in meta-analyses of the literature, the mortality rate with HFpEF usually has been lower relative to that with HFrEF. In the **M**eta-**A**nalysis **G**lobal **G**roup **i**n

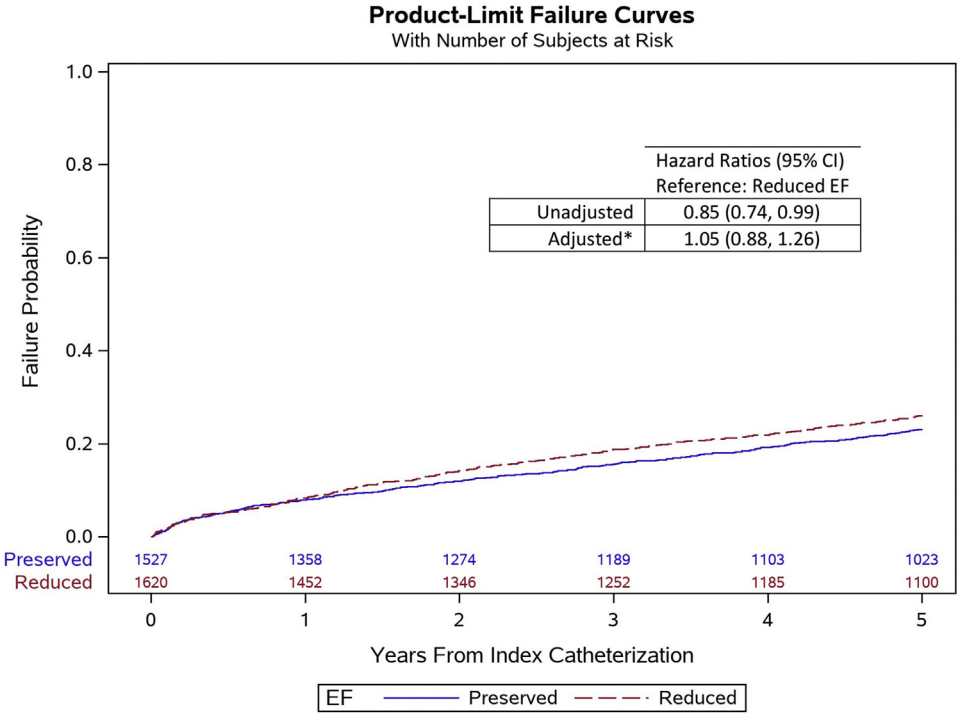

Figure 2. Unadjusted Kaplan-Meier event plot of 5-year mortality by ejection fraction (EF). CI, confidence interval. *Adjusted f**or** age, race, gender, hypertension, systolic blood pressure, heart rate, diabetes, hyperlipidemia, cerebrovascular disease, peripheral vascular disease, history of smoking, Charlson comorbidity index, body mass index, beta-blocker use, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker use, hydralazine use, nitrates use, aspirin use, clopidogrel use, statin use, diuretic use, serum creatinine level, blood urea nitrogen level, hemoglobin level, and sodium level. Reduced is defined as left ventricular EF $\leq$ 40 in this graph.

Chronic Heart Failure (MAGGIC) collaboration, the risk-adjusted 4-year mortality rate was around 32% for patients with HFrEF and 25% for patients with HFpEF.[18] Our analysis reflects a substantially lower-risk, ambulatory population without CHD, with a significantly lower 5-year mortality rate, and closer in range to the MAGGIC group data. In our data, crude mortality rates were lower among patients with HFpEF compared that among patients with HFrEF if defined as an EF $\leq$ 40%. In a slightly larger population, and defining HFrEF as an EF $<$ 50%, the crude mortality rates are similar. These differences were further attenuated after adjustment for baseline characteristics.

Our analysis extends the 1987 to 2001 longitudinal data from Olmsted County, Minnesota to a population with

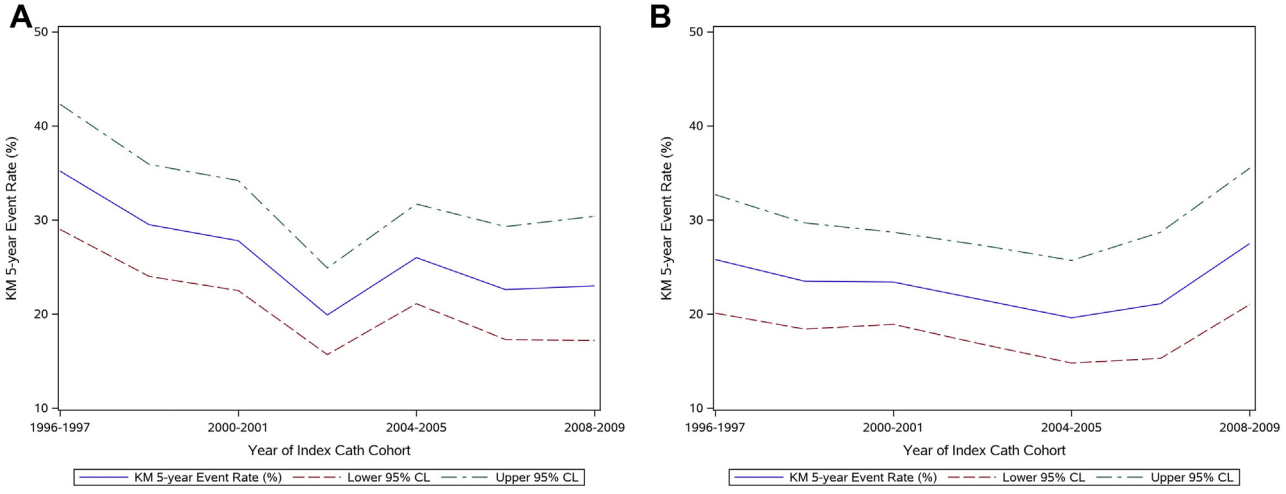

Figure 3. 5-year Kaplan-Meier (KM) event rates (95% confidence interval [CI]) by ejection fraction (EF) and year of index catheterization (cath) cohort. From 1996 through 2009, the risk of death decreased among heart failure patients with no coronary heart disease and reduced EF (unadjusted hazard ratio 0.92; 95% CI 0.88-0.97) but not among those with preserved EF (unadjusted hazard ratio 0.99; 95% CI 0.93-1.05; *P* interaction: 0.095). CL, confidence limit.

nonischemic HF, by almost another decade.[2] Our data support findings from clinical trials of a lower risk of death—particularly cardiovascular death—in patients with HF over the past 3 decades, given the changing landscape of increasing background medical therapy available for patients with HFrEF.[19] Even after excluding a population with CHD, we found a persistent trend of patients with nonischemic HFrEF experiencing a lower mortality rate over the time span of the study. After adjusting for some baseline characteristics and use of medications such as beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, hydralazine, nitrates, clopidogrel, and statin—which increased in many cases between 1996 and 2009—there was no significant change in mortality rate within our study period. However, in the population with nonischemic HFpEF, adjusted and unadjusted mortality trends were flat. This finding is consistent with the absence of therapies in that time period shown to substantively improve outcomes in patients with HFpEF.

Taken together, these results reinforce the effect of the significant burden of comorbidities on morbidity and mortality in patients with HFpEF. Although cause of death is not available for our cohort, prior studies suggest that 30%-40% of deaths in patients with HFpEF are noncardiovascular in nature.[20,21] Despite the exclusion of patients with CHD, the baseline characteristics of our population with nonischemic HFpEF are similar to those of prior community populations with HFpEF; patients were generally more often female, older, and had a higher body mass index, compared with patients with HFrEF.[2,17] We need still more knowledge to understand and characterize how systemic inflammatory conditions such as aging, obesity, and diabetes invoke myocardial oxidative stress and fibrosis in HFpEF.[22] Novel understanding of circulating biomarkers in nonischemic HFpEF may further enhance risk stratification and provide therapeutic targets.[23] Recently, sodium−glucose cotransporter 2 inhibitors have been shown to benefit patients with HFrEF, both with and without diabetes.[24,25] Ongoing clinical trials (NCT03057951 and NCT03619213) will evaluate whether altering primary metabolic—vs primarily cardiovascular—pathways with sodium−glucose cotransporter 2 inhibitors will provide tangible benefits for patients with HFpEF.

This study is subject to limitations inherent in single-centre retrospective studies, with its data being from 1996 to 2014. Given that all patients were referred for cardiac catheterization, our population likely had a higher pretest probability for CHD and was younger. However, prior studies suggest that a substantial portion of anatomically proven coronary artery disease is missed, if relying solely on stress-test diagnosis compared with angiography.[8] Therefore, given the high incidence of CHD in HF, our study population represents the gold standard for diagnosis of nonischemic cardiomyopathy.[3] Our analysis is strengthened by the requirement of coronary angiography in all patients and the availability of long-term follow up. Additionally, we cannot distinguish among different phenotypes of HFpEF. Severe valvular heart disease was excluded. However, in this respect, this analysis is analogous to prior retrospective studies using administrative and chart abstraction data.[2] Another limitation is that only patients with symptomatic HFpEF were included in this analysis, as was prespecified in our statistical analysis plan for consistency with prior work.[15] This approach may have introduced additional bias. However, as we were unable to systematically confirm HFpEF with biomarker or hemodynamic data, we felt that including patients in NYHA class I with HFpEF would create a bias toward a population that may not have HF. Lastly, although no comparison was made between patients with HF and a left ventricular ejection fraction of $\geq$ 50% vs $\leq$ 40%, sensitivity analyses demonstrated consistent findings when defining preserved EF as an EF $\geq$ 50%.

This study demonstrates that despite exclusion of the high-risk CHD population, patients with nonischemic HFpEF have a risk of all-cause mortality similar to that for patients with a reduced EF. Future research is needed to understand whether these and other phenotypic differences in patients with HF will alter risk and outcomes.

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Supplementary Material

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