Patient Sex Does Not Modify Ejection Fraction as a Predictor of Death in Heart Failure: Insights from the APPROACH Cohort

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BACKGROUND: Normal and low ejection fraction (EF) heart failure patients appear to have similar outcomes.

OBJECTIVE: The object of this study was to determine whether sex modifies the effects of left ventricular EF on prevalent heart failure mortality.

DESIGN: Prospective cohort study.

PATIENTS: Patients (n=6, 095) with a diagnosis of heart failure and a measure of EF undergoing cardiac catheterization in Alberta, Canada between April 1999 and December 2004; follow-up continued through October 2005.

MEASUREMENTS: All-cause mortality was assessed in analyses stratified by patient sex and EF ($\leq 50\%$ vs. $>50\%$).

MAIN RESULTS: Overall, female heart failure patients were older, had more hypertension, valvular disease, less systolic impairment and coronary artery disease. Baseline medication use was similar in the four sex-EF groups. Low EF heart failure mortality over 6.5 years was slightly higher but was not significantly modified by patient sex. This relationship remained unchanged after adjustment for differences in baseline characteristics and process of care (women normal EF, reference group; men normal EF adjusted HR 1.1, 95% CI 0.9–1.3; women low EF adjusted HR 1.5, 95% CI 1.1–2.0; men low EF adjusted HR 1.6, 95% CI 1.2–2.1).

CONCLUSIONS: Patient sex did not appear to modify the negative effects of low EF on long-term survival in this prospective study of prevalent heart failure. The small absolute difference in survival between low and normal EF heart failure highlights the need for further research into optimal therapy for the latter, a less well-understood condition.

KEY WORDS: heart failure; ejection fraction; sex differences; prognosis; death.

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The importance of patient sex in heart failure (HF) treatment and outcomes was dramatically emphasized when sex differences in digoxin effects were described in the Digitalis Investigators Group (DIG) trial.¹ Despite this, women with HF tend to be underrepresented in clinical trials.^{2,3} Many studies suggest better outcomes for women with HF,^{2–6} although others have found similar outcomes.^{7,8}

Well-recognized sex differences in HF patients could potentially lead to sex differences in HF outcomes.^{2,3} Female HF patients tend to be older, have more hypertension, and less coronary artery disease than their male counterparts.^{2,3} Women with HF may be treated differently than men.^{5,7} Most importantly, women with HF are more likely to have a normal ejection fraction (EF), while men with HF are more likely to have a low EF.^{2,3,8}

Normal and low EF HF have several key differences.⁹ The phrase 'normal EF HF' is often used interchangeably with 'diastolic HF' or 'HF with preserved systolic function', although the need for further measures of diastolic function to confirm the latter diagnoses is controversial.^{9,10} There does not appear to be a clear consensus on the definition of a normal EF, and the definition of normal EF is missing from recent HF guidelines.¹¹ Values of normal EF between 40–60% seem most common in the literature. In contrast to the clear treatment guidelines for LEF HF,¹¹ the course and management of normal EF HF are less well understood.^{9–11} Traditionally, low EF HF has been seen as a marker of poor prognosis in HF.^{12,13} However, increasing evidence suggests normal EF HF has similar outcomes to low EF HF.^{14–16} It is unclear whether this is the same in both men and women. An interaction between patient sex and EF has been suggested by at least two previous studies.^{17,18}

We hypothesized that sex modifies the effects of EF on prognosis, such that men with low EF HF would have greater mortality compared to the other groups. We defined low EF as $\leq 50\%$, as has been done in previous studies.^{10,14,15} We examined mortality in known HF patients stratified by patient sex and EF using a subgroup of the Alberta Provincial

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Project for Outcome Assessment in Coronary Heart Disease (APPROACH) population. The richness of the APPROACH data, derived from an ongoing population-based prospective cohort of patients presenting for cardiac catheterization, allowed adjustment for clinical, process of care, medications, and revascularization, all of which are known predictors of mortality.

METHODS

Study Population and Measures

All data were derived from APPROACH, a prospective data collection initiative that captures detailed clinical information on all patients undergoing coronary angiography in Alberta, Canada, a province with a population of approximately 3.2 million people. APPROACH participants were included in this study if they had a baseline ejection fraction measurement (at cardiac catheterization or by echocardiography) and their cardiologist had made a clinical diagnosis of HF prior to catheterization between April 1, 1999 and December 31, 2004. The APPROACH study protocol was reviewed and approved by the Ethics Review Boards of the University of Calgary and the University of Alberta. Further details of this database have been described elsewhere.¹⁹

Briefly, this database contains detailed clinical and socio-demographic information including patient age, sex, indication for catheterization (e.g., acute coronary syndrome, stable angina, arrhythmia, congestive heart failure, non-ischemic cardiomyopathy, valvular or congenital heart disease), comorbidities (hypertension, hyperlipidemia, diabetes mellitus, renal insufficiency, dialysis, peripheral vascular disease, cerebrovascular disease, pulmonary disease, malignancy, liver or gastrointestinal disease, and prior myocardial infarction (MI), thrombolysis or revascularization), baseline medication use (beta-blockers, calcium channel blockers, long-acting nitrates, angiotensin receptor blockers or converting enzyme inhibitors, lipid lowering agents, or anti-platelet agents) and coronary angiography results (left ventricular EF, valvular disease and coronary anatomy). In some instances, EF estimates from catheterization are not performed, but echocardiography estimates of EF are recorded. Coronary arteries are labeled as "diseased" when they contain a lesion causing 50% stenosis. Patients are enrolled into the registry at the time of angiography and therapeutic interventions such as thrombolytic therapy and revascularization procedures (including coronary artery bypass grafting (CABG) surgery) are tracked. All-cause mortality is ascertained by means of a semiannual merge with data from the Alberta Bureau of Vital Statistics.

Statistical Analysis

Patients were stratified by sex and EF, and EF >50% was considered normal. Baseline variables were compared among the four sex-EF groups (women normal EF, men normal EF, women low EF, men low EF) using the χ^2 tests for categorical variables and ANOVA for continuous variables. These sex-EF groupings allow for exploration of effect-modification by sex in an additive, rather than multiplicative, framework.²⁰ Survival of the four groups was estimated using the Kaplan-Meier method. A Cox proportional hazards analysis was then used to

compare survival through October 31, 2005 (up to 6.5 years post-catheterization) across sex-EF groups using mutually exclusive dummy variables. In order to optimize risk adjustment, all factors known to affect heart failure prognosis were included sequentially by category (clinical, medications, process of care). Model 1 included clinical characteristics (including age, indication for catheterization, comorbidities, extent of coronary disease, valvular disease, and gradations of EF). Model 2 included all the factors in Model 1 as well as medication use, and Model 3 included all the factors in Model 2 as well as revascularization received. We intentionally do not use bivariate screening for variable selection to avoid the risk of introducing bias related to inappropriate bivariate exclusion of potential prognostic variables.²¹ Risk-adjusted survival curves were derived from the Cox proportional hazards analysis, and were calculated using the corrected group prognosis method.²² A predetermined level of statistical significance of $p \leq .05$ was used in all analyses. Statistical analyses were performed using SAS software (version 9.0, SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

The selection of APPROACH patients for this study is depicted in Fig. 1. Approximately 20% of patients with prevalent HF did not have an available EF (5.4% missing, 13.8% not measured). Patients without an EF measurement differed significantly from the remaining 6,095 patients included in the analyses. They were significantly more likely to be male, older and to have aortic valve disease, diabetes mellitus, peripheral vascular disease (PVD), cerebrovascular disease, and renal failure requiring dialysis, and were less likely to have hyperlipidemia and normal coronary arteries. These findings reflect the fact that EF is often intentionally not measured in patients who have renal insufficiency or who are clinically unstable.

Tables 1 and 2 compare the baseline characteristics and cardiac catheterization results of male and female study patients within low and normal EF groups. Overall, female patients ($n = 2,200$) were slightly older, more likely to have hypertension, valvular disease, normal coronary arteries or left main disease, and less likely to have previous CABG surgery than their male counterparts ($n = 3,895$). However, there were significant sex differences within both EF groups (Tables 1 and 2).

Men and women in both EF groups had slightly different patterns of co-morbidities and indications for catheterization. Female patients had significantly milder EF impairment compared to their male counterparts (women: 60.9% mild (EF 35–50%), 33.4% moderate (EF 20–34%), and 5.7% severe impairment (EF <20%); men: 50.8%, 39.4%, and 9.8%, respectively; $P < .0001$).

Process of Care

Baseline cardiovascular medication use was similar among the four sex-EF groups (Table 3), with no difference in the use of beta-blockers, angiotensin receptor blockers, or lipid lowering agents. Women with normal EF HF had slightly lower acetylsalicylic acid (ASA) use and more calcium channel blocker (CCB) use compared to the other three groups. Women with low EF HF used less long-acting nitrates than the other three

Figure 1. Selection of study patients from APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease).

groups. While clopidogrel/ticlodipine use was slightly higher in female compared to male low EF HF patients, there was a suggestion of a reversal of this pattern in normal EF patients. Angiotensin converting enzyme inhibitor usage was slightly higher in the low compared to the normal EF groups, but there did not appear to be any sex difference.

In unadjusted analysis, there were significant differences in revascularization within the first year of baseline catheterization between men and women in both EF groups. Normal EF women were significantly less likely to undergo percutaneous coronary intervention (PCI) compared to normal EF men, and had the lowest PCI use of the four sex-EF groups. Low EF women were significantly more likely to receive PCI than low EF men. In contrast, women with low EF heart failure were significantly less likely to undergo coronary artery bypass graft (CABG) surgery than their male counterparts, and had the lowest CABG use of the four sex-EF groups. There was a similar (non-significant) trend for lower use of CABG among women with normal EF heart failure.

Survival

There were no sex differences in either EF group in crude mortality at 1 year; the low EF group had higher mortality compared to the normal EF group (12% low EF men and

women vs. 8% normal EF men and women). Both men and women with low EF HF had significantly higher mortality compared to the reference group of women with normal EF HF (Table 4): women-normal EF reference; men-normal EF HR 1.00 (95% CI 0.82–1.20); women-low EF HR 1.28 (95% CI 1.08–1.53); men-low EF HR 1.36 (95% CI 1.17–1.58). Unadjusted survival curves (Fig. 2, Panel A) suggest these relationships persisted throughout the six-and-one-half-year follow-up period. Sequential adjustment for clinical factors, medications, and revascularization had little effect on these relationships, as seen in Figure 2 Panel B: women normal EF reference group; men-normal EF adjusted HR 1.1 (95% CI 0.9–1.3); women-low EF adjusted HR 1.7 (95% CI 1.2–2.2); men-low EF adjusted HR 1.8 (95% CI 1.4–2.3).

DISCUSSION

In this population of patients with a known diagnosis of HF, we found expected differences in baseline clinical characteristics between the four sex-EF groups. Despite the clinical differences in these groups, including differences in the pattern of revascularization use, survival was remarkably similar. LV EF was a more important prognostic factor than patient sex, and patient sex did not appear to modify the effects of EF on long-

Table 1. Baseline Characteristics Stratified by Ejection Fraction and Patient Sex*

Patient characteristic	Sex-ejection fraction groups					
	Low ejection fraction			Normal ejection fraction		
	Men (n=2,733)	Women (n=1,203)	P	Men (n=1,162)	Women (n=997)	P
Age			<.001			<.001
<65 y	1,212 (44.4)	414 (34.4)		465 (40.0)	320 (32.1)	
65–74 y	907 (33.2)	393 (32.7)		408 (35.1)	327 (32.8)	
>75 y	614 (22.5)	396 (32.9)		289 (24.9)	350 (35.1)	
Age, mean (SD), y	65.2 (11.8)	68.1 (11.9)	<.001	66.3 (11.7)	69.0 (11.3)	<.001
Catheterization Indication			<.001			.002
ACS [†]	1,335 (48.9)	649 (54.0)		586 (50.4)	465 (46.6)	
Stable angina	314 (11.5)	95 (7.9)		179 (15.4)	128 (12.8)	
Arrhythmia	87 (3.2)	24 (2.0)		22 (1.9)	7 (0.7)	
HF [‡]	603 (22.1)	261 (21.7)		154 (13.3)	171 (17.2)	
CM [§]	137 (5.0)	42 (3.5)		20 (1.7)	14 (1.4)	
Valvular disease	149 (5.5)	93 (7.7)		141 (12.1)	173 (17.4)	
CHD	14 (0.5)	4 (0.3)		2 (0.2)	3 (0.3)	
Comorbidities						
Hypertension	1,599 (58.5)	807 (67.1)	<.001	749 (64.5)	707 (70.9)	.001
Hyperlipidemia	1,505 (55.1)	656 (54.5)	.76	666 (57.3)	515 (51.7)	.008
Diabetes mellitus	850 (31.1)	452 (37.6)	<.001	322 (27.7)	291 (29.2)	.45
Renal insufficiency	233 (8.5)	89 (7.4)	.24	82 (7.1)	61 (6.1)	.38
Dialysis	85 (3.1)	35 (2.9)	.74	37 (3.2)	32 (3.2)	.97
PVD [¶]	371 (13.6)	130 (10.8)	.02	147 (12.7)	123 (12.3)	.83
CVD	309 (11.3)	136 (11.3)	.99	140 (12.1)	146 (14.6)	.08
Pulmonary disease	769 (28.1)	350 (29.1)	.54	389 (33.5)	379 (38.0)	.03
Malignancy	154 (5.6)	58 (4.8)	.30	77 (6.6)	65 (6.5)	.92
Liver/GI [#] disease	218 (8.0)	109 (9.1)	.26	105 (9.0)	111 (11.1)	.10
Prior CABG**	225 (8.2)	60 (5.0)	<.001	68 (5.9)	41 (4.1)	.07
Prior MI ^{††}	1575 (57.6)	694 (57.7)	.97	552 (47.5)	407 (40.8)	.002
Prior PCI ^{‡‡}	130 (4.8)	46 (3.8)	.19	64 (5.5)	37 (3.7)	.05
Prior thrombolysis	98 (3.6)	48 (4.0)	.54	44 (3.8)	25 (2.5)	.09

*Values are number (percentage) unless otherwise indicated

[†]ACS: acute coronary syndrome

[‡]HF: heart failure

[§]CM: non-ischemic cardiomyopathy

^{||}CHD: congenital heart disease

[¶]PVD: peripheral vascular disease

^{||}CVD: cerebrovascular disease

[#]GI: gastrointestinal disease

**CABG: coronary artery bypass graft

^{††}MI: myocardial infarction

^{‡‡}PCI: percutaneous coronary intervention

term survival. This relationship remained unchanged when adjusted for differences in baseline characteristics and process of care between the four sex-EF patient groups.

These results should be taken in the context of what is known about sex differences within the whole APPROACH population. Apparent differences in revascularization use at one year between the sex-EF groups are likely related to differences in clinical characteristics, as men and women in the whole APPROACH study population have equivalent use of PCI and nearly equivalent use of CABG when analyses were appropriately adjusted.²³ Our group has also demonstrated an absence of significant sex differences in medical therapy for MI patients in Calgary, Alberta, a group that would have overlapped with APPROACH.²⁴ Furthermore, women within the total APPROACH population, particularly those with high risk anatomy or interventional revascularization, had a significantly higher risk of death early post-catheterization, but this difference normalized within four to six months.²⁵

This population-based study with a wealth of clinical data builds on previous work examining the role of patient sex on

HF mortality by investigating a potential interaction between patient sex and EF. Prior studies have suggested a survival advantage for female HF patients, although most have not been able to examine the contribution of EF to this sex difference. For example, female patients in the Olmsted County incident HF cohort had lower mortality than male patients,⁴ and female patients hospitalized for the first time with HF in New York State also had better outcomes, including in-hospital mortality and readmission within one year.⁵ In both of these studies, data on EF were not available.^{4,5} Male sex also was independently associated with greater mortality in several HF randomized controlled trials, including a subanalysis of the Digitalis Investigation Group (DIG) NEF trial (all study participants had EF greater than 45%),²⁶ the Metoprolol Extended-Release Randomized Intervention Trial (MERIT)-HF (all participants had EF less than 25%),²⁷ the Danish Investigators of Arrhythmia and Mortality (DIAMOND) HF trial (no EF restriction),²⁸ and the Cardiac Insufficiency Bisoprolol Study (CIBIS II) (all participants had EF ≤35% and had New York Heart Association class III and IV symptoms).⁶ However, select patient populations in the latter studies may affect generalizability of these results. In contrast,

Table 2. Baseline Cardiac Catheterization Results Stratified by Ejection Fraction and Patient Sex*

Catheterization results	Sex-ejection fraction groups					
	Low ejection fraction			Normal ejection fraction		
	Men (n=2,733)	Women (n=1,203)	P	Men (N=1,162)	Women (N=997)	P
CAD [†] pattern			<.001			<.001
Normal	380 (13.9)	204 (17.0)		232 (20.0)	280 (28.1)	
Minimal disease	319 (11.7)	154 (12.8)		205 (17.7)	176 (17.7)	
1 or 2-vessel disease	291 (10.7)	140 (11.7)		127 (11.0)	74 (7.4)	
2-vessel disease + PLAD [‡]	520 (19.1)	223 (18.6)		188 (16.2)	111 (11.1)	
3-vessel disease	481 (17.6)	181 (15.1)		124 (10.7)	75 (7.5)	
3-vessel + PLAD [‡]	393 (14.4)	91 (7.6)		124 (10.7)	52 (5.2)	
Left main disease	343 (13.6)	209 (17.4)		158 (13.6)	299 (23.0)	
Valvular disease			.01			.002
Aortic	75 (2.7)	37 (3.1)		57 (2.6)	53 (5.3)	
Mitral	51 (1.9)	42 (3.5)		67 (5.8)	92 (9.2)	
Aortic + Mitral	23 (0.8)	14 (1.2)		17 (1.5)	28 (2.8)	

* Values are number (percentage) unless otherwise indicated

[†] CAD: coronary artery disease

[‡] PLAD: proximal left anterior descending artery

two other cohort studies of patients following hospitalization for HF found little or no sex differences in outcomes.^{7,8}

Despite the potential for an interaction between patient sex and EF in heart failure outcomes, this does not appear to have been extensively investigated. An interaction between male sex and EF was suggested by two different single center retrospective studies. Male sex appeared to be an important predictor of mortality only in young (<75 years of age) patients with normal EF (EF ≥ 40%) admitted for the first time with a primary diagnosis of HF.¹⁸ Male patients with EF <30% had the lowest survival, with similar survival seen in the other sex-EF groups in another study of hospitalized HF patients.¹⁷

In contrast to these previous studies, the current study examined the relationship of patient sex and EF in HF mortality, using geographically representative, province-wide data, with long-term prospective follow-up over greater than 6 years. A wide variety of clinical and process of care variables describing this population were available and included in the survival analysis, but had virtually no effect on the results. Other reasons that might explain the discrepant results include a higher threshold for normal EF (50% vs. 30% or

40%) in the current study, and a more inclusive, heterogeneous study population not limited to patients hospitalized for HF, potentially a sicker group.

This study examined prevalent HF; information about the duration or symptom severity was unavailable. Capturing study participants at time of cardiac catheterization has the potential disadvantage of a somewhat select population, including lower severity of renal failure and a higher prevalence of CAD and fewer women. Although a cardiac procedure-based cohort, 32% of this study population had no or minimal CAD. An advantage of this catheterization-based study population was the availability of detailed information about coronary anatomy, which was included in multivariate survival analysis, unlike many previous studies of EF and HF outcomes.⁵⁻¹⁸

An important limitation to our results is the 20% of the APPROACH cohort who were either missing an EF measurement, or EF was not measured. It is a clinical reality that EF is not always measured during catheterization. While we know that these patients differ in ways that could potentially affect the association between sex and EF and mortality, we are unable to account for this in this study.

Table 3. Baseline Cardiovascular Medication Usage Stratified by Ejection Fraction and Patient Sex*

Medication	Sex-ejection fraction groups					
	Low ejection fraction			Normal ejection fraction		
	Men (n=2,733)	Women (n=1,203)	P	Men (n=1,162)	Women (n=997)	P
Beta-blockers	1,551 (56.8)	667 (55.4)	.19	621 (53.4)	520 (52.2)	.59
CCBs [†]	313 (11.5)	163 (13.6)	.11	213 (18.3)	220 (22.1)	.08
Long-acting nitrates	669 (24.5)	166 (13.8)	.001	331 (28.5)	302 (30.3)	.48
ARBs [‡]	70 (2.6)	30 (2.5)	.81	32 (2.8)	38 (3.8)	.18
ACE inhibitors [§]	1770 (64.8)	765 (63.6)	.56	649 (55.9)	580 (58.2)	.49
Lipid lowering	844 (30.9)	383 (31.8)	.46	388 (33.4)	313 (31.4)	.61
ASA	1,950 (71.4)	876 (72.8)	.18	812 (69.9)	647 (64.9)	.01
Other anti-platelet [¶]	252 (9.2)	146 (12.1)	.009	139 (12.0)	95 (9.5)	.16

*Values are number (percentage)

[†]CCBs: Calcium channel blockers

[‡]ARBs: Angiotensin receptor blockers

[§]ACE: Angiotensin converting enzyme

^{||} ASA: Acetylsalicylic acid

[¶] Clopidogrel and Ticlopidine

Table 4. Crude and Adjusted Hazard Ratios for All-Cause Mortality Stratified by Ejection Fraction and Patient Sex*

Sex-ejection fraction groups	Unadjusted	Model 1†	Model 2§	Model 3
Women: normal EF [‡]	1.00	1.00	1.00	1.00
Men: normal EF [‡]	1.00 (0.82, 1.20)	1.06 (0.87, 1.29)	1.07 (0.88, 1.30)	1.09 (0.90, 1.33)
Women: low EF [‡]	1.28 (1.08, 1.53)	1.68 (1.25, 2.24)	1.67 (1.24, 2.23)	1.51 (1.13, 2.03)
Men: low EF [‡]	1.36 (1.17, 1.58)	1.80 (1.37, 2.36)	1.78 (1.36, 2.35)	1.61 (1.22, 2.12)

*All data are presented as HR (95% CI)

[‡]EF: indicates ejection fraction

[†]Model 1: age, indication, comorbidities, extent of coronary disease, valvular disease, and fine gradations of ejection fraction

[§]Model 2: Model 1 and medication

^{||} Model 3: Model 2 and revascularization received

Information about medication use was also captured at the time of catheterization. The four groups were quite similar with respect to use of major classes of cardiovascular medications, despite limited evidence to identify optimal medical management of normal EF HF.⁹ A previous study of community-dwelling older adults found patterns of medication use differed by EF and HF history.¹³ However, the current study can not rule out differences over the patients' course of disease as additional information about medication use over time was missing. Additionally, digoxin and diuretic use at baseline were only available from 2004 onwards, and thus were not included in the survival models. There were, however, no significant differences in use between the four groups in the available data (data not shown), consistent with the similar use of other

medications. Given the similarity of crude and adjusted survival risk in the four groups, we believe it is unlikely that adding this missing information to the survival models would alter our findings.

Despite the potential weaknesses of the current study, we conclude that low EF has negative effects on HF survival that do not appear to be modified by patient sex, and that the difference in survival between normal and low EF HF is small in this cardiac procedure cohort, confirming recent studies.^{14–16} This does not diminish the need to better understand the relationship between sex and EF in HF. Current convention uses the same normal EF for both sexes, but evaluating whether this is appropriate merits further investigation.² Further, imbalances between the sexes in EF groups and the prevalence, incidence and survival of HF should not be overlooked.^{2,3} Women are more likely to develop normal EF HF, where men are more likely to develop low EF HF,^{2,3} however, improvements observed in heart failure mortality have been greater in men,^{3,4} and patients with low EF HF.¹⁵ This has significant public health implications, as in absolute numbers, more women live with and die from HF, particularly normal EF HF,^{2,3,13} and it appears that the proportion of HF patients presenting with normal EF HF is increasing.¹⁵ Despite this, women remain under-represented in clinical trials,^{2,3} and the level of evidence guiding treatment of normal EF HF is suboptimal.^{9,10} Clearly, it is critical that optimal therapy for patients with normal EF HF be identified, and that sex differences in the development, course and treatment effectiveness of HF not be overlooked.

CONCLUSION

Although there were several sex differences in baseline characteristics among HF patients, patient sex did not modify the negative effects of low EF on long-term survival in this prospective study of prevalent heart failure. The small absolute survival difference between low and normal EF HF highlights the need to identify optimal management of the latter condition.

Figure 2. Survival Curves by ejection fraction and patient sex. Unadjusted survival (Panel A) and risk-adjusted survival (Panel B) over 6.5 years post-catheterization by ejection fraction and patient sex adjusted for age, indication for catheterization, comorbidities, extent of coronary disease, valvular disease, fine gradations of ejection fraction, medication and revascularization received (model 3).

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