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Discriminating clinical features of heart failure with preserved vs. reduced ejection fraction in the community

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Aims Heart failure (HF) is a major public health burden worldwide. Of patients presenting with HF, 30–55% have a preserved ejection fraction (HFPEF) rather than a reduced ejection fraction (HFREF). Our objective was to examine discriminating clinical features in new-onset HFPEF vs. HFREF.

Methods and results Of 712 participants in the Framingham Heart Study (FHS) hospitalized for new-onset HF between 1981 and 2008 (median age 81 years, 53% female), 46% had HFPEF (EF >45%) and 54% had HFREF (EF ≤45%). In multivariable logistic regression, coronary heart disease (CHD), higher heart rate, higher potassium, left bundle branch block, and ischaemic electrocardiographic changes increased the odds of HFREF; female sex and atrial fibrillation increased the odds of HFPEF. In aggregate, these clinical features predicted HF subtype with good discrimination (*c*-statistic 0.78). Predictors were examined in the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study. Of 4436 HF patients (median age 75 years, 47% female), 32% had HFPEF and 68% had HFREF. Distinguishing clinical features were consistent between FHS and EFFECT, with comparable discrimination in EFFECT (*c*-statistic 0.75). In exploratory analyses examining the traits of the intermediate EF group (EF 35–55%), CHD predisposed to a decrease in EF, whereas other clinical traits showed an overlapping spectrum between HFPEF and HFREF.

Conclusion Multiple clinical characteristics at the time of initial HF presentation differed in participants with HFPEF vs. HFREF. While CHD was clearly associated with a lower EF, overlapping characteristics were observed in the middle of the left ventricular EF range spectrum.

Keywords Heart failure • Epidemiology • Risk factors • Ejection fraction

Introduction

Heart failure (HF) is a major public health problem worldwide, and the lifetime risk of developing HF is one in five for men and women at 40 years of age.[1] Of patients presenting with acute decompensated HF, 30–55% are estimated to have HF with preserved ejection fraction (HFPEF) rather than reduced ejection fraction (HFREF).[2–4] The extent to which HFPEF and HFREF are overlapping vs. distinct phenotypes remains unclear.[5,6] Patients with HF in the community often experience cardiovascular death; however, non-cardiovascular comorbidities may also contribute greatly to mortality, particularly in patients with HFPEF.[7] While the clinical course and

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survival after HF-onset have been described for HFPEF and HFREF, differences in factors present at or before the onset of HF symptoms have not been systematically compared between HF subtypes. Understanding the relations of different clinical factors to the type of HF may lend important pathophysiological insights. Few studies have examined characteristics other than left ventricular ejection fraction (LVEF) that might distinguish HFPEF from HFREF in the clinical setting.[8] We sought to examine the differences in the clinical characteristics between newly diagnosed HFPEF and HFREF in a large community-based study, and to further validate our findings in a large hospital-based cohort of patients with HF.

Methods

Derivation study sample

The Framingham Heart Study (FHS) original and offspring cohorts have been described previously.[9,10] In brief, men and women enrolled in the original cohort have undergone periodic examinations approximately every 2 years and those in the offspring cohort approximately every 4 years since initial enrolment. At each visit, health history updates, physical examinations, and blood tests were performed. We included participants with initial HF hospitalization occurring between 1981 and 2008 who also had an evaluation of LVEF near the time of hospitalization. Informed consent was obtained from participants, and the research protocol was approved by the institutional review board of Boston Medical Center.

Definition of initial heart failure hospitalization

At each examination, interim cardiovascular disease events were identified and medical records were obtained. Initial HF hospitalization was confirmed by a panel of three physicians after systematic review of outpatient and hospital records using established protocols and FHS criteria.[11] Participants with prevalent HF at the baseline examination were excluded.

Antecedent clinical factors

Data on antecedent clinical variables were obtained from the most recent FHS examination prior to HF-onset. Blood pressure (BP) was the average of two seated measurements, and hypertension was defined as a systolic BP $\geq$140 mmHg, a diastolic BP $\geq$90 mmHg, or the current use of antihypertensive medication. A significant heart murmur was defined as a systolic murmur grade $\geq$3/6 or any diastolic murmur heard on physician's examination. Total cholesterol levels were obtained, and diabetes was defined as a fasting glucose $\geq$126 mg/dL, non-fasting glucose $\geq$200 mg/dL, or the use of insulin or oral hypoglycaemic medications.

A history of major coronary heart disease (CHD) was defined as myocardial infarction or acute coronary insufficiency [prolonged ischaemic symptoms with new echocardiogram (ECG) abnormalities in the absence of biomarker elevations indicative of infarction] prior to HF-onset, as adjudicated by a three-physician panel after review of medical records. Atrial fibrillation was determined after examining all available ECGs before or on the day of HF-onset.

Initial heart failure hospitalization characteristics

The characteristics at HF-onset were abstracted from emergency department records at the time of hospitalization. The first-documented BP, heart rate, respiratory rate, and blood tests were ascertained, and all ECGs from the date of HF-onset were reviewed. Left ventricular ejection fraction was determined from the ECG or radionuclide ventriculogram performed at or near the HF-onset date. Assessments of LVEF were eligible if performed during the initial HF hospital admission, or within 1 year prior to HF-onset if no intervening myocardial infarction had occurred, as determined by review of interim medical records and clinical visits. A total of 104 participants underwent LVEF assessment prior to the HF event, with a mean of 4.3 $\pm$ 7.3 months between cardiac imaging and HF-onset. Heart failure was *a priori* classified as HFPEF (EF >45%) or HFREF (EF $\leq$45%).[12] Secondary analyses were conducted, classifying HF as normal (EF >55%), mild-moderately depressed (EF 35–55%), or severely depressed EF (<35%).

External validation cohort

Demographic and clinical characteristics predictive of the type of HF (HFPEF vs. HFREF) in FHS participants were examined in the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study, a hospital-based registry of newly admitted patients with HF occurring between April 1999 and March 2001 at one of 86 hospital corporations in Ontario, Canada.[13–15] In brief, patients with a primary diagnosis of HF according to the International Classification of Diseases, Ninth Revision in the Canadian Institute for Health Information discharge abstract database, who also met the Framingham HF criteria were identified for detailed chart abstraction of clinical, laboratory, ECG parameters, and LVEF measurements. Patients with available LVEF assessment were included in the external validation cohort. After exclusion of patients with HF hospitalization within the prior 3 years, a cohort of newly admitted patients was identified.[16] Ethics approval was obtained from all participating institutions before the study.

Statistical analysis

Using *t*-, χ^2, and Fisher's exact tests as appropriate, we compared characteristics in participants with HFPEF vs. HFREF. Multivariable logistic regression was used to examine the relation of clinical predictors and the type of HF (HFPEF vs. HFREF). First, age- and sex-adjusted analyses were conducted. A final multivariable model was then constructed using backward selection, with consideration of age- and sex-adjusted covariates (*Table 1*) at $P < 0.10$ and retention at $P < 0.05$. In the final model fit in the entire sample, testing for potential interactions between sex and covariates was performed if the regression coefficients indicated opposite directional effects between men and women in the stratified analyses. Participants with non-missing values of covariates considered in the multivariable model were included. The predicted risk of HFPEF vs. HFREF was calculated from the final model.

The final FHS multivariable model was then examined in EFFECT using three performance measures: equality of regression coefficients, discrimination, and calibration. First, each covariate in the multivariable model yielded two regression coefficients—one estimated within FHS and the other estimated *de novo* in EFFECT. Coefficients were compared using a standard *z*-test.[17] Three *c*-statistics were computed to examine discrimination for the EFFECT study by (i) applying the final FHS model—with coefficients estimated in FHS—to the EFFECT cohort, (ii) applying the final FHS covariates—with coefficients estimated in EFFECT—to the EFFECT cohort, (iii) using a stepwise multivariable model ('best model') constructed using all available covariates in EFFECT. We used the Hosmer–Lemeshow χ^2-statistic to assess model calibration. The FHS model was recalibrated in EFFECT to account for any potential over- or underestimate of risk due to differences in HFPEF prevalence. We applied the final FHS coefficients without the *y*-intercept to the EFFECT data. An iterative process was then used to modify the *y*-intercept so that the predicted probabilities

Table 1 Clinical characteristics of participants with the initial heart failure event in the Framingham Heart Study and Enhanced Feedback For Effective Cardiac Treatment study

	FHS (derivation cohort)			EFFECT (validation cohort)		
	HFPEF (n = 326)	HFREF (n = 386)	P-value[a]	HFPEF (n = 1437)	HFREF (n = 2999)	P-value[a]
Pre-onset variables						
Age at HF, years	82 (82–88)	80 (73–86)	0.02	77 (70–84)	75 (66–81)	<0.001
Female	215 (66)	162 (42)	<0.001	928 (65)	1170 (39)	<0.001
Coronary heart disease	111 (34)	226 (59)	<0.001	411 (29)	1575 (53)	<0.001
Significant murmur	67 (22)	50 (13)	0.004	N/A	N/A	N/A
Hypertension	244 (79)	294 (78)	0.93	801 (56)	1453 (49)	<0.001
Systolic BP, mmHg	145 (23)	144 (23)	0.96	N/A	N/A	N/A
Diastolic BP, mmHg	74 (12.1)	74 (12.5)	0.94	N/A	N/A	N/A
Diabetes mellitus	64 (20)	105 (28)	0.02	451 (32)	1091 (37)	<0.001
Current smoker	57 (18)	77 (21)	0.47	161 (13)	478 (19)	<0.001
Prior atrial fibrillation	123 (38)	117 (30)	0.04	N/A	N/A	N/A
Hypertension treatment	192 (62)	220 (59)	0.39	N/A	N/A	N/A
Total cholesterol, mg/dL	213 (49)	208 (46)	0.16	N/A	N/A	N/A
BMI, kg/m^2	28 (6)	28 (5)	0.07	N/A	N/A	N/A
Time-of-onset variables						
Clinical characteristics						
Systolic BP, mmHg	149 (34)	142 (32)	0.006	156 (34)	144 (32)	<0.001
Diastolic BP, mmHg	82 (20)	81 (19)	0.76	82 (20)	83 (20)	0.39
Pulse pressure, mmHg	67 (25)	61 (22)	0.001	74 (28)	62 (24)	<0.001
Heart rate, b.p.m.	90 (27)	94 (23)	0.04	93 (27)	97 (25)	<0.001
Respiratory rate, per min	24 (7)	25 (7)	0.05	26 (7)	26 (7)	0.75
Laboratory characteristics						
Haemoglobin, g/dL	12 (2)	13 (2)	0.003	12 (2)	13 (2)	<0.001
Sodium, mEq/L	138 (5)	138 (5)	0.80	138 (5)	138 (5)	0.17
Potassium, mEq/L	4.2 (0.7)	4.4 (0.6)	<0.001	4.2 (0.7)	4.3 (0.7)	0.03
eGFR, mL/min/1.73 m^2	55 (24)	54 (29)	0.67	59 (29)	57 (26)	0.03
BUN, mg/dL	27 (16)	30 (18)	0.02	27 (18)	28 (18)	0.002
ECG characteristics						
Atrial fibrillation	109 (33)	77 (20)	<0.001	466 (34)	682 (23)	<0.001
Left bundle branch block	18 (6)	69 (18)	<0.001	64 (5)	621 (21)	<0.001
Right bundle branch block	37 (11)	39 (10)	0.59	84 (6)	183 (6)	0.83
Any ST segment elevation	29 (9)	124 (32)	<0.001	86 (6)	437 (15)	<0.001
Any ST segment depression	91 (28)	151 (39)	0.002	326 (24)	730 (25)	0.34
Any T-wave inversion	182 (56)	280 (73)	<0.001	367 (27)	1028 (35)	<0.001

Data are shown as n (%) for dichotomous and mean (SD) for continuous variables with the exception of age, which is represented as median (interquartile range).
BP, blood pressure; SD, standard deviation; BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; N/A, not available.
[a]Unadjusted P-value for difference between HFPEF and HFREF within each cohort.

were comparable to the observed risk. Importantly, recalibration does not affect comparisons of regression coefficients or discrimination. Analyses were performed using SAS version 8.2 (Cary, NC, USA).

Results

Between 1981 and 2008, there were 986 initial acute HF hospitalizations among FHS original and offspring cohort participants free of HF at baseline; 834 (85%) of the initial events included an evaluation of LVEF at or within 1 year prior to HF-onset; 712 (72%) participants had complete covariate data. Of these, 326 participants (46%) had HFPEF and 386 (54%) had HFREF. The EFFECT cohort included 9943 participants with an initial hospitalization for HF, of whom 4436 (45%) underwent in-hospital LVEF evaluation between 1999 and 2001; 1437 had HFPEF (32%) and 2999 had HFREF (68%).

Characteristics stratified by left ventricular ejection fraction

Women represented two-fifth of cases of HFREF and two-third of cases of HFPEF in both FHS and EFFECT (*Table 1*). A history of CHD was more common in HFREF, whereas a significant murmur and atrial fibrillation were more prevalent among those with HFPEF.

Table 2 Predictors of heart failure with preserved ejection fraction vs. heart failure with reduced ejection fraction in 712 Framingham Heart Study participants

	Age- and sex-adjusted models		Final multivariable model	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Pre-onset variables				
Age at HF-onset, per 10 years	1.06 (0.91–1.24)	0.45		
Female	2.60 (1.90–3.56)	<0.0001	2.82 (1.99–3.98)	<0.0001
Coronary heart disease	0.41 (0.30–0.56)	<0.0001	0.48 (0.30–0.61)	<0.0001
Significant murmur	1.73 (1.14–2.62)	0.01		
Hypertension	0.91 (0.62–1.33)	0.62		
Systolic BP, per 11 mmHg	0.93 (0.79–1.09)	0.38		
Diastolic BP, per 12 mmHg	1.05 (0.89–1.23)	0.57		
Diabetes mellitus	0.74 (0.51–1.08)	0.12		
Current smoker	0.95 (0.62–1.45)	0.82		
Prior atrial fibrillation	1.52 (1.10–2.11)	0.01		
Hypertension treatment	1.05 (0.76–1.44)	0.77		
Total cholesterol, per 49 mg/dL	0.98 (0.83–1.16)	0.78		
BMI, per 5 kg/m^2	1.18 (1.02–1.38)	0.04		
Time-of-onset variables				
Clinical characteristics				
Systolic BP, per 33 mmHg	1.18 (1.02–1.38)	0.03		
Diastolic BP, per 19 mmHg	1.00 (0.86–1.16)	0.98		
Pulse pressure, per 24 mmHg	1.25 (1.07–1.46)	0.006		
Heart rate, per 25 b.p.m.	0.81 (0.69–0.94)	0.006	0.69 (0.57–0.82)	<0.0001
Respiratory rate, per 8/min	0.81 (0.68–0.96)	0.01		
Laboratory characteristics				
Haemoglobin, per 2 g/dL	0.83 (0.70–0.98)	0.03		
Sodium, per 5 mEq/L	1.03 (0.89–1.20)	0.70		
Potassium, per 0.6 mEq/L	0.75 (0.64–0.88)	0.0005	0.79 (0.67–0.93)	0.0045
eGFR, per 26 mL/min/1.73 m^2	1.00 (1.00–1.01)	0.25		
BUN, per 17 mg/dL	0.87 (0.74–1.02)	0.09		
Anaemia	1.34 (0.97–1.85)	0.08		
ECG characteristics				
Atrial fibrillation	2.18 (1.53–3.10)	<0.0001	2.18 (1.47–3.23)	0.0001
Left bundle branch block	0.24 (0.14–0.43)	<0.0001	0.30 (0.22–0.57)	0.0002
Right bundle branch block	1.39 (0.84–2.28)	0.20		
Any ST segment elevation	0.20 (0.13–0.32)	<0.0001	0.35 (0.22–0.57)	<0.0001
Any ST segment depression	0.59 (0.42–0.81)	0.001		
Any T-wave inversion	0.49 (0.35–0.67)	<0.0001	0.61 (0.43–0.87)	0.0058

BP, blood pressure; BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

On hospital presentation, participants with HFREF had a higher systolic BP, heart rate, haemoglobin, and serum potassium when compared with those with HFPEF. Atrial fibrillation was more common in HFPEF, and left bundle branch block was more common in HFREF.

Predictors of heart failure with preserved vs. reduced ejection fraction in Framingham Heart Study

Age- and sex-adjusted odds ratios for HFPEF are shown in *Table 2*. Atrial fibrillation and female sex were both associated with a greater than two-fold increased odds of having HFPEF. Other factors favouring HFPEF in age- and sex-adjusted analyses included prior atrial fibrillation, higher BMI, and a higher systolic BP. The most significant determinants of HFREF were CHD, which was associated with a greater than 2.5-fold increased odds of HFREF (95% CI 1.8–3.3, $P < 0.0001$), and left bundle branch block, with more than three-fold odds (95% CI 1.9–4.9, $P < 0.0001$).

After adjustment for other clinical characteristics, female sex and atrial fibrillation were associated with more than two-fold greater odds of HFPEF, whereas male sex, a history of CHD, a higher heart rate, higher serum potassium, left bundle branch block, and ischaemic ECG changes increased the odds of HFREF. Sex-stratified analyses showed only minor differences between men and women,

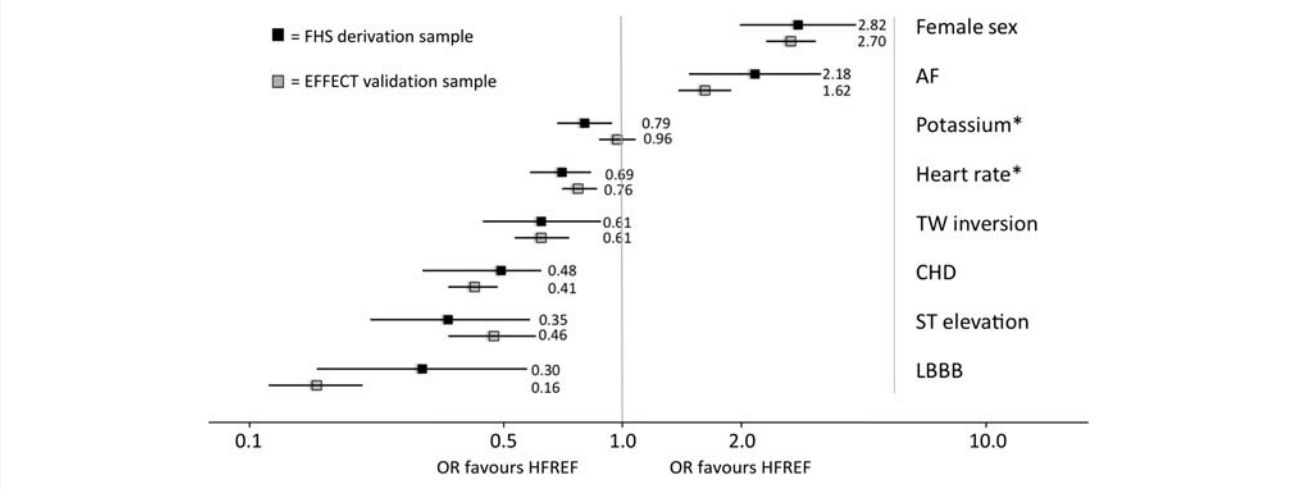

Figure 1 Discriminating clinical features of heart failure with reduced ejection fraction vs. heart failure with preserved ejection fraction in the derivation and validation samples. Odds ratios indicate the odds of HFPEF associated with the condition present in dichotomous variables, and per 1 mEq/L increase in serum potassium and per 25 b.p.m. increase in the heart rate for continuous variables (indicated by asterisk).

Table 3 Comparison of regression coefficients in the Framingham Heart Study vs. the Enhanced Feedback For Effective Cardiac Treatment study for covariates included in the final Framingham Heart Study risk function

	FHS			EFFECT			Comparison of beta-coefficients	
Covariate	**Beta[a]**	**SE**	***P*-value**	**Beta[a]**	**SE**	***P*-value**	***Z*-statistic**	***P*-value**
Female	1.035	0.176	<0.0001	0.997	0.074	<0.0001	−0.198	0.84
Coronary heart disease	−0.849	0.180	<0.0001	−0.902	0.077	<0.0001	0.268	0.79
Heart rate, per 1 b.p.m.	−0.015	0.004	0.0045	−0.011	0.002	<0.0001	−1.182	0.24
Potassium, per 1 mEq/L	−0.398	0.140	<0.0001	−0.041	0.057	0.48	−2.361	0.02
Atrial fibrillation	0.778	0.202	0.0001	0.481	0.081	<0.0001	1.367	0.17
Left bundle branch block	−1.213	0.323	0.0002	−1.828	0.142	<0.0001	1.743	0.08
Any ST elevation	−1.053	0.247	<0.0001	−0.787	0.133	<0.0001	−0.951	0.34
Any T-wave inversion	−0.496	0.180	0.0058	−0.487	0.080	<0.0001	−0.048	0.96

SE, standard error.
[a]Beta-coefficients are expressed per 1 unit increase for continuous variables and for the condition being present in dichotomous variables.

and none of the interaction terms between sex and covariates was significant. The final model had good discrimination (*c*-statistic = 0.78), and calibration (Hosmer–Lemeshow χ^2 statistic = 7.46, $P = 0.49$). The final model details and examples of calculated predicted risk can be found in Supplementary material online, *Table S1*.

In order to exclude significant valvular disease in participants classified as HFPEF,[18] a sensitivity analysis was performed excluding the 67 participants with a significant murmur prior to the onset of HF from the HFPEF group in FHS, which yielded similar results (see Supplementary material online, *Table S2*).

In secondary analyses, we classified HF into three LVEF groups: normal, mild-moderately depressed, and severely depressed. A history of CHD and ischaemic ECG changes appeared to be associated with increased odds of depressed LVEF regardless of severity, whereas other characteristics were associated with largely intermediate odds for the middle LVEF group (see Supplementary material online, *Table S3*).

Discriminating clinical features of heart failure with preserved vs. reduced ejection fraction in the Enhanced Feedback For Effective Cardiac Treatment study

The multivariable model derived from the Framingham Heart Study was applied to the EFFECT cohort. When the regression coefficients were estimated in EFFECT, the odds ratios for HFPEF were similar in FHS and EFFECT (*Figure 1*), with female sex and atrial fibrillation favouring HFPEF, and other characteristics favouring HFREF except serum potassium, which did not discriminate between the two types of HF in EFFECT. Regression coefficients had the same directional effects, and were of similar magnitude with the exception of serum potassium (*Table 3*). When the FHS final model regression coefficients were applied to EFFECT, the *c*-statistic was only modestly

Table 4 Multivariable model discrimination and calibration indices within the Framingham Heart Study and the Enhanced Feedback For Effective Cardiac Treatment study

Model	c-statistic	Hosmer and Lemeshow goodness-of-fit test	
		χ^2	*P*-value
FHS model in FHS	0.780	7.46	0.49
FHS model (including beta-coefficients) in EFFECT	0.748	604.81	<0.0001
FHS model after recalibration in EFFECT	0.748	21.54	0.006
FHS model in EFFECT (EFFECT beta-coefficients)	0.759	9.02	0.34
EFFECT 'best model'	0.782	7.75	0.46

attenuated (*c*-statistic 0.78 in FHS and 0.75 in EFFECT, *Table 4*). When compared with the 'best model' within EFFECT (see Supplementary material online, *Table S4*), the FHS risk function discriminated nearly as well (*c*-statistic 0.75 vs. 0.78). *Figure 2A* displays the predicted vs. actual risk of HFPEF in FHS and EFFECT by the decile of risk using the final FHS model. Because the prevalence of HFPEF between the two cohorts differed in FHS compared with EFFECT (46 vs. 32%), the application of the FHS model to EFFECT led to a systematic overestimation of HFPEF compared with observed values (*Figure 2B*), which improved after recalibration of the model (*Figure 2C*).

Discussion

Among participants with new-onset acute HF, the clinical characteristics at the time of hospital presentation were distinct between HFPEF and HFREF in the community as well as the hospital setting. In particular, male sex, a history of CHD, a higher admission heart rate, left bundle branch block, and ischaemic electrocardiographic changes all significantly increased the odds of HFREF, whereas female sex and atrial fibrillation on presentation were associated with higher odds of HFPEF. These associations were remarkably robust when examined within two very different cohorts: FHS, a prospective community-based cohort, and EFFECT, a hospital-based registry involving virtually all of the large hospitals in a large Canadian province.

Few prior studies have compared both the clinical features at the time of HF presentation and pre-onset comorbidities between participants with HFPEF vs. HFREF. Our group previously reported risk factors associated with HFPEF and HFREF in an earlier series of 534 cases in FHS.[12] The present analysis extends these findings by including more contemporary incident HF cases and examining risk factors in more detail, and by externally validating the findings in an independent cohort.

Although HFREF and HFPEF increase mortality to a similar degree,[19] there are clear differences in causes of death between

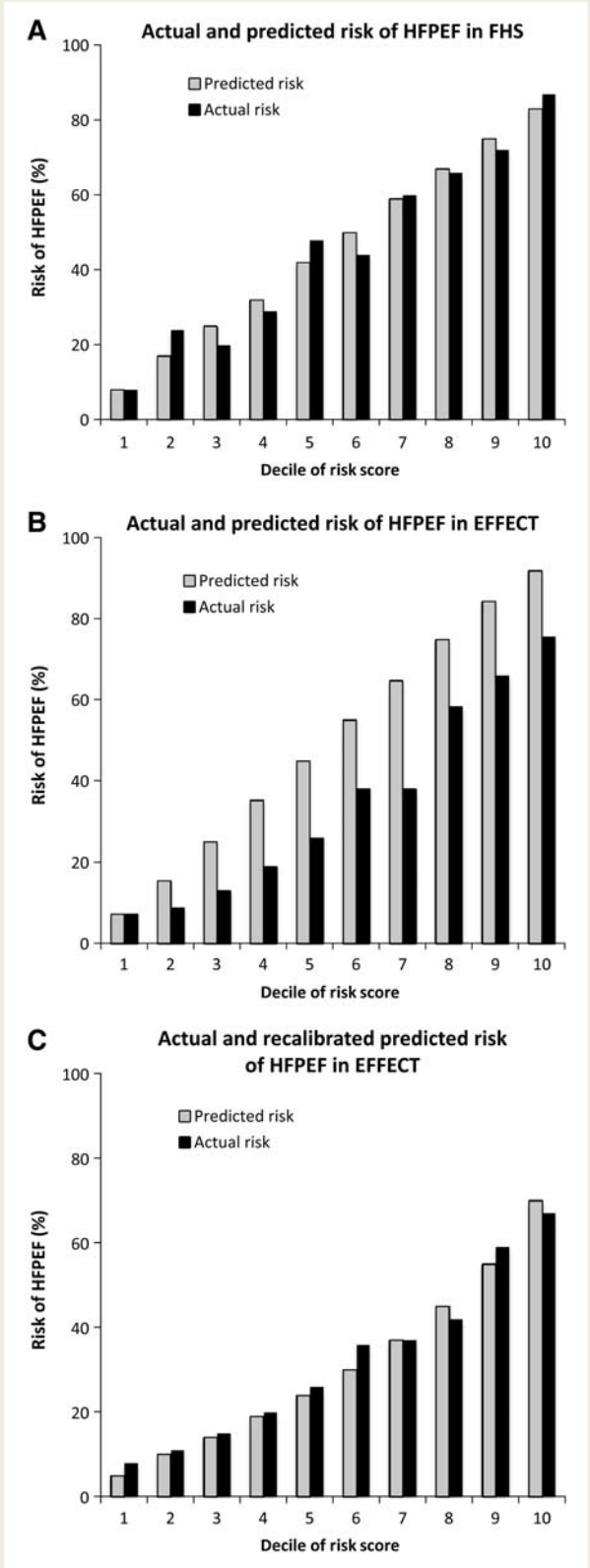

Figure 2 The actual and predicted risk of heart failure with preserved ejection fraction vs. heart failure with reduced ejection fraction by the decile of the Framingham Heart Study risk function. (*A*) Framingham Heart Study participants, (*B*) Enhanced Feedback For Effective Cardiac Treatment participants, and (*C*) Enhanced Feedback For Effective Cardiac Treatment participants after recalibration.

the two subtypes of HF,[7,20] with a higher burden of non-cardiovascular causes of death in HFPEF compared with HFREF. We examined differences in clinical presentation and co-morbid conditions, which may lead to further insights into pathophysiology of the two subtypes of HF. Our findings support the notion that HFPEF and HFREF are distinguishable across a spectrum of LVEF values, but substantial overlap exists. A number of clinical features appeared to differ across the spectrum of LVEF values used to define HFPEF vs. HFREF; some traits in HF were independent of LVEF. Notably, CHD predisposed to a lower LVEF in our study.

While ischaemic heart disease can contribute to HFPEF and HFREF,[21,22] overt CHD and ischaemic electrocardiographic changes on admission clearly favoured a diagnosis of HFREF over HFPEF. This finding has been corroborated by prior studies.[4,8,23–27] It may be that ischaemia is systematically under-recognized in HFPEF. It is known, for example, that at-risk women are less frequently evaluated for CHD compared with men,[28] and it may be that unrecognized or clinically silent ischaemia in women contributes to HFPEF. Our data support the concept that ischaemic heart disease manifest as acute coronary syndrome or macrovascular disease tends to precede HFREF. In contrast, microvascular or clinically silent disease may predispose to HFPEF, although the role of coronary artery disease in HFPEF remains unclear.[29]

Our study also demonstrated that participants presenting with incident HFPEF had concomitant atrial fibrillation on admission much more commonly than those with HFREF, despite a history of atrial fibrillation being common in both types of HF. Since atrial fibrillation leads to the loss of atrial contribution and heart rate control, it may be particularly poorly tolerated in individuals with diastolic dysfunction.

Men were more likely to present with HFREF, indicating that sex differences in cardiac responses to stress may play an important role, consistent with previous studies.[4,8,23–27] Previous data from FHS participants without HF show that isolated systolic hypertension leads to concentric left ventricular hypertrophy in women, whereas a pattern of eccentric hypertrophy is generally seen in men.[30] This and other sex-specific responses to risk factors may contribute to the discrepancy in type of HF with respect to sex.

While our study demonstrates significant differences in the clinical presentation, it is also important to highlight the features that were common to both types of HF. In prior studies, older age,[4,8,23–27] hypertension[4,23,24,27] and obesity[4,8,25] were all associated with HFPEF as opposed to HFREF. However, in our study, age, hypertension, and BMI did not discriminate between HFPEF vs. HFREF, suggesting that these clinical factors were common to both types of HF.

Several limitations merit consideration. First, various cut-off points for LVEF have been used to define HFPEF, and any partition in LVEF is clearly along a continuum of measured LVEF. Lower LVEF is a powerful predictor of cardiovascular outcomes in HF patients; however, once elevated >45% LVEF does not further contribute to this risk,[31] lending more weight to this cut-point. Our analysis excluded participants who did not undergo assessment of LV systolic function near the time of HF-onset. However, this was a small proportion of participants in the FHS sample (15%). A greater proportion in EFFECT did not undergo LVEF assessment, which may bias results, although the proportion of patients imaged was similar to other unselected populations hospitalized for HF.[23] Framingham Heart Study participants were predominantly white, limiting the generalizability of our findings. We also found that a higher serum potassium level at the time of hospitalization discriminated between the HF subtypes in FHS, but not in EFFECT. This may be due to differences in the ACE inhibitor or diuretic use, and we were not able to adjust for medication differences on HF presentation. We studied participants with diagnosed HF based on rigorous Framingham criteria,[11] rather than participants with suspected HF, thus implications of our findings with regard to diagnostic utility are limited. In that regard, it is important to realize that despite moderate capacity to discriminate between HFPEF and HFREF, pursuing cardiac imaging to evaluate structural disease in new-onset HF is the standard of care.[32]

Despite these limitations, a clear strength of our study is the combination of two very different but complementary study settings with similar characterization of HF subtypes, which expands the generalizability of our findings considerably. The FHS, as a longitudinal cohort, was ideal for initial examination of differences in clinical profiles, given detailed phenotyping, unbiased ascertainment of incident HF cases, and near-complete follow-up. In contrast, EFFECT as a much larger hospitalized population-cohort allowed external validation of our results.

In summary, many pre-onset and clinical characteristics at the time of HF presentation differed in participants presenting with HFPEF vs. HFREF, both in the community and in the hospital setting. While CHD predisposed to a lower LVEF, other clinical traits differed in prevalence across the spectrum of LVEF. These findings suggest that HFPEF and HFREF are overlapping clinical syndromes along a continuum of LV function. Future investigations on differences could lead to improved treatment strategies for patients with HF. Most importantly, further defining risk factor profiles for HFPEF and HFREF could lead to targeted preventive efforts in 'at-risk' individuals.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002;**106**:3068–3072.
2. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure study. *Eur Heart J* 2006;**27**:2338–2345.
3. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function. *J Am Coll Cardiol* 2004;**43**:317–327.
4. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;**355**:251–259.
5. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation* 2011;**123**:2006–2013.
6. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. *Circulation* 2011;**123**:1996–2004.
7. Lee DS, Gona P, Albano I, Larson MG, Benjamin EJ, Levy D, Kannel WB, Vasan RS. A systematic assessment of causes of death after heart failure onset in the community. *Circ Heart Fail* 2011;**4**:36–43.
8. Ghali JK, Kadakia S, Cooper RS, Liao YL. Bedside diagnosis of preserved versus impaired left ventricular systolic function in heart failure. *Am J Cardiol* 1991;**67**:1002–1006.
9. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann N Y Acad Sci* 1963;**107**:539–556.
10. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham Offspring study. *Am J Epidemiol* 1979;**110**:281–290.
11. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;**285**:1441–1446.
12. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction. *Circulation* 2009;**119**:3070–3077.
13. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 2003;**290**:2581–2587.
14. Tu JV, Donovan LR, Lee DS, Wang JT, Austin PC, Alter DA, Ko DT. Effectiveness of public report cards for improving the quality of cardiac care: the EFFECT study. *JAMA* 2009;**302**:2330–2337.
15. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;**355**:260–269.
16. Lee DS, Austin PC, Stukel TA, Alter DA, Chong A, Parker JD, Tu JV. Dose-dependent impact of recurrent cardiac events on mortality in patients with heart failure. *Am J Med* 2009;**122**:162–169 e1.
17. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;**286**:180–187.
18. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;**28**:2539–2550.
19. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. *JAMA* 2006;**296**:2209–2216.
20. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. *Circ Heart Fail* 2008;**1**:91–97.
21. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, Fabsitz RR, Howard BV. Congestive heart failure despite normal left ventricular systolic function in a population-based sample. *Am J Cardiol* 2000;**86**:1090–1096.
22. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function. *J Am Coll Cardiol* 2006;**47**:76–84.
23. Masoudi FA, Havranek EP, Smith G, Fish RH, Steiner JF, Ordin DL, Krumholz HM. Gender, age, and heart failure with preserved left ventricular systolic function. *J Am Coll Cardiol* 2003;**41**:217–223.
24. Lenzen MJ, Scholte op Reimer WJ, Boersma E, Vantrimpont PJ, Follath F, Swedberg K, Cleland J, Komajda M. Differences between patients with a preserved and a depressed left ventricular function. *Eur Heart J* 2004;**25**:1214–1220.
25. Philbin EF, Rocco TA, Lindenmuth NW, Ulrich K, Jenkins PL. Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. *Am J Med* 2000;**109**:605–613.
26. McDermott MM, Feinglass J, Sy J, Gheorghiade M. Hospitalized congestive heart failure patients with preserved versus abnormal left ventricular systolic function. *Am J Med* 1995;**99**:629–635.
27. Pernenkil R, Vinson JM, Shah AS, Beckham V, Wittenberg C, Rich MW. Course and prognosis in patients $>$ or $=$ 70 years of age with congestive heart failure and normal versus abnormal left ventricular ejection fraction. *Am J Cardiol* 1997;**79**:216–219.
28. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Pepine CJ, Mankad S, Sharaf BL, Rogers WJ, Pohost GM, Lerman A, Quyyumi AA, Sopko G. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: part II. *J Am Coll Cardiol* 2006;**47**(3 Suppl.):S21–S29.
29. Ohara T, Little WC. Evolving focus on diastolic dysfunction in patients with coronary artery disease. *Curr Opin Cardiol* 2010;**25**:613–621.
30. Krumholz HM, Larson MG, Levy D. Sex differences in cardiac adaptation to isolated systolic hypertension. *Am J Cardiol* 1993;**72**:310–313.
31. Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005;**112**:3738–3744.
32. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. *Circulation* 2009;**119**:e391–e479.