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Relative Importance of History of Heart Failure Hospitalization and N-Terminal Pro–B-Type Natriuretic Peptide Level as Predictors of Outcomes in Patients With Heart Failure and Preserved Ejection Fraction

Søren L. Kristensen, MD, PhD,*† Pardeep S. Jhund, MB, PhD,* Lars Køber, MD, DMSc,‡ Robert S. McKelvie, MD, PhD,§ Michael R. Zile, MD,‖ Inder S. Anand, MD, DPhil (Oxon),¶ Michel Komajda, MD,# John G.F. Cleland, MD,** Peter E. Carson, MD,†† John J.V. McMurray, MD*

ABSTRACT

OBJECTIVES The aim of this study was to investigate N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and recent heart failure (HF) hospitalization as predictors of future events in heart failure – preserved ejection fraction (HF-PEF).

BACKGROUND Recently, doubt has been expressed about the value of a history of HF hospitalization as a predictor of adverse cardiovascular outcomes in patients with HF and HF-PEF.

METHODS We estimated rates and adjusted hazard ratios (HRs) for the composite endpoint of cardiovascular death or HF hospitalization, according to history of recent HF hospitalization and baseline NT-proBNP level in the I-PRESERVE (Irbesartan in Heart Failure with Preserved systolic function) trial.

RESULTS Rates of composite endpoints in patients with (n = 804) and without (n = 1,963) a recent HF hospitalization were 12.78 (95% confidence interval [CI]: 11.47 to 14.24) and 4.49 (95% CI: 4.04 to 4.99) per 100 person-years, respectively (HR: 2.71; 95% CI: 2.33 to 3.16). For patients with NT-proBNP concentrations >360 pg/ml (n = 1,299), the event rate was 11.51 (95% CI: 10.54 to 12.58) compared to 3.04 (95% CI: 2.63 to 3.52) per 100 person-years in those with a lower level of NT-proBNP (n = 1468) (HR: 3.19; 95% CI: 2.68 to 3.80). In patients with no recent HF hospitalization and NT-proBNP ≤360 pg/ml (n = 1,187), the event rate was 2.43 (95% CI: 2.03 to 2.90) compared with 17.79 (95% CI: 15.77 to 20.07) per 100 person-years when both risk predictors were present (n = 523; HR: 6.18; 95% CI: 4.96 to 7.69).

CONCLUSIONS Recent hospitalization for HF or an elevated level of NT-proBNP identified patients at higher risk for cardiovascular events, and this risk was increased further when both factors were present. (J Am Coll Cardiol HF 2015;3:478–86) © 2015 by the American College of Cardiology Foundation.

From the *BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, United Kingdom; †Department of Cardiology, Gentofte University Hospital, Copenhagen, Denmark; ‡Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; §Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada; ‖Ralph H. Johnsons Veterans Affairs Medical Center and Medical University of South Carolina, Charleston, South Carolina; ¶Division of Cardiology, University of Minnesota, Minneapolis, Minnesota; #Université Paris 6 and Hospital Pitié-Salpétrière, Paris, France; **Harefield Hospital, Imperial College, London, United Kingdom; and the ††Washington DC Veterans Affairs Medical Center and Georgetown University, Washington, DC. Dr. Kristensen was supported by a postdoctoral grant from the Danish Independent Research Council; and a research fellowship from the Heart Failure Association of the European Society of Cardiology. Dr. Komajda is on the speakers bureau for Bristol-Myers Squibb, Sanofi, AstraZeneca, Menarini, MSD, and Servier; and is consultant for Servier and Amgen. Dr. Cleland has received honoraria as steering committee member of CORONA from AstraZeneca; and research support from Roche. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Although several studies have shown that previous hospitalization for worsening heart failure (HF), especially if recent, is a powerful predictor of future nonfatal and fatal cardiovascular (CV) events in patients with HF and reduced ejection fraction (HF-REF) (1–3), the TOPCAT (Treatment of Preserved Cardiac Function with an Aldosterone Antagonist Trial) (4) cast doubt upon that relationship in patients with heart failure with preserved ejection fraction (HF-PEF). There were 2 enrollment strata in TOPCAT: patients were eligible for inclusion on the basis of a hospitalization within the previous year, not necessarily for HF but during which they received treatment for it (n = 2,464), or alternatively, by having an elevated plasma concentration of natriuretic peptide within the previous 60 days (n = 981). The rate of the primary composite endpoint of CV death, hospitalization for HF, or resuscitation from cardiac arrest (the latter was a minor component of the composite) was lower in the stratum of patients recently hospitalized (6.0 per 100 patient years in the placebo group) than in the natriuretic peptide stratum (8.5 per 100 patient years in the placebo group) (4). Moreover, there was an interaction between enrollment stratum and treatment effect ($p < 0.01$) whereby spironolactone appeared to reduce the primary endpoint in patients included on the basis of a natriuretic peptide measurement (placebo-to-spironolactone hazard ratio [HR] of 0.65; 95% confidence interval [CI]: 0.49 to 0.87) but not in those randomized on the basis of prior hospitalization (HR: 1.01; 95% CI: 0.84 to 1.21). These findings have raised concerns about the value of the patient's medical history of HF hospitalization as a means of enhancing diagnostic certainty and predicting event rates in trials of HF-PEF (5). To investigate this issue further, we examined the relationships of recent HF hospitalization prior to inclusion and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels assessed at baseline with event rates in the I-PRESERVE (Irbesartan in Heart Failure with Preserved systolic function) trial (6).

METHODS

I-PRESERVE examined the effects of the angiotensin II receptor antagonist irbesartan on morbidity and mortality in patients with HF-PEF; outcomes of patients randomly assigned to receive irbesartan did not differ from those of patient who received placebo (6). In the present study, we analyzed clinical outcomes of HF hospitalization and CV death according to baseline NT-proBNP concentration, history of recent hospitalization for HF, and combinations of those factors.

PATIENTS. The rationale, design, and results from I-PRESERVE have been described previously in detail (7–9). The trial enrolled 4,028 patients with left ventricular ejection fraction of at least 45% who were ≥60 years of age and had HF symptoms corresponding to New York Heart Association (NYHA) functional classes II to IV. Patients in NYHA functional class II were required to have had a hospitalization for HF within 6 months before enrollment.

ABBREVIATIONS AND ACRONYMS

HF = heart failure

HF-PEF = heart failure with preserved ejection fraction

NYHA = New York Heart Association

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Although most patients enrolled in I-PRESERVE had their concentration of NT-proBNP measured at their randomization visit, the result was not available to investigators at the time of enrolment, unlike TOPCAT, and this measurement was not used to determine study eligibility (9).

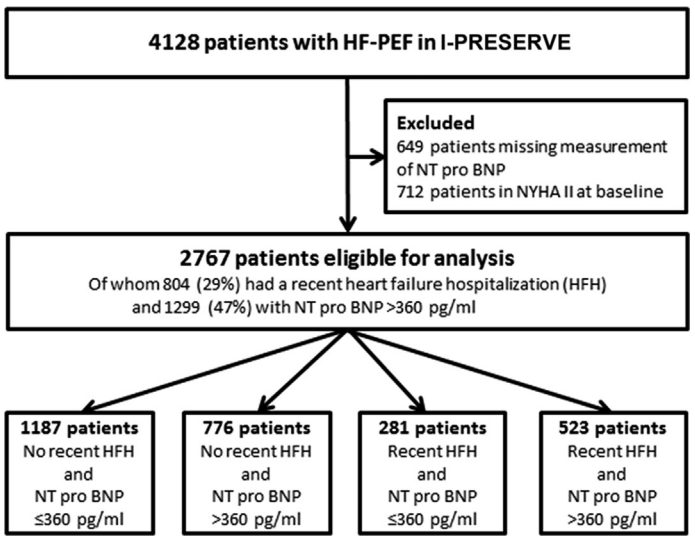
We restricted our main analysis to patients who were in NYHA functional class III or IV at baseline and who had had NT-proBNP concentration measured (**Figure 1**). We excluded patients in NYHA functional class II from the main analysis because they were all required to have a recent HF hospitalization. However, in a sensitivity analysis, we carried out the same analyses in all patients with a NT-proBNP measurement, regardless of NYHA functional class.

We report baseline characteristics of patients according to the presence or absence of HF hospitalization in the 6 months prior to study inclusion and baseline level of NT-proBNP, dichotomized at 360 pg/ml (the entry threshold for TOPCAT). In the sensitivity analysis, we dichotomized NT-proBNP at 300 pg/ml.

OUTCOMES. We studied the composite outcome of CV death or HF hospitalization, as well as each of the components of this composite separately. Deaths and hospitalizations were adjudicated by an independent endpoint committee.

STATISTICAL ANALYSES. Baseline characteristics are mean ± SD for continuous variables and frequencies and percentages for categorical variables. Differences in baseline characteristics according to recent hospitalization for HF and NT-proBNP levels were assessed using a chi-square test for categorical covariates and either 2-sided Student *t* tests or analyses of variance for continuous variables, as appropriate. Incidence rates of the outcomes of interest are presented according to 100 person-years, and the risk of HF hospitalization, CV death, and composite outcome were estimated as HRs in age- and sex-adjusted Cox regression models; and likelihood ratio tests were conducted comparing models with and without inclusion of recent HF hospitalization and NT-proBNP levels. In addition,

FIGURE 1 Flow Chart of the Study Population



Flow diagram for patients analyzed. Because patients who were in New York Heart Association (NYHA) functional class II (n = 712) required hospitalization for heart failure (HFH) in the 6 months before randomization, we restricted our main analysis to patients who were in NYHA functional class III or IV (n = 3,416). Of these, 649 patients did not have N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement. As a result, 2,767 patients were eligible for primary analysis. These patients were dichotomized according to whether they had a history of recent heart failure hospitalization (within 6 months) and whether they had a plasma NT-proBNP concentration of >360 pg/ml.

we assessed risk estimates in a multivariate analysis previously validated for the I-PRESERVE study (8), which included adjustments for age, sex, body mass index, ejection fraction, heart rate, systolic blood pressure, ischemic cause, congestion on radiographs, kidney function, blood urea nitrogen level, and neutrophil count and history of atrial fibrillation, myocardial infarction, diabetes, and stroke/transient ischemic attack.

Analyses were repeated using the 4 specific combinations of the 2 risk predictors as a categorical variable: 1) no recent hospitalization for HF plus NT-proBNP ≤360 pg/ml (reference); 2) no recent hospitalization for HF plus NT-proBNP>360 pg/ml; 3) recent hospitalization for HF plus NT-proBNP ≤360 pg/ml; and 4) recent hospitalization for HF plus NT-proBNP >360 pg/ml. In a sensitivity analysis including NYHA II patients, the same groups were created using an NT-proBNP cutpoint of 300 pg/ml. We also performed a subgroup analysis of patients with atrial fibrillation to assess whether the prognostic value of elevated NT-proBNP (>360 pg/ml) was similar or different in these patients.

We did not include randomized treatment in our model because irbesartan had no effect on any outcome in I-PRESERVE. All p values are 2-sided, and a p value of <0.05 was considered significant. All analyses were performed separately for each dataset, using Stata version 11 software (Stata Corp., College Station, Texas).

RESULTS

Characteristics of the patients analyzed are listed in Table 1. Patients are grouped according to history of HF hospitalization in the previous 6 months and NT-proBNP concentrations lower and higher than 360 pg/ml.

PATIENTS WITH RECENT HF HOSPITALIZATION COMPARED TO THOSE WITHOUT. Of the 2,767 patients included in the present analyses, 804 (29%) had a history of recent HF hospitalization. There were some notable differences compared to patients without recent HF hospitalization. Patients with recent HF hospitalization were slightly older (72 vs. 71 years of age), had a lower mean estimated glomerular filtration rate (eGFR) and twice the prevalence of atrial fibrillation (AF), and greater use of diuretic medicine, mineralocorticoid receptor antagonists, and beta-blockers. Their median level of NT-proBNP was significantly higher than in those without a history of recent HF hospitalization (609 vs. 254 pg/ml, respectively).

PATIENTS WITH AN ELEVATED NT-proBNP LEVEL COMPARED TO THOSE WITHOUT. Baseline NT-proBNP was >360 pg/ml in 1,299 patients (47%). Patients with an elevated NT-proBNP level were older (mean age 73 vs. 70 years of age), more likely to be male (44% vs. 34%, respectively), and had markedly lower mean eGFR (63 vs. 74 l/min/1.73m^2, respectively). They were also more likely to have ischemic heart disease (31% vs. 22%, respectively) and had a 4-fold higher prevalence of AF (44% vs. 10%, respectively) compared to patients with NT-proBNP ≤360 pg/ml. All other comorbidities were also more common in patients with higher NT-proBNP levels, and use of all medications listed was more frequent in these patients, with the exception of calcium channel blockers.

Rates of the composite endpoint of HF hospitalization and CV death are presented in Table 2 and Figure 2. This composite outcome occurred in 674 patients (24%) overall, with a rate per 100 patient years of 6.56 (95% CI: 6.08 to 7.07).

OUTCOMES ACCORDING TO HISTORY OF HF HOSPITALIZATION. In a sex- and age-adjusted Cox regression model, patients with recent HF hospitalization were more than twice as likely to

TABLE 1 Baseline Characteristics According to Previous Hospitalization for Heart Failure and NT-proBNP Levels

	All Patients (n = 2,767)	No HF Hospitalization Within 6 Months (n = 1,963 [71%])	HF Hospitalization Within 6 Months (n = 804 [29%])	NT-proBNP ≤360 pg/ml (n = 1,468 [53%])	NT-proBNP >360 pg/ml (n = 1,299 [47%])
Age, yrs	72 ± 7	71 ± 7	72 ± 7*	70 ± 7	73 ± 7*
Female	1,694 (61%)	1,185 (60%)	509 (63%)	964 (66%)	730 (56%)*
Racial distribution			*		
Caucasian	2,565 (93%)	1,800 (92%)	765 (95%)	1,355 (92%)	1,210 (93%)
Black	57 (2%)	40 (2%)	17 (2%)	29 (2%)	28 (2%)
Other	145 (5%)	123 (6%)	22 (3%)	84 (6%)	61 (5%)
Ejection fraction	0.60 ± 0.09	0.60 ± 0.09	0.58 ± 0.09*	0.61 ± 0.09	0.58 ± 0.09*
NYHA functional class			*		*
III	2,677 (97%)	1,924 (98%)	753 (94%)	1,437 (98%)	1,240 (95%)
IV	90 (3%)	39 (2%)	51 (6%)	31 (2%)	59 (5%)
Heart rate, beats/min	71 ± 10	70 ± 10	74 ± 11*	71 ± 9	72 ± 11*
Blood pressure, mm Hg	136 ± 15	137 ± 15	135 ± 14*	137 ± 14	135 ± 15*
Body mass index, kg/m^2	30 ± 5	30 ± 5	29 ± 6	30 ± 5	29 ± 5*
NT-proBNP, pg/ml	323 (130-901)	254 (111-659)	609 (215-1,519)*	136 (73-220)	955 (560-1,687)*
eGFR, l/min/1.73 m^2	69 ± 19	70 ± 19	65 ± 19*	74 ± 18	63 ± 19*
Ischemia cause	728 (26%)	510 (26%)	218 (27%)	323 (22%)	405 (31%)*
Hypertension cause	1,756 (64%)	1,271 (65%)	485 (60%)*	1,043 (71%)	713 (55%)*
Medical history					
Hypertension	2,455 (89%)	1,750 (89%)	705 (87%)	1,337 (91%)	1,118 (86%)*
Atrial fibrillation	724 (26%)	389 (20%)	335 (42%)*	147 (10%)	577 (44%)*
Diabetes	779 (28%)	533 (27%)	246 (31%)	387 (26%)	392 (30%)*
Stroke	272 (10%)	196 (10%)	76 (10%)	120 (8%)	152 (12%)*
PCI or CABG	375 (14%)	297 (15%)	78 (10%)*	173 (12%)	202 (16%)*
ICD	8 (0%)	4 (0%)	4 (1%)	3 (0%)	5 (0%)
Pacemaker	161 (6%)	98 (5%)	63 (8%)*	36 (3%)	125 (10%)*
Taking medication					
Loop-diuretic	2,247 (81%)	1,495 (76%)	752 (94%)*	1,133 (77%)	1,114 (86%)*
ACEi/ARB	696 (25%)	486 (25%)	210 (26%)	327 (22%)	369 (28%)*
Beta-blocker	1,579 (57%)	1,065 (54%)	514 (64%)*	804 (55%)	775 (60%)*
Calcium-channel blocker	1,139 (41%)	843 (43%)	296 (37%)*	666 (45%)	473 (36%)*
Mineralocorticoid antagonists	422 (15%)	210 (11%)	212 (26%)*	161 (11%)	261 (20%)*
Digoxin	378 (14%)	206 (11%)	172 (21%)*	76 (5%)	302 (23%)*

Values are mean ± SD, n (%), or median (interquartile range). *p < 0.05 for difference between hospitalization or no hospitalization for heart failure within 6 months, and NT-proBNP of ≤360 pg/ml and >360 pg/ml, respectively.

ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; NT-proBNP = N-terminal proB-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

experience the composite outcome of CV death and HF hospitalization compared to patients with no history of recent HF hospitalization (HR: 2.71; 95% CI: 2.33 to 3.16; p < 0.01) (Figure 2). In separate analyses of components of the composite endpoint (Table 2, Figure 3), recent hospitalization for HF was associated with a higher risk of both components, although it seemed to be more strongly associated with HF hospitalization (HR: 3.35; 95% CI: 2.75 to 4.07) than with risk of CV death (HR: 2.18; 95% CI: 1.79 to 2.65). Likelihood ratio tests (Table 3) also indicated better improvement of prediction of HF hospitalization (chi-square = 141.7) than CV death (chi-square = 58.2) when recent HF hospitalization was included in the model.

OUTCOMES ACCORDING TO NATRIURETIC PEPTIDE LEVEL. In a sex- and age-adjusted Cox regression models, patients with NT-proBNP level >360 pg/ml were 3 times more likely to experience composite outcomes of CV death and HF hospitalization than patients with NT-proBNP level ≤360 pg/ml (HR: 3.19; 95% CI: 2.68 to 3.71; p < 0.001) (Figure 2).

A higher NT-proBNP level was associated with similarly higher risks of HF hospitalization (HR: 3.50; 95% CI: 2.78 to 4.40) and CV death (HR: 3.19; 95% CI: 2.54 to 4.00) than an NT-proBNP level of 360 pg/ml or less (Figure 3), and it also yielded similar improvements in prediction in likelihood ratio tests (chi-square = 130.1 vs. chi-square = 113.4, respectively).

TABLE 2 Rates of the Composite Outcome of Cardiovascular Death or Heart Failure Hospitalization, and the 2 Components of the Composite Separately

	No. of Patients	No. of Events (%)	Event Rate per 100 Patient-Years	Sex- and Age-Adjusted HR	Fully Adjusted HR*
N	2,767	674 (24%)	6.56 (6.08-7.07)	-	
No HF hospitalization in the last 6 months	1,963	347 (18%)	4.49 (4.04-4.99)	1.00 (ref)	1.00 (ref)
HF hospitalization in the last 6 months	804	327 (41%)	12.78 (11.47-14.24)	2.71 (2.33-3.16)	2.05 (1.74-2.43)
NT-proBNP ≤360 pg/ml	1,468	183 (13%)	3.04 (2.63-3.52)	1.00 (ref)	1.00 (ref)
NT-proBNP >360 pg/ml	1,299	491 (38%)	11.51 (10.54-12.58)	3.19 (2.68-3.80)	2.25 (1.85-2.74)
Combinations					
No HF hosp + NT-proBNP ≤360 pg/ml	1,187	120 (10%)	2.42 (2.03-2.90)	1.00 (ref)	1.00 (ref)
No HF hosp + NT-proBNP >360 pg/ml	776	227 (29%)	8.16 (7.17-9.30)	2.83 (2.26-3.54)	2.24 (1.76-2.88)
HF hosp + NT-proBNP ≤360 pg/ml	281	63 (22%)	5.86 (4.58-7.50)	2.42 (1.78-3.29)	2.19 (1.60-3.00)
HF hosp + NT-proBNP >360 pg/ml	523	264 (50%)	17.79 (15.77-20.07)	6.18 (4.96-7.69)	4.06 (3.16-5.21)
Heart failure hospitalization	2,767	404 (15%)	3.93 (3.56-4.33)		
No HF hospitalization in the last 6 months	1,963	185 (9%)	2.40 (2.07-2.77)	1.00 (ref)	1.00 (ref)
HF hospitalization in last 6 months	804	219 (27%)	8.56 (7.50-9.77)	3.35 (2.75-4.07)	2.46 (1.98-3.05)
NT-proBNP ≤360 pg/ml	1,468	102 (7%)	1.70 (1.40-2.06)	1.00 (ref)	1.00 (ref)
NT-proBNP >360 pg/ml	1299	302 (23%)	7.08 (6.33-7.93)	3.50 (2.78-4.40)	2.29 (1.77-2.97)
Combinations					
No HF hosp + NT-proBNP ≤360 pg/ml	1,187	57 (5%)	1.15 (0.89-1.50)	1.00 (ref)	1.00 (ref)
No HF hosp + NT-proBNP >360 pg/ml	776	128 (16%)	4.60 (3.87-5.47)	3.34 (2.44-4.59)	2.46 (1.76-3.44)
HF hosp + NT-proBNP ≤360 pg/ml	281	45 (16%)	4.19 (3.12-5.61)	3.59 (2.43-5.31)	3.03 (2.03-4.53)
HF hosp + NT-proBNP >360 pg/ml	523	174 (33%)	11.73 (10.11-13.61)	8.38 (6.18-11.35)	5.10 (3.62-7.17)
Cardiovascular death	2,767	408 (15%)	3.66 (3.23-4.03)	-	
No HF hospitalization in the last 6 months	1,963	221 (11%)	2.73 (2.39-3.12)	1.00 (ref)	1.00 (ref)
HF hospitalization in the last 6 months	804	187 (23%)	6.13 (5.31-7.07)	2.18 (1.79-2.65)	1.64 (1.32-2.03)
NT-proBNP ≤360 pg/ml	1,468	105 (7%)	1.68 (1.39-2.03)	1.00 (ref)	1.00 (ref)
NT-proBNP >360 pg/ml	1,299	303 (23%)	6.20 (5.54-6.93)	3.19 (2.54-4.00)	2.33 (1.81-3.00)
Combinations					
No HF hosp + NT-proBNP ≤360 pg/ml	1,187	75 (6%)	1.48 (1.18-1.86)	1.00 (ref)	1.00 (ref)
No HF hosp + NT-proBNP >360 pg/ml	776	146 (19%)	4.82 (4.10-5.67)	2.78 (2.10-3.69)	2.25 (1.67-3.04)
HF hosp + NT-proBNP ≤360 pg/ml	281	40 (14%)	2.52 (1.76-3.60)	1.71 (1.12-2.61)	1.56 (1.02-2.40)
HF hosp + NT-proBNP >360 pg/ml	523	157 (30%)	8.44 (7.22-9.87)	4.99 (3.77-6.60)	3.36 (2.44-4.61)

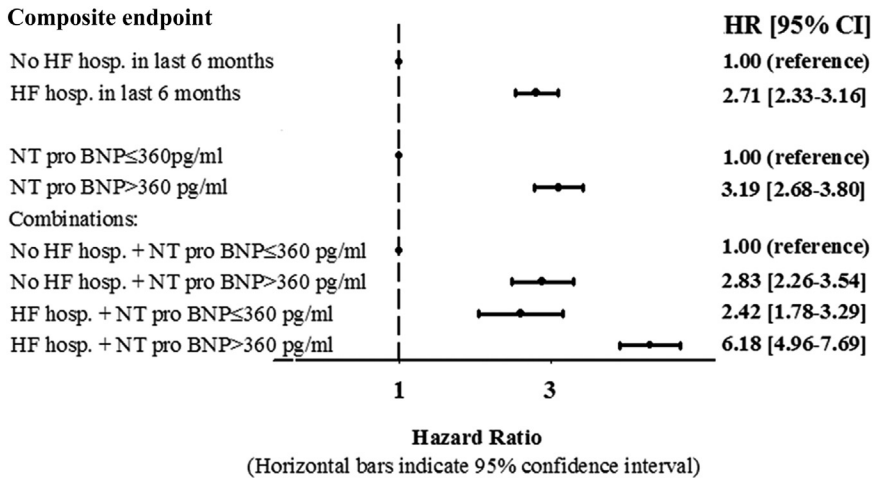
*Adjusted for age, sex, body mass index, ejection fraction, heart rate, systolic blood pressure, ischemic cause, congestion on radiograph, kidney function, blood urea nitrogen level, neutrophil count, and history of atrial fibrillation, myocardial infarction, diabetes, and stroke/transient ischemic attack.

HR = hazard ratio; other abbreviations as in Table 1.

OUTCOMES ACCORDING TO COMBINATIONS OF THE 2 RISK PREDICTORS. The 2 risk predictors overlapped in that 65% of patients with recent hospitalization for HF had NT-proBNP >360 pg/ml, and 40% of those with NT-proBNP >360 pg/ml also had had a recent HF hospitalization. We combined the 2 risk predictors to create 4 distinct risk groups (Table 2). Event rates for the composite endpoint and HF hospitalization and CV death separately are shown in Table 2.

For the composite outcome, the highest rate (17.79 events per 100 person-years) was observed in patients with both an NT-proBNP level >360 pg/ml and a recent HF hospitalization. Conversely, the lowest rate (2.42 events per 100 person-years) was observed in patients with neither a NT-proBNP level of >360 pg/ml nor a recent HF hospitalization. The composite primary outcome occurred at an intermediate rate in patients with one or the other risk predictor. These patients had a 2- to 3-fold higher risk of CV death or HF hospitalization, whereas patients with both a higher NT-proBNP and a recent HF hospitalization had a 6-fold higher risk of this outcome (both in comparison to patients with neither risk predictor) (Figure 3). When the 2 groups with only 1 of the risk predictors were compared, an NT-proBNP level >360 pg/ml was associated with a higher risk of CV death than a recent HF hospitalization in the previous 6 months (HR: 1.63; 95% CI: 1.10 to 2.42; $p < 0.01$). We found no significant differences for the risk of HF hospitalization and the composite outcome, although each risk predictor alone or combined was more strongly associated with the risk of HF hospitalization than CV death. Finally, combining the 2 risk predictors yielded improved risk prediction compared to each of the separate, and more so for the risk of HF hospitalization (Table 3).

FIGURE 2 Risk of Composite Outcome



Sex- and age-adjusted risks of composite outcome according to recent heart failure (HF) hospitalization and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level.

OUTCOMES IN FULLY ADJUSTED ANALYSES. In multivariate Cox regression analyses, with previously validated covariates such as kidney function, ejection fraction, and atrial fibrillation, risk estimates associated with prior HF hospitalization and elevated NT-proBNP were weakened but remained significantly higher, and the pattern of markedly higher risk in the presence of both predictors was consistent with the primary analyses.

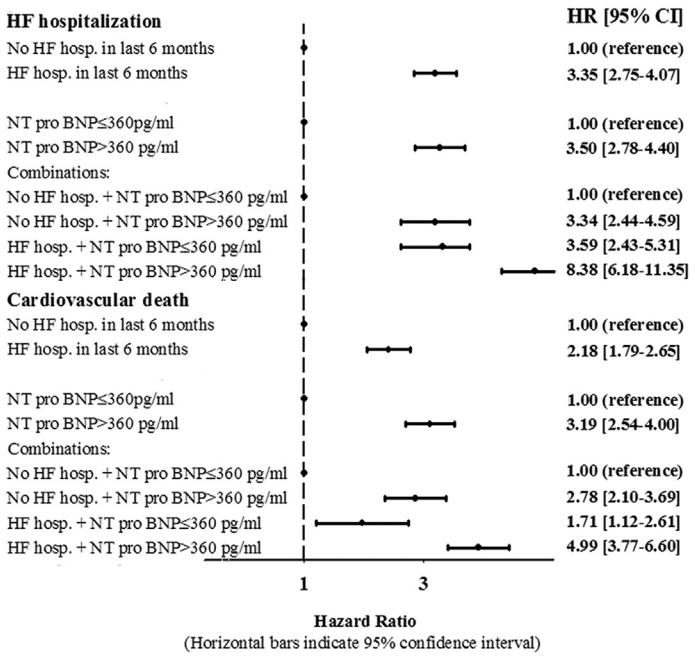
SENSITIVITY ANALYSES. Results of the sensitivity analysis including patients in NYHA II functional class are shown in the Online Appendix. Results were entirely consistent with the findings of the main analysis. In patients with atrial fibrillation, the higher risks associated with an elevated NT-proBNP level, as evaluated by using the fully adjusted hazard ratios, were similar to those in patients without atrial fibrillation, with the possible exception of CV death. However, the number of patients with atrial fibrillation was modest (n = 428), and the 95% CI intervals around the hazard ratio point estimates were wide.

DISCUSSION

In this analysis of the I-PRESERVE trial, we found that both the elevated natriuretic peptide level and the history of recent HF hospitalization identified patients at higher risk for HF hospitalization, CV death, and the composite of both outcomes. The combination was an even better predictor of risk.

Patients could therefore be divided into 4 distinct risk groups in which those with neither an elevated NT-proBNP level nor a recent HF hospitalization were at lowest risk, those with 1 or the other risk predictor were at intermediate risk (2- to 3-fold higher than patients with neither risk predictor), and patients with both of the predictors were at highest risk (5- to 8-fold higher than patients with neither). NT-proBNP level was, however, a more powerful individual predictor of future CV death than recent HF hospitalization. In a subgroup analysis, we found that the risk associated with a higher NT-proBNP (using the same cutpoint of 360 pg/ml) were, perhaps surprisingly, similarly elevated in patients with and without atrial fibrillation for all outcomes examined, with the possible exception of CV death. However, because of the relatively modest number of patients (n = 428) with atrial fibrillation (and small number of events in these patients), no definitive conclusion can be drawn, and it remains possible that a higher NT-proBNP threshold would be more appropriate for risk prediction in these patients than in patients without atrial fibrillation. In the present study, the rate of CV death or HF hospitalization in patients with an elevated NT-proBNP was 11.5 per 100 person-years. However, in TOPCAT, it is likely that NT-proBNP was used primarily to determine eligibility in patients without a recent HF hospitalization (4). In I-PRESERVE, the rate of CV death or HF hospitalization in patients with elevated NT-proBNP but without a recent HF hospitalization was only 8.2 per 100

FIGURE 3 Risk of Heart Failure Hospitalization and Cardiovascular Death



Sex- and age-adjusted risks of heart failure (HF) hospitalization and cardiovascular death shown separately, according to recent heart failure hospitalization and N-terminal pro–B-type natriuretic peptide (NT-proBNP) level.

person-years. This rate is similar to that observed in patients randomized through the natriuretic peptide stratum into the placebo arm of TOPCAT (8.5 per 100 person-years for the slightly broader primary composite endpoint of CV death, hospitalization for heart failure, or resuscitation from cardiac arrest).

What differed substantially between the 2 trials were the event rates in patients enrolled on the basis of recent HF hospitalization. The rate of CV death or HF hospitalization in these patients in I-PRESERVE was 12.8 per 100 patient years. This is considerably higher than the rate of 6.0 per 100 patient years for the primary composite endpoint in those enrolled through the hospitalization stratum in TOPCAT and assigned to placebo (also 6.0 per 100 person-years in the spironolactone arm). This comparison assumed that NT-proBNP level was not available in patients enrolled in this way in TOPCAT. The CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity)-Preserved study also provided a useful comparison (10). In that trial, in which NT-proBNP measurements were not available, the rate of the composite of CV death or HF hospitalization (the same composite reported here for I-PRESERVE) was 5.7 per 100 person-years in patients without a history (at any time) of HF hospitalization and 10.8 per 100 person-years in those with such a history. In other words, the rates of the same composite outcomes in patients with prior HF hospitalization in I-PRESERVE were very similar to those in CHARM-Preserved, and both were much higher than that in TOPCAT.

We believe there are 3 potential explanations for these differences in event rate, all of which have important implications for the design of future trials in HF-PEF. One possibility is that, in TOPCAT, hospitalization had to be within 12 months, whereas in I-Preserve it had to be within 6 months. Following HF hospitalization, the increased risk of another event diminishes rapidly over time, although we don't believe that a difference of 6 months can explain the disparity between rates in I-PRESERVE and those in TOPCAT, especially because a history of HF hospitalization at any time in CHARM-Preserved was associated with an almost doubled rate of the primary composite outcome compared to no such history. A second possibility is the protocol wording related to what was meant by prior hospitalization. In I-PRESERVE this was stated as: "A subject will be considered to have been hospitalized for heart failure if the primary reason for admission was heart failure and treatment directed specifically for heart failure," whereas in TOPCAT, the wording was: "At least one hospital admission in the last 12 months for which heart failure was a major component of the hospitalization." This subtle difference may have been critically important in that the former required an admission for HF, whereas the latter accepted an admission with HF (i.e., admissions for another reason during which patients received treatment for or had symptoms of HF, e.g., atrial fibrillation). Such patients may not be at the same risk of future HF events as those who have had a recent admission primarily because of HF. Finally, if patients were enrolled in TOPCAT on the basis of a previous hospitalization, despite knowledge of a low natriuretic peptide level, this selection bias would have created a group similar to those in I-PRESERVE with a history of HF hospitalization but NT-proBNP level ≤360 pg/ml. In I-PRESERVE, these individuals had a primary outcome rate of only 5.9 per 100 patient years compared with 12.8 per 100 patient years in all patients with a previous HF hospitalization, regardless of NT-proBNP level (and a rate of 10.8 per 100 patient years in CHARM patients with a previous HF hospitalization, with unknown natriuretic peptide levels). Clearly, 5.9 per 100 patient years is very similar to the rate of 6.0 per 100 patient years for the primary composite endpoint in those enrolled on the basis of prior hospitalization in TOPCAT.

TABLE 3 Contribution to Cardiovascular Outcome Prediction by Recent Heart Failure Hospitalization and NT-proBNP in I-PRESERVE

	Variable Chi-Square	p Value
Effect of adding variables to model with age and sex only		
Composite outcome		
HF hospitalization in the last 6 months	158.5	<0.0001
NT-proBNP, 360 pg/ml	190.8	<0.0001
Combined	293.1	<0.0001
HF hospitalization		
HF hospitalization in the last 6 months	141.7	<0.0001
NT-proBNP, 360 pg/ml	130.1	<0.0001
Combined	229.4	<0.0001
Cardiovascular death		
HF hospitalization in the last 6 months	58.2	<0.0001
NT-proBNP, 360 pg/ml	113.4	<0.0001
Combined	144.6	<0.0001
Effect of adding variable to fully adjusted model*		
Composite outcome		
HF hospitalization in the last 6 months	69.5	<0.0001
NT-proBNP, 360 pg/ml	70.3	<0.0001
Combined	127.1	<0.0001
HF hospitalization		
HF hospitalization in the last 6 months	65.6	<0.0001
NT-proBNP, 360 pg/ml	41.6	<0.0001
Combined	100.2	<0.0001
Cardiovascular death		
HF hospitalization in the last 6 months	19.9	<0.0001
NT-proBNP, 360 pg/ml	46.4	<0.0001
Combined	60.2	<0.0001

*Adjusted for age, sex, body mass index, ejection fraction, heart rate, systolic blood pressure, ischemic cause, congestion on radiograph, kidney function, blood urea nitrogen level, neutrophil count, and history of atrial fibrillation, myocardial infarction, diabetes, and stroke/transient ischemic attack.

Abbreviations as in Table 1.

These findings provide lessons for future trials conducted in patients with HF-PEF. Ease of recruitment in a clinical trial always reflects a balance between the restriction of the pool of patients available for recruitment imposed by the inclusion and exclusion criteria, the desire to ensure patients have the disease in question and the intent to enroll patients at sufficient risk of the pre-specified efficacy outcome to ensure the study has the statistical power to test its hypothesis. In patients with HF-PEF, a history of HF hospitalization (especially if recent) and a raised NT-proBNP level identify patients at higher risk of CV death or HF hospitalization, although NT-proBNP is a somewhat stronger predictor, especially of a robust outcome such as CV mortality. The highest risk patients are those who have both of these predictors, but such individuals represented only 19% of the total in I-PRESERVE. Requiring both of these for inclusion in a HF-PEF trial is likely to be overly restrictive. However, 47% of patients had a high NT-proBNP, 29% had a history of recent HF hospitalizations, and 57% of patients had at least 1 of these 2 risk predictors, placing them at intermediate risk. Using one or the other of these criteria would greatly expand the pool of available patients, but with the trade-off of a lower event rate. Importantly, permitting inclusion of patients on the basis of prior HF hospitalization despite a known low natriuretic peptide concentration will select a relatively low risk group (but one that still has twice the risk of patients without either risk predictor). This consideration must be weighed against the difficulty in recruiting HF-PEF patients for clinical trials; it took 36 months to recruit patients for I-PRESERVE and 66 months for TOPCAT. Patients with neither a high natriuretic peptide level nor a recent HF hospitalization have such a low event rate (especially of HF hospitalization) that they probably should not be recruited in event-driven outcome trials, especially as it may also be difficult to be certain of the diagnosis HF-PEF in such individuals. Defining what is meant by "prior HF hospitalization" is also likely to be critical, and investigators and sponsors should consider examination of source documents to verify such events.

STUDY LIMITATIONS. As with any study of this type, there are some limitations. I-PRESERVE had specific inclusion and exclusion criteria, therefore our findings may not be generalized to all patients with HF-PEF. This was also not a pre-specified analysis. Our main analysis excluded patients in NYHA functional class II because the protocol required such patients to have a recent history of heart failure hospitalization, although the sensitivity analysis including all patients gave similar findings.

In the present study, we focused on the identification of HF-PEF patients at high risk for HF hospitalization and CV death. However, it is important to remember that these are not the only important outcomes in heart failure and improvement in symptoms and quality of life are key goals of therapy in HF-PEF.

CONCLUSIONS

Future trials in HF-PEF should require either a higher natriuretic peptide level or a carefully defined history of recent HF hospitalization (or both) in order to identify patients at sufficient risk of future events.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. John J.V. McMurray, Institute of Cardiovascular and Medical Sciences, BHF Cardiovascular Research Centre, University of Glasgow, Glasgow G12 8TA, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with HF-PEF, both recent HFH and an elevated level of N-terminal pro–B-type natriuretic peptide identified patients at high risk for readmission and cardiovascular deaths. These risks were greatest when both factors were present.

TRANSLATIONAL OUTLOOK: Using one or the other of these criteria would greatly expand the pool of available patients for clinical trials in HF-PEF while maintaining the event rate. However, the history of HFH should be verified.

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APPENDIX For supplemental tables, please see the online version of this article.