Title: 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.

Short title: Predictors of outcome in HF-PEF

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Abstract

Background: Recently, doubt has been expressed about the value of a history of heart failure (HF) hospitalization as a predictor of adverse cardiovascular outcomes in patients with HF and preserved ejection fraction (HF-PEF).

Objectives: The aim of this study was to investigate N-terminal pro B-type natriuretic peptide (NT pro BNP) levels and recent HF hospitalization, as predictors of future events in HF-PEF.

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

Results: Rates of the composite endpoint in patients with (n=804) and without (n=1963) a recent HF hospitalization were 12.78 (95% CI 11.47-14.24) and 4.49 (4.04-4.99) per 100 person-years, respectively; HR 2.71 (2.33-3.16). For patients with NT pro BNP >360 pg/ml (n=1299), the event rate was 11.51 (10.54-12.58) compared to 3.04 (2.63-3.52) per 100 person-years in those with a lower level of NT pro BNP (n=1468); HR 3.19 (2.68-3.80). In patients with no recent HF hospitalization and NT pro BNPd360 pg/ml (n=1187), the event rate was 2.43 (2.03-2.90) compared with 17.79 (15.77-20.07) per 100 person-years when both risk predictors were present (n=523); HR 6.18 (4.96-7.69).

Conclusions: Recent hospitalization for HF or an elevated level of NT pro BNP identified patients at higher risk for cardiovascular events and this risk was increased further when both factors were present.

Keywords: heart failure, heart failure with preserved ejection fraction, prognostic markers, outcomes, NT pro BNP

Abbreviations

CI	Confidence interval
HF	Heart failure
HF-PEF	Heart failure and preserved ejection fraction
HR	Hazard ratio
I-Preserve	the Irbesartan in Heart Failure with Preserved systolic function trial
NYHA	New York Heart Association functional class
NT pro BNP	N-terminal pro B-type natriuretic peptide
TOPCAT	the Treatment of Preserved Cardiac Function with an Aldosterone Antagonist Trial

Introduction

Although several studies have shown that prior hospitalization for worsening heart failure (HF), especially if recent, is a powerful predictor of future non-fatal and fatal cardiovascular events in patients with HF and reduced ejection fraction (HF-REF)[1-3], the Treatment of Preserved Cardiac Function with an Aldosterone Antagonist Trial (TOPCAT)[4] has cast doubt upon this relationship in patients with HF with preserved ejection fraction (HF-PEF). There were two enrolment strata in TOPCAT, with patients 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=2464) 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 cardiovascular death, hospitalization for HF or resuscitation from cardiac arrest (the latter was a minor component of the composite) was lower in the recent-hospitalization stratum (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 enrolment 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: spironolactone hazard ratio [HR] 0.65 [95% CI 0.49-0.87]) but not in those randomized on the basis of a prior hospitalization (HR 1.01 [0.84-1.21]). These findings have raised concerns about the value of a 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 pro BNP) levels assessed at baseline with event rates in the Irbesartan in Heart Failure with Preserved systolic function trial (I-Preserve).[6]

Methods

I-Preserve examined the effects of the angiotensin II receptor antagonist, irbesartan on morbidity and mortality in patients with HF-PEF; outcomes did not differ between patients randomly assigned to irbesartan or placebo.[6] In the present study, we analyzed clinical outcomes, namely HF hospitalization and cardiovascular death, according to baseline NT pro BNP level, history of recent hospitalization for HF, and combinations of these factors.

Patients

The rationale, design, and results from I-Preserve have been described in detail.[7-9] The trial enrolled 4028 patients with a left ventricular ejection fraction of at least 45% who were 60 years of age or older and had HF symptoms corresponding to New York Heart Association (NYHA) functional class II to IV. Patients who were in NYHA functional class II were required to have a hospitalization for HF in the 6 months before enrollment.

Although most patients enrolled in I-Preserve had a measurement of NT pro BNP at their randomization visit, the result was not available to investigators at the time of enrolment, unlike in 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 a measurement of NT pro BNP (Figure 1). We excluded patients in NYHA class II from the main analysis because of 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 pro BNP measurement, irrespective of NYHA 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 pro BNP, dichotomized at 360 pg/ml (the entry threshold for TOPCAT). In the sensitivity analysis, we dichotomized NT pro BNP at 300 pg/ml.

Outcomes

We studied the composite outcome of cardiovascular death or HF hospitalization, as well as each of the components of this composite, separately. Deaths and hospitalizations were adjudicated by an independent end-point committee.

Statistical analyses

Baseline characteristics are presented as means with standard deviations for continuous variables and frequencies and percentages for categorical variables. Differences in baseline characteristics according to recent hospitalization for HF and NT pro BNP levels were assessed using a chi-squared test for categorical covariates and either two-sided t-tests or analyses of variance for continuous variables, as appropriate. Incidence rates of the outcomes of interest are presented per 100 person-years, and the risk of HF hospitalization, cardiovascular death and the 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 pro BNP levels. In addition, we assessed risk estimates in a multivariate analysis previously validated for the I-Preserve study[8], which included adjustments for age, sex, BMI, ejection fraction, heart rate, systolic blood pressure, ischemic etiology, congestion on x-ray, kidney function, blood urea nitrogen, neutrophils, and history of atrial fibrillation, myocardial infarction, diabetes, and stroke/transient ischemic attack.

The analyses were repeated using the four specific combinations of the two risk predictors as a categorical variable; i) no recent hospitalization for HF + NT pro BNPd360 pg/ml (reference), ii) no recent hospitalization for HF + NT pro BNP>360 pg/ml, iii) recent hospitalization for HF + NT pro BNPd360 pg/ml, and iv) recent hospitalization for HF + NT

pro BNP>360 pg/ml. In a sensitivity analysis including NYHA II patients, the same groups were created using a NT pro BNP cut-point of 300 pg/ml. We also performed a subgroup analysis on patients with atrial fibrillation to assess whether the prognostic value of elevated NT pro BNP (>360 pg/ml) was similar or different in these patients.

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

Results

The characteristics of the patients analyzed are listed in Table 1. Patients are grouped according to 1) history of HF hospitalization in last 6 months and 2) NT pro BNP levels d and >360 pg/ml.

Patients with recent heart failure hospitalization compared to those without

Of the 2767 patients included in the present analyses, 804 (29%) had a history of recent HF hospitalization. There were some notable differences compared to patients without a recent HF hospitalization. Patients with a recent HF hospitalization were slightly older (72 vs. 71 years), had a lower mean estimated glomerular filtration rate (eGFR), twice the prevalence of atrial fibrillation (AF), and greater use of diuretics, mineralocorticoid receptor antagonists and beta-blockers. The median level of NT pro BNP was significantly higher compared to those without a history of recent HF hospitalization (609 vs. 254 pg/ml).

Patients with an elevated NT pro BNP level compared to those without

Baseline NT pro BNP was >360 pg/ml in 1299 (47%) patients. Patients with an elevated NT pro BNP were older (mean age 73 vs. 70 years), more likely to be men (44% vs. 34%), and had a markedly lower mean eGFR (63 vs. 74 l/min/1.73m^2). They were also more likely to have ischemic heart disease (31% vs. 22%) and had a four-fold higher prevalence of AF (44% vs. 10%) compared to patients with a NT pro BNP d360 pg/ml. All other comorbidities were also more common in patients with a higher NT pro BNP 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 cardiovascular death are presented in Table 2 and Figure 2. This composite outcome occurred in 674 (24%) patients overall, with a rate per 100 patient-years of 6.56 (95% CI 6.08-7.07).

Outcomes according to history of HF hospitalization

In a sex- and age-adjusted Cox regression model, patients with a recent HF hospitalization were more than twice as likely to experience the composite outcome of CV death or HF hospitalization compared to patients with no history of recent HF hospitalization (HR 2.71 [2.33-3.16]; p<0.01) (Figure 2). In separate analyses of components of the composite endpoint (Table 2 and 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 [2.75-4.07]) than with risk of cardiovascular death (HR 2.18 [1.79-2.65]). Likelihood ratio tests (Table 3) also indicated better improvement of prediction of HF hospitalization (χ^2=141.7**)** than cardiovascular death (χ^2=58.2**)** **w**hen recent HF hospitalization was included in the model.

Outcomes according to natriuretic peptide level

In a sex- and age-adjusted Cox regression model, patients with a NT pro BNP level >360 pg/ml were more than three times as likely to experience the composite outcome of CV death or HF hospitalization compared to patients with a NT pro BNP level d360 pg/ml (HR 3.19 [2.68-3.71]; p<0.001) (Figure 2).

A higher NT pro BNP level was associated with similarly higher risks of HF hospitalization (HR 3.50 [2.78-4.40]) and cardiovascular death (HR 3.19 [2.54-4.00]) compared to a NT pro BNP level of 360 pg/ml or less (Figure 3), and it also yielded similar improvements in prediction in likelihood ratio tests (χ^2=130.1 vs. χ^2=113.4).

Outcomes according to combinations of the two risk-predictors

The two risk-predictors overlapped in that 65% of patients with a recent hospitalization for HF had a NT pro BNP >360 pg/ml and 40% of those with NT pro BNP>360 pg/ml had also

had a recent HF hospitalization. We combined the two risk-predictors, to create four distinct risk-groups (Table 2). Event rates for the composite endpoint, and HF hospitalization and cardiovascular death separately, are shown in this table.

For the composite outcome, the highest rate (17.79 events per 100 person-years) was observed in patients with both a NT pro BNP 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 pro BNP >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 2-3 fold higher risk of CV death or HF hospitalization whereas patients with both a higher NT pro BNP and a recent HF hospitalization had a 6-fold higher risk of this outcome (both comparisons to patients with neither risk-predictor) (Figure 3). When the two groups with only one of the risk-predictors were compared, a NT pro BNP level >360 pg/ml was associated with a higher risk of cardiovascular death than a recent HF hospitalization in the prior 6 months (HR 1.63 [1.10-2.42]; $p<0.01$). 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 two risk predictors yielded improved risk prediction compared to each of the separate, and more so for the risk of HF hospitalization (Table 3).

Outcomes in fully adjusted analyses

In multivariate Cox regression analyses, with previously validated covariates such as kidney function, ejection fraction and atrial fibrillation, the risk estimates associated with prior HF hospitalization and elevated NT pro BNP were weakened but remained significantly higher,

and the pattern of markedly higher risk in presence of *both* predictors was consistent with the primary analyses.

Sensitivity analyses

The results of the sensitivity analysis including patients in NYHA II functional class are shown in the Appendix. These were entirely consistent with the findings of the main analysis. In patients with atrial fibrillation, the higher risks associated with an elevated NT pro BNP, as evaluated using the fully adjusted hazard ratios, were similar to those in patients without atrial fibrillation, with the possible exception of cardiovascular death. However, the number of patients with atrial fibrillation was modest (n=428) and the 95% confidence intervals around the hazard ratio point estimates were wide.

Discussion

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

Patients could therefore be categorized into four distinct risk-groups where those with neither an elevated NT pro BNP nor a recent heart failure hospitalization were at lowest risk, those with one or other risk-predictor were at intermediate risk (2 to 3-fold higher than patients with neither risk-predictor) and patients with both were at highest risk (5 to 8-fold higher than patients with neither). NT pro BNP was, however, a more powerful individual predictor of future cardiovascular death than recent heart failure hospitalization. In a subgroup analysis, we found that the risk associated with a higher NT pro BNP (using the same cut-point 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 cardiovascular 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 pro BNP threshold would be more appropriate for risk-prediction in these patients than in patients without atrial fibrillation. In the present study, the rate of cardiovascular death or HF hospitalization in patients with an elevated NT pro BNP was 11.5 per 100 person years. However, in TOPCAT, it is likely that NT pro BNP was primarily used to determine eligibility in patients *without* a recent HF hospitalization.[4] In I-Preserve, the rate of cardiovascular death or HF hospitalization in patients with an elevated NT pro BNP but *without* a recent HF hospitalization was only 8.2 per 100 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 cardiovascular death, hospitalization for heart failure or resuscitation from cardiac arrest).

What differed substantially between the two trials were the event rates in patients enrolled on the basis of a recent HF hospitalization. The rate of cardiovascular 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 assumes that a NT pro BNP level was not available in patients enrolled in this way in TOPCAT. CHARM-Preserved also provides a useful comparison.[10] In that trial, in which NT pro BNP measurements were not available, the rate of the composite of cardiovascular death or HF hospitalization (the same composite as 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 rate of the same composite outcome in patients with prior HF hospitalization was very similar in I-Preserve and CHARM-Preserved and both were much higher than in TOPCAT.

We believe that there are 3 potential explanations for this difference 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 TOPCAT, especially as a history of prior HF hospitalization *at any time* in CHARM-Preserved was associated with almost double the 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 stated: *"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. AF. 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. Lastly, if patients were enrolled in TOPCAT on the basis of a prior 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 a NT pro BNP level d360 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 prior HF hospitalization, irrespective of NT pro BNP level (and a rate of 10.8 per 100 patient years in CHARM patients with a prior 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.

These findings provide lessons for future trial conduct in HF-PEF. Ease of recruitment into 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 prior HF hospitalization (especially if recent) and a raised NT pro BNP identify patients at higher risk of CV death or HF hospitalization, although NT pro BNP is a somewhat stronger predictor, especially of a robust outcome such as cardiovascular 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 pro BNP, 29% had a history of recent HF hospitalization and 57% of patients had at least one of these two risk-predictors, placing them at intermediate risk. Using one or 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 in 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 shouldn't 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.

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 cardiovascular 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.

Conclusion

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.

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References

1. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. Arch intern med 1997;157:99-104.
2. Abrahamsson P, Swedberg K, Borer JS, et al. Risk following hospitalization in stable chronic systolic heart failure. Eur J Heart Fail 2013;15:885-91.
3. Solomon SD, Dobson J, Pocock S, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation 2007;116:1482-7.
4. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92.
5. McMurray JJ, O'Connor C. Lessons from the TOPCAT trial. N Engl J Med 2014;370:1453-4.
6. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. The New England journal of medicine 2008;359:2456-67.
7. Carson P, Massie BM, McKelvie R, et al. The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial: Rationale and design. J Card Fail 2005;11:576-85.
8. Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circ Heart Fail 2011;4:27-35.
9. McKelvie RS, Komajda M, McMurray J, et al. Baseline plasma NT-proBNP and clinical characteristics: results from the irbesartan in heart failure with preserved ejection fraction trial. J Card Fail 2010;16:128-34.
10. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.

Table 1 Baseline characteristics according to prior hospitalization for Heart Failure, and NT pro BNP levels.

	All patients	No HF hosp. in last 6 months	HF hosp. in last 6 months	NT pro BNP d360 pg/ml	NT pro BNP >360 pg/ml
N	2767	1963 (71%)	804 (29%)	1468 (53%)	1299 (47%)
Age, mean – yr	72 ± 7	71 ± 7	72 ± 7*	70 ± 7	73 ± 7*
Female sex, no. (%)	1694 (61%)	1185 (60%)	509 (63%)	964 (66%)	730 (56%)*
Race, no (%):			*		
Caucasian	2565 (93%)	1800 (92%)	765 (95%)	1355 (92%)	1210 (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 class			*		*
III	2677 (97%)	1924 (98%)	753 (94%)	1437 (98%)	1240 (95%)
IV	90 (3%)	39 (2%)	51 (6%)	31 (2%)	59 (5%)
Heart rate /bpm	71 ± 10	70 ± 10	74 ± 11*	71 ± 9	72 ± 11*
Syst. BP/mm Hg	136 ± 15	137 ± 15	135±14*	137 ± 14	135 ± 15*
Body mass index	30 ± 5	30 ± 5	29 ± 6	30 ± 5	29 ± 5*
NT pro BNP, median	323	254	609*	136	955*
Interquartile range	130-901	111-659	215-1519	73-220	560-1687
eGFR - l/min/1.73m^2	69 ± 19	70 ± 19	65 ± 19*	74 ± 18	63 ± 19*
Ischemic etiology	728 (26%)	510 (26%)	218 (27%)	323 (22%)	405 (31%)*
Hypertensive etiology	1756 (64%)	1271 (65%)	485 (60%)*	1043 (71%)	713 (55%)*
Medical history, no. (%)					
Hypertension	2455 (89%)	1750 (89%)	705 (87%)	1337 (91%)	1118 (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%)*
Medication, no. (%)					
Loop-diuretic	2247 (81%)	1495 (76%)	752 (94%)*	1133 (77%)	1114 (86%)*
ACEi/ARB	696 (25%)	486 (25%)	210 (26%)	327 (22%)	369 (28%)*
Beta-blocker	1579 (57%)	1065 (54%)	514 (64%)*	804 (55%)	775 (60%)*
Calcium-channel blocker	1139 (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%)*

*p-value <0.05 for difference between hospitalization or no hospitalization for heart failure within 6 months, and NT-ProBNP d 360 pg/ml, and >360 pg/ml, respectively

Table 2 Rates of the composite outcome of cardiovascular death or heart failure hospitalization, and the two components of the composite separately.

	Number of Patients	Number of events	Event rate per 100 py	Sex and age adjusted HRs	Fully adjusted HRs*
Composite endpoint	2767	674 (24%)	6.56 (6.08-7.07)	-	
No HF hospitalization in last 6 mo.	1963	347 (18%)	4.49 (4.04-4.99)	1.00 (ref)	1.00 (ref)
HF hospitalization in last 6 mo.	804	327 (41%)	12.78 (11.47-14.24)	2.71 (2.33-3.16)	2.05 (1.74-2.43)
NT pro BNPd360 pg/ml	1468	183 (13%)	3.04 (2.63-3.52)	1.00 (ref)	1.00 (ref)
NT pro BNP>360 pg/ml	1299	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 pro BNPd360 pg/ml	1187	120 (10%)	2.42 (2.03-2.90)	1.00 (ref)	1.00 (ref)
No HF hosp + NT pro BNP>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 pro BNPd360 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 pro BNP>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	2767	404 (15%)	3.93 (3.56-4.33)		
No HF hospitalization in last 6 mo.	1963	185 (9%)	2.40 (2.07-2.77)	1.00 (ref)	1.00 (ref)
HF hospitalization in last 6 mo.	804	219 (27%)	8.56 (7.50-9.77)	3.35 (2.75-4.07)	2.46 (1.98-3.05)
NT pro BNPd360 pg/ml	1468	102 (7%)	1.70 (1.40-2.06)	1.00 (ref)	1.00 (ref)
NT pro BNP>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 pro BNPd360 pg/ml	1187	57 (5%)	1.15 (0.89-1.50)	1.00 (ref)	1.00 (ref)
No HF hosp + NT pro BNP>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 pro BNPd360 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 pro BNP>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	2767	408 (15%)	3.66 (3.23-4.03)	-	
No HF hospitalization in last 6 mo.	1963	221 (11%)	2.73 (2.39-3.12)	1.00 (ref)	1.00 (ref)
HF hospitalization in last 6 mo.	804	187 (23%)	6.13 (5.31-7.07)	2.18 (1.79-2.65)	1.64 (1.32-2.03)
NT pro BNPd360 pg/ml	1468	105 (7%)	1.68 (1.39-2.03)	1.00 (ref)	1.00 (ref)
NT pro BNP>360 pg/ml	1299	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 pro BNPd360 pg/ml	1187	75 (6%)	1.48 (1.18-1.86)	1.00 (ref)	1.00 (ref)
No HF hosp + NT pro BNP>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 pro BNPd360 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 pro BNP>360 pg/ml	523	157 (30%)	8.44 (7.22-9.87)	4.99 (3.77-6.60)	3.36 (2.44-4.61)

HF- heart failure, NT pro BNP – N-terminal pro B-type natriuretic peptide, HR –Hazard ratio.

*Adjusted for age, sex, BMI, ejection fraction, heart rate, systolic blood pressure, ischemic etiology, congestion on x-ray, kidney function, blood urea nitrogen, neutrophils, and history of atrial fibrillation, myocardial infarction, diabetes, and stroke/transient ischemic attack.

Table 3 Contribution to cardiovascular outcome prediction by recent heart failure hospitalization and NT pro BNP in I-Preserve.

	Variable χ^2	*P*
Effect of adding variables to model with age and sex only		
Composite outcome		
HF hospitalization last 6 months	158.5	<0.0001
NT pro BNP (360 pg/ml)	190.8	<0.0001
Combined	293.1	<0.0001
HF hospitalization:		
HF hospitalization last 6 months	141.7	<0.0001
NT pro BNP (360 pg/ml)	130.1	<0.0001
Combined	229.4	<0.0001
Cardiovascular death		
HF hospitalization last 6 months	58.2	<0.0001
NT pro BNP (360 pg/ml)	113.4	<0.0001
Combined	144.6	<0.0001
Effect of adding variable to fully adjusted model*		
Composite outcome:		
HF hospitalization last 6 months	69.5	<0.0001
NT pro BNP (360 pg/ml)	70.3	<0.0001
Combined	127.1	<0.0001
HF hospitalization:		
HF hospitalization last 6 months	65.6	<0.0001
NT pro BNP (360 pg/ml)	41.6	<0.0001
Combined	100.2	<0.0001
Cardiovascular death		
HF hospitalization last 6 months	19.9	<0.0001
NT pro BNP (360 pg/ml)	46.4	<0.0001
Combined	60.2	<0.0001

*Adjusted for age, sex, BMI, ejection fraction, heart rate, systolic blood pressure, ischemic etiology, congestion on x-ray, kidney function, blood urea nitrogen, neutrophils, and history of atrial fibrillation, myocardial infarction, diabetes, and stroke/transient ischemic attack.

Figure legends (short titles and captions).

Figure 1 Flow chart of the study population

Flow chart of the study population

Figure 2 Risk of the composite outcome

Sex- and age-adjusted risk of the composite outcome according to recent heart failure hospitalization and NT pro BNP level

Figure 3 Risk of heart failure hospitalization and cardiovascular death

Sex- and age-adjusted risk of heart failure hospitalization and cardiovascular death separately, according to recent heart failure hospitalization and NT pro BNP level