Prognostic Value of Baseline Plasma Amino-Terminal Pro-Brain Natriuretic Peptide and Its Interactions With Irbesartan Treatment Effects in Patients With Heart Failure and Preserved Ejection Fraction

Findings From the I-PRESERVE Trial

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Background—Plasma concentrations of natriuretic peptides (NPs) are associated with morbidity and mortality in patients with systolic heart failure (HF). However, the role of NP as a prognostic marker in patients with HF and preserved ejection fraction (HFpEF) has not been studied in a large cohort of well-characterized patients. Moreover, it is unclear whether treatments have a differential effect on morbidity and mortality across the spectrum of NP levels.

Methods and Results—N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured at baseline in 3480 patients in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Trial). In a multivariable Cox regression model, NT-proBNP above the median of 339 pg/mL was independently associated with an increased risk of the primary end point of all-cause mortality and prespecified cardiovascular hospitalizations (adjusted hazard ratio [HR], 1.79; 95% CI, 1.56 to 2.10; $P<0.001$); all-cause mortality (adjusted HR, 2.04; 95% CI, 1.68 to 2.47; $P<0.001$); and a composite of HF events, including death due to worsening HF or sudden death or hospitalization due to worsening HF (adjusted HR, 1.77; 95% CI, 1.43 to 2.20; $P<0.001$). There were significant interactions between the effect of irbesartan and median split of baseline NT-proBNP for the primary outcome ($P=0.005$), all-cause mortality ($P=0.05$), and the HF composite outcome ($P<0.001$). Use of irbesartan was associated with improved outcomes in patients with NT-proBNP below, but not above, the median. After adjusting for 20 baseline covariates, irbesartan still had a beneficial effect on the primary outcome (HR, 0.74; 95% CI, 0.60 to 90; $P=0.003$), all-cause mortality (HR, 0.75; 95% CI, 0.56 to 0.99; $P=0.046$), and HF composite outcome (HR, 0.57; 95% CI, 0.41 to 0.80; $P=0.001$) in patients with NT-proBNP below the median.

Conclusions—The unexpected benefit of irbesartan in lower-risk patients with HFpEF in this post hoc analysis may indicate effects on early, but not later, high-risk stages of the disease. These findings question the strategy of using elevated plasma concentrations of NP as a patient selection criterion in HFpEF trials. More studies are needed to support or contest this practice.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00095238.

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Key Words: heart failure, diastolic ■ ventricular ejection fraction ■ pro-brain natriuretic peptide (1–76) ■ pathophysiology ■ prognosis ■ biological markers

Higher levels of natriuretic peptides have been independently associated with mortality and morbidity in patients with heart failure (HF) and reduced ejection fraction (HFrEF).[1,2] Data on natriuretic peptide level as a prognostic marker in patients with HF and preserved EF (HFpEF) are limited and suggest that higher plasma concentrations of natriuretic peptides are associated with an increased likelihood of morbid and fatal events.[3–6] Recently, HF clinical trials have begun to exclude patients with low concentrations of plasma natriuretic peptides to increase the likelihood that the

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patients being enrolled have HF and to increase the number of outcome events and, presumably, statistical power.[7–11] This approach to patient selection assumes that the study intervention will have a similar or even greater effect in the higher-risk patients, but this presumption is not well established.[12–15] Indeed, a recent post hoc analysis of CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) showed that patients in the lowest tertile of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) had greater benefit from rosuvastatin compared with patients in higher tertiles.[15] Higher plasma NT-proBNP concentrations may identify patients with more advanced HF that is refractory to the benefits of a particular therapy. Post hoc analyses of data from the Irbesartan in Heart Failure with Preserved Ejection Fraction Trial (I-PRESERVE) were conducted to explore the relationship of baseline measurements of NT-proBNP with prognosis and to test for interactions with the effects of the angiotensin receptor blocker irbesartan.

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Methods

Study Design and Patient Selection

I-PRESERVE was a randomized, placebo-controlled, double-blind, multicenter trial that enrolled 4128 men and women with symptomatic HFpEF to evaluate the efficacy of the angiotensin receptor blocker irbesartan.[16] Briefly, patients aged ≥60 years with symptomatic (New York Heart Association class II to IV) HF, a left ventricular (LV) EF ≥45%, and at least 1 hospitalization for HF during the previous 6 months were eligible for enrollment. Patients who had not been hospitalized were required to have ongoing class III or IV symptoms with corroborative evidence of HF or a likely substrate for HFpEF, such as electrocardiographic or echocardiographic evidence of LV hypertrophy or, if atrial fibrillation was absent, left atrial enlargement. The primary end point was the composite of all-cause mortality and protocol-specified cardiovascular hospitalizations (HF, myocardial infarction, stroke, ventricular or atrial arrhythmias). The secondary end points were (1) all-cause mortality and (2) the composite of HF death or hospitalization. Deaths and hospitalizations were adjudicated by a blinded independent end point committee, using prespecified criteria.

NT-proBNP and Other Measurements

Plasma NT-proBNP was measured at baseline in 3480 (84%) of the 4128 patients. The baseline characteristics of patients with NT-proBNP measurements included in this analysis were not different from all the patients randomized in the study, as shown in a previous publication.[17] Plasma samples drawn at baseline were stored at −20°C, and NT-proBNP was measured using Elecsys 2010 (Roche Diagnostic; Basel, Switzerland) in a central laboratory (LabCorp Belgium). Several other laboratory variables, such as hemoglobin, serum albumin, electrolyte, and creatinine levels, also were measured at baseline. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation.[18] The large number of other baseline variables and their relationships to plasma NT-proBNP in the I-PRESERVE cohort have been reported previously.[17] The presence of atrial fibrillation, estimated glomerular filtration rate, and age were the strongest correlates of baseline NT-proBNP.

Data Analysis

First, the relationship between the natural logarithm of the skewed distribution of baseline levels of NT-proBNP were entered into Cox regression models along with several other baseline assessments to confirm that NT-proBNP was independently associated with the study end points. Indicator variables representing the quartiles of the baseline NT-proBNP levels also were analyzed to examine the trend in estimates of the natural logarithm of the hazard ratio (HR), the dependent variable in Cox models. Testing for interactions with treatment is greatly simplified by a 2-way split of subjects, and statistical power is enhanced by analysis of larger subgroups with extreme differences.[19] Furthermore, in practice, patients often are split into only a few prognostic groups that are treated differently, or a single threshold value is set for enrollment of subjects into clinical trials. Because there are no predefined thresholds of NT-proBNP for selecting patients who might benefit more or less from treatment with an angiotensin II receptor blocker, analyses were done by arbitrarily splitting the sample, using the median NT-proBNP, into 2 risk groups. Recognizing that the median in this sample is not necessarily the most informative threshold for using NT-proBNP to select patients for a clinical trial and the potential loss of information when using a dichotomous split rather than a continuous measure, the median split of NT-proBNP was entered into Cox regression models to at least be assured that this particular split was independently associated with the study end points.

The adjusted models included the following baseline variables that have been associated with ≥1 study outcome: age, sex, New York Heart Association class, ischemic etiology, hypertension etiology, history of atrial fibrillation, history of diabetes, history of chronic obstructive pulmonary disease, hospitalization in the previous 6 months, body mass index, presence of jugular venous distension, systolic blood pressure, heart rate, hemoglobin level, pulmonary congestion on chest radiograph, EF, estimated glomerular filtration rate, serum albumin, sodium, and neutrophil count. This list includes all the I-PRESERVE variables included in the recently developed prognostic models except for the Minnesota Living with Heart Failure score, which was not collected for a substantial fraction of the subjects in the present analysis, and a history of myocardial infarction, which is somewhat redundant with the variable indicating an ischemic etiology for HF.[6]

Cox regression analyses of the study outcomes were used to test for interactions between treatment (irbesartan or placebo) and the NT-proBNP subgroups. First, the treatment effect (HR) was examined in each quartile of baseline NT-proBNP. Because the treatment effect was similar in the 2 lower quartiles and in the 2 upper quartiles for all end points, the test for interaction using the median split was believed to be reasonable. Whenever the test for the interaction term was significant, suggesting that the effect of irbesartan was not the same in the 2 subgroups defined by the median NT-proBNP, the effect of irbesartan was examined in each subgroup separately. Unadjusted Kaplan-Meier curves for the irbesartan and placebo groups within each NT-proBNP subgroup were compared by the log-rank test. The baseline characteristics of the irbesartan and placebo groups were compared within each NT-proBNP subgroup (Student t test for continuous variables, χ^2 test of proportions) and were added to Cox regression analyses of the treatment effect within each subgroup to help determine whether baseline differences could explain any observed treatment effects within an NT-proBNP subgroup. Additional analyses added a set of baseline covariates that were associated with the baseline NT-proBNP and study end points and might have confounded the test for interaction.

SPSS version 12.0 (SPSS Inc; Chicago, IL) statistical software was used for all analyses. A 2-tailed $P \leq 0.05$ was considered statistically significant without adjustments for making multiple comparisons in these exploratory analyses.

Results

Association Between Baseline NT-proBNP and Outcome Events

The NT-proBNP levels at baseline were highly skewed, ranging from 0 to 28 670 pg/mL with a mean±SD of 869±1746 pg/mL and median of 339 pg/mL (interquartile range, 133 to 964 pg/mL). During a mean follow-up of 49.5

Table 1. Univariable and Multivariable Analysis of Study End Points by Baseline NT-proBNP as a Continuous Variable and by Quartile

	Events/Patients (% Events)	HR (ln HR)	95% CI	*P*
Primary end point				
ln NT-proBNP*	1248/3480 (35.9)	1.76	1.68–1.85	<0.001
ln NT-proBNP†	1175/3260 (36.0)	1.46	1.37–1.57	<0.001
NT-proBNP Q1†	137/831 (16.5)		Reference	
NT-proBNP Q2†	227/807 (28.1)	1.62 (0.482)	1.31–2.00	<0.001
NT-proBNP Q3†	331/814 (40.7)	2.04 (0.713)	1.66–2.52	<0.001
NT-proBNP Q4†	480/808 (59.4)	3.05 (1.115)	2.49–3.79	<0.001
All-cause mortality				
ln NT-proBNP*	735/3480 (21.1)	1.91	1.79–2.03	<0.001
ln NT-proBNP†	695/3260 (21.3)	1.57	1.45–1.71	<0.001
NT-proBNP Q1†	67/831 (8.1)		Reference	
NT-proBNP Q2†	113/807 (14.0)	1.55 (0.438)	1.14–2.98	0.005
NT-proBNP Q3†	180/814 (22.1)	2.05 (0.718)	1.53–2.75	<0.001
NT-proBNP Q4†	335/808 (41.5)	3.68 (1.303)	2.74–4.95	<0.001
HF composite outcome				
ln NT-proBNP*	598/3480 (17.2)	1.92	1.79–2.06	<0.001
ln NT-proBNP†	561/3260 (17.2)	1.44	1.31–1.58	<0.001
NT-proBNP Q1†	42/831 (5.1)		Reference	
NT-proBNP Q2†	106/807 (13.1)	2.3 (0.833)	1.61–3.30	<0.001
NT-proBNP Q3†	158/814 (19.4)	2.62 (0.963)	1.84–3.73	<0.001
NT-proBNP Q4†	255/808 (31.6)	3.72 (1.314)	2.59–5.34	<0.001

The following baseline variables were included in the multivariable analysis: age, sex, New York Heart Association class, ischemic etiology, hypertension etiology, history of atrial fibrillation, history of diabetes, history of chronic obstructive pulmonary disease, hospitalization in the previous 6 months, body mass index, jugular venous distension, systolic blood pressure, heart rate, hemoglobin level, pulmonary congestion on chest radiograph, ejection fraction, estimated glomerular filtration rate, serum albumin, sodium, and neutrophil count. HF indicates heart failure; HR, hazard ratio; ln, natural logarithm; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q, quartile.

*Univariable analysis.

†Multivariable analysis.

months, 1248 (35.9%) of the 3480 patients with an NT-proBNP measurement at baseline had a primary end point, 735 (21.1%) died, and 598 (17.2%) had an HF composite outcome.

Baseline natural logarithm NT-proBNP as a continuous variable was independently associated with an increased risk of all end points, even after adjustment for several other baseline characteristics (Table 1). As reported for septile of baseline NT-proBNP,[6] there was a progressive approximately linear increase in the logarithm of the HRs across quartiles of NT-proBNP and in the crude percentage of patients who experienced each outcome during follow-up (Figure 1, Table 1). Collapsing the quartiles above and below the median, the adjusted risks of the primary end point (HR, 1.79; 95% CI, 1.56 to 2.10; $P<0.001$), all-cause mortality (HR, 2.04; 95% CI, 1.68 to 2.47; $P<0.001$), and composite of HF events (HR, 1.77; 95% CI, 1.43 to 2.20; $P<0.001$) were all higher in patients with above-median NT-proBNP (Table 2).

Interaction Between Baseline NT-proBNP and Irbesartan Effect

As previously reported, irbesartan had no significant effect on the primary or secondary outcomes in the entire I-PRESERVE cohort or in the 8 prespecified subgroups (age, sex, EF, use of angiotensin-converting enzyme inhibitors, use of β-blockers, diabetes, hospitalization for HF within 6-months, and geographic region) defined by other baseline characteristics.[16] The analysis of interactions with baseline NT-proBNP concentration, reported in the study, was not prespecified. Nevertheless, as seen in Table 3, HRs for the treatment effect in NT-proBNP quartiles 1 and 2 for all outcomes are similar; hence, these 2 quartiles were combined, as were quartiles 3 and 4. There was a significant interaction between the effect of irbesartan and the median split of the baseline NT-proBNP for the primary outcome ($P=0.005$), all-cause mortality ($P=0.05$), and the HF composite outcome ($P<0.0001$) (Table 3). The interaction was due to a beneficial effect of irbesartan seen in patients below, but not above, the median NT-proBNP level. In the subgroup with NT-proBNP below the median, the primary composite outcome occurred in 24.7% patients in the placebo group and 19.1% in the irbesartan group (HR, 0.74; 95% CI, 0.60 to 0.90; $P=0.003$); all-cause mortality occurred in 12.3% patients in the placebo group and 9.4% in the irbesartan group (HR, 0.75; 95% CI, 0.56 to 0.99; $P=0.046$); and the HF composite outcome occurred in 11.0% patients in the placebo group and 6.6% in

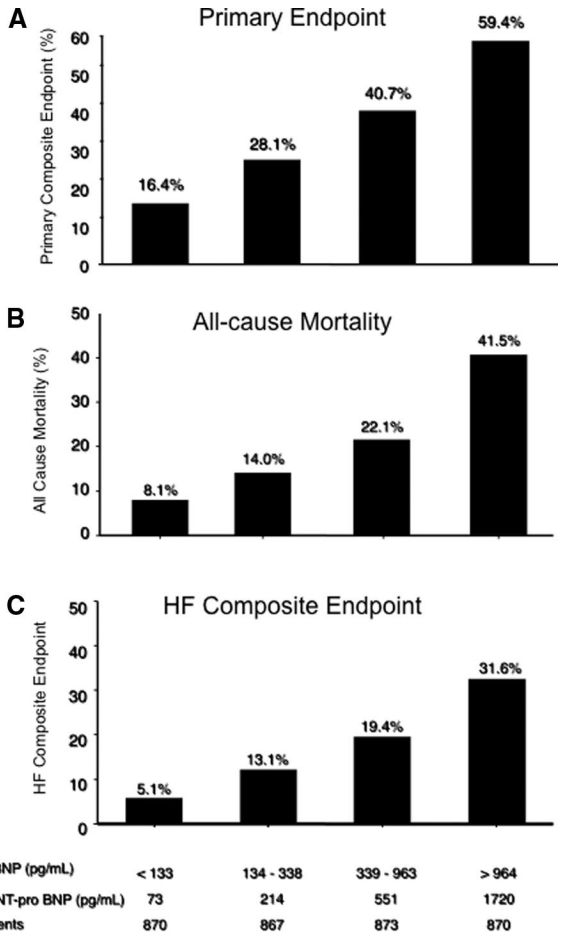

Figure 1. Crude event rates for the primary composite outcome (**A**), all-cause mortality (**B**), and HF composite outcome (**C**) by quartile of baseline NT-proBNP. HF indicates heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide.

the irbesartan group (HR, 0.57; 95% CI, 0.41 to 0.80; $P=0.001$). Figure 2 shows the unadjusted time-to-event curves by treatment group for the time to first primary outcome, all-cause mortality, and first HF outcome in the subgroups defined by the NT-proBNP median split. As can be seen, the beneficial effects of irbesartan were only evident in the group with NT-proBNP below the median.

Baseline characteristics of patients stratified by NT-proBNP and assigned treatment were examined to determine whether the irbesartan effects that were apparent below the median baseline NT-proBNP might be explained by an imbalance in the baseline characteristics in the irbesartan and placebo subgroups (Table 4). There were no significant differences between the placebo and irbesartan groups below or above the baseline NT-proBNP level. After adjusting for 20 small, but nonsignificant baseline differences between the placebo and irbesartan groups (see list in the Data Analysis section), irbesartan still appeared to have a beneficial effect on the primary composite outcome (HR, 0.74; 95% CI, 0.60 to 90; $P=0.003$), all-cause mortality (HR, 0.75; 95% CI, 0.56 to 0.99; $P=0.046$), and the HF composite outcome (HR, 0.57; 95% CI, 0.41 to 0.80; $P=0.001$) in the group below the median NT-proBNP.

Some differences were observed between patients who fell above or below the median NT-proBNP (Table 4), particularly in the prevalence of atrial fibrillation and in median estimated glomerular filtration rate that were previously shown to be correlated with the NT-proBNP levels. When the test for interaction was repeated to include either or both of these variables as covariates, the interaction between treatment and NT-proBNP remained significant for all end points.

Discussion

Previous studies have found that natriuretic peptide levels are elevated in patients with HFrEF and independently correlated with mortality and morbidity.[1,2] Therefore, some have suggested that these biomarkers should be used to select patients at higher risk for enrollment in clinical trials. In patients with HFpEF, although natriuretic peptide levels also are increased,[3–6,17,20,21] the relationship with outcomes has been studied prospectively in only a few cohorts.[3] Furthermore, whether patients with higher levels of natriuretic peptides, and hence risk, are more likely to benefit from treatments has not been reported. The results of this secondary analysis of data collected for the I-PRESERVE, a large cohort of well-characterized patients with HFpEF, confirm that plasma NT-proBNP concentrations are independently associated with higher rates of all-cause mortality alone or as a composite with cardiovascular hospitalizations.[6]

Table 2. Relative HR and 95% CI of Primary End Point, All-Cause Mortality, HF Composite Event (Sudden Death and HF Deaths) in Relation to Baseline NT-proBNP Median (339 pg/mL)

	Events/Patients (% Events)	HR	95% CI	*P*
Primary end point				
Baseline NT-proBNP median	1248/3480 (35.9)	2.83	2.51–3.20	<0.001
Baseline NT-proBNP+covariates*	1175/3260 (36)	1.79	1.56–2.10	<0.001
All-cause mortality				
Baseline NT-proBNP median	735/3480 (21.1)	3.31	2.80–3.90	<0.001
Baseline NT-proBNP+covariates*	695/3259 (21.3)	2.04	1.68–2.47	<0.001
HF composite event				
Baseline NT-proBNP median	598/3480 (17.2)	3.44	2.86–4.13	<0.001
Baseline NT-proBNP+covariates*	561/3260 (17.2)	1.77	1.43–2.20	<0.001

Abbreviations as in Table 1.
*Adjusted for covariates listed in Table 1.

Table 3. Event Rates and Adjusted* Relative HR of the Primary End Point, All-Cause Mortality, and HF Outcomes by Quartile and Median Baseline NT-proBNP Patient Subgroups

			Cox Model		
	Placebo	Irbesartan	HR	95% CI	*P*
Quartile analysis					
Primary end point					
Q1	82/452 (18.1)	61/418 (14.6)	0.78	0.561–1.089	0.146
Q2	141/451 (31.3)	98/416 (23.6)	0.71	0.545–0.912	0.008
Q3	167/427 (39.1)	186/446 (41.7)	1.054	0.856–1.299	0.619
Q4	248/427 (58.1)	265/443 (59.8)	1.058	0.890–1.259	0.521
All-cause mortality					
Q1	37/452 (8.2)	32/418 (7.7)	0.92	0.571–1.472	0.72
Q2	74/451 (16.4)	46/416 (11.1)	0.65	0.449–0.937	0.021
Q3	90/427 (21.1)	101/446 (22.6)	1.046	0.787–1.389	0.758
Q4	171/427 (40)	184/443 (41.5)	1.037	0.842–1.278	0.0729
HF composite outcomes					
Q1	27/452 (6)	18/418 (4.3)	0.7	0.388–1.280	0.25
Q2	72/451 (16)	37/416 (8.9)	0.52	0.346–0.765	0.001
Q3	75/427 (17.6)	93/446 (20.9)	1.18	0.871–1.6	0.285
Q4	129/427 (30.2)	147/443 (33.2)	1.11	0.877–1.408	0.381
Median analysis					
Primary end point					
NT-proBNP <339 pg/mL	223/903 (24.7)	159/834 (19.1)	0.74	0.60–0.90	0.003
NT-proBNP >339 pg/mL	415/854 (48.6)	451/889 (50.7)	1.05	0.92–1.20	0.47
					0.005†
All-cause mortality					
NT-proBNP <339 pg/mL	111/903 (12.3)	78/834 (9.4)	0.75	0.56–0.99	0.046
NT-proBNP >339 pg/mL	261/854 (30.6)	285/889 (32.1)	1.03	0.87–1.22	0.71
					0.05†
HF composite outcomes					
NT-proBNP <339 pg/mL	99/903 (11)	55/834 (6.6)	0.57	0.41–0.80	0.001
NT-proBNP >339 pg/mL	204/854 (23.7)	240/889 (27)	1.13	0.94–1.37	0.19
					<0.0001†

Data are presented as no. events/no. patients (%), unless otherwise indicated. Abbreviations as in Table 1.
*Adjusted for covariates listed in Table 1.
†*P* for interaction.

Perhaps the most interesting and unexpected finding of the present study is that it does not support the notion that the benefits of treatment with an angiotensin II receptor blocker are more likely to be detected in patients with higher levels of NT-proBNP. The present data do not allow us to address the possible mechanisms underlying this finding. Perhaps patients with HFpEF and higher levels of NT-proBNP have advanced structural disease that is not amenable to this pharmaceutical intervention. In a study of 119 patients with Doppler echocardiographically confirmed diastolic dysfunction, the highest levels of BNP were seen in patients with worse LV diastolic function and more restrictive filling.[21] Likewise, in a small study of 181 patients, the median NT-proBNP in patients with normal or mild diastolic dysfunction (n=109) was 376 pg/mL compared with 1419 pg/mL in patients with moderate to severe diastolic dysfunction (n=72).[22] Therefore, if advanced diastolic dysfunction with restrictive filling represents a structurally irreversible stage in the natural history of HFpEF, therapy may be less beneficial in such patients. However, because the I-PRESERVE enrollment criteria did not include Doppler echocardiographic measurements for inclusion into the study, we do not have data to support this hypothesis. Furthermore, patients with higher levels of NT-proBNP have other risk factors, such as atrial fibrillation and worse renal function, that may be less amenable or even aggravated by a particular treatment. However, adjusting for these types of differences did not explain the observed interaction.

The findings of this post hoc analysis should not be extrapolated to HFrEF or other forms of treatment for HFpEF. They may only apply to patients treated with angiotensin receptor blockers in the early stages of HFpEF. Prospectively designed studies are needed to confirm this finding and provide more insights into the observed interac-

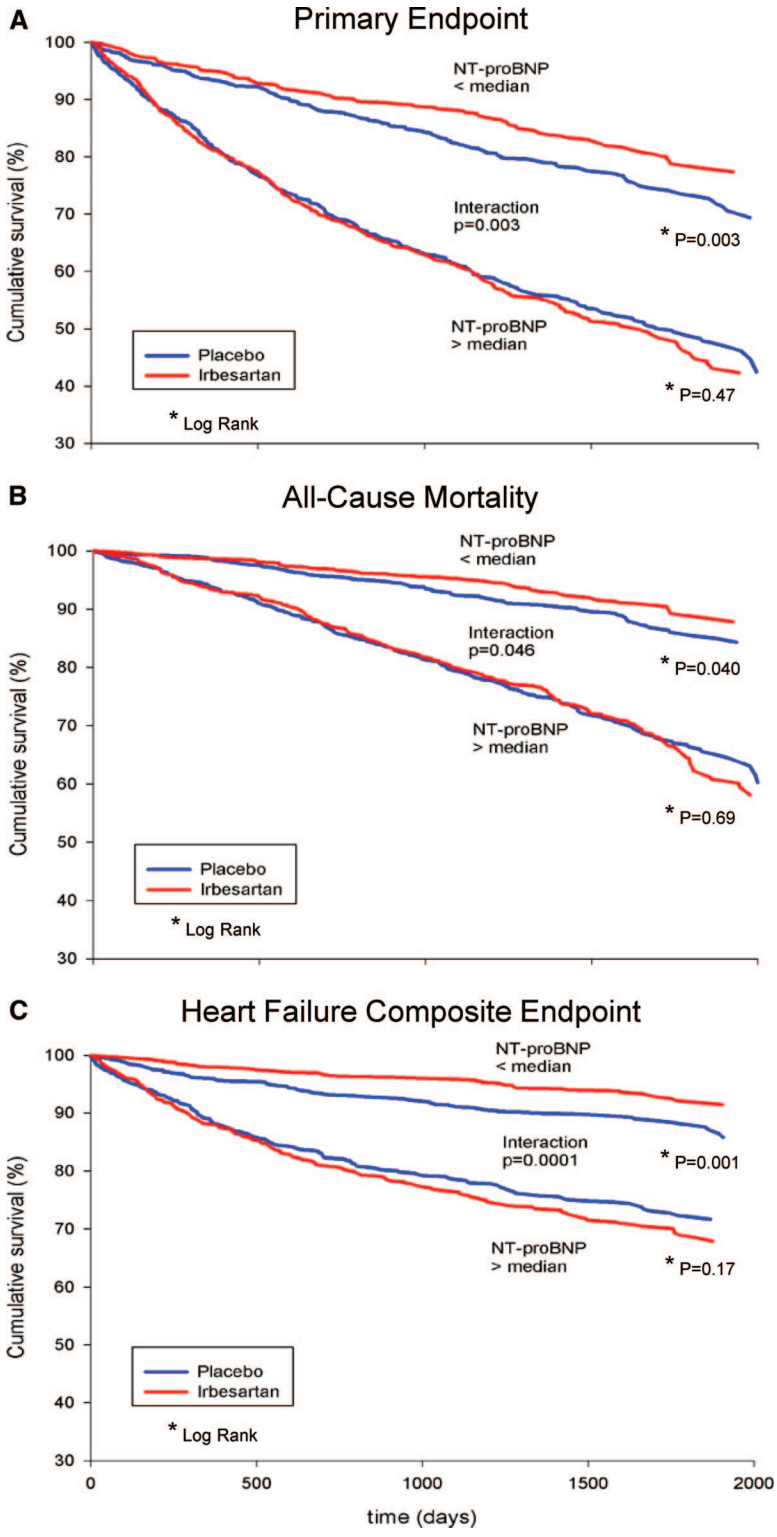

Figure 2. Kaplan-Meier curves for time to primary composite outcome (**A**), all-cause mortality (**B**), and HF composite outcome (**C**) in groups above and below the median baseline NT-proBNP. Abbreviations as in Figure 1.

tion between the effect of irbesartan or other treatments and NT-proBNP in patients with HFpEF. We are not aware of any other analyses to determine whether the effects of an angiotensin II receptor blocker depend on the circulating levels of NT-proBNP in patients with HFpEF. However, in PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) trial, there was a nonsignificant interaction between the angiotensin-converting enzyme inhibitor perindopril and NT-proBNP that appeared to be in the opposite direction of the present study.[14] Even in HFrEF, only 1 study (Australia-New Zealand Carvedilol Heart Failure Trial)[12] has shown a significantly greater treatment effect in higher-risk patients with above-median baseline BNP, whereas no significant interaction was found between NT-proBNP and treatment ($P=0.93$) in COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival).[13] In contrast, in the CORONA trial that

Table 4. Baseline Characteristics in 3480 Patients by NT-proBNP Median and Treatment

	NT-proBNP Below Median (n=1737)			NT-proBNP Above Median (n=1737)		
	Placebo	Irbesartan	*P*	Placebo	Irbesartan	*P*
Age, y	70±6.5	70±6.4	0.96	74±7.1	73±6.9	0.11
Male sex	37	34.3	0.24	41	46.7	0.02
White race	93.6	93.2	0.62	93.9	94.4	0.83
NYHA class III+IV vs I+II	81.1	82.6	0.40	76.8	77.8	0.6
Ischemic etiology	20.6	21.5	0.68	28.1	31.5	0.04
Hypertension etiology	71.4	71.6	0.94	55.6	56.2	0.79
History						
Hospitalization in previous 6 mo	32.8	34.2	0.54	54.9	51.5	0.16
Angina pectoris	40	39.7	0.90	41.5	44.2	0.47
Myocardial infarction	18.2	18.9	0.68	29.2	30.1	0.65
Atrial fibrillation	12.2	11.2	0.50	47.7	44.8	0.23
Diabetes mellitus	25.9	24.3	0.45	29.4	30.9	0.48
Valvular disease	6.4	6.2	0.87	15.3	14.8	0.77
Stroke or TIA	7.8	8.6	0.50	11.2	10.8	0.77
COPD or asthma	8.5	6.1	0.06	9.3	12.4	0.04
Anemia at baseline	8.2	8.4	0.98	17.1	16.5	0.56
Body mass index, kg/m^2	30.2±5.1	30.2±5.3	0.97	28.8±5.1	29.2±5.1	0.16
Systolic BP, mm Hg	136±14	138±14	0.03	136±15	136±15	0.92
Diastolic BP, mm Hg	80±8	79±8	0.78	78±9.4	79±9.3	0.70
Heart rate, beats/min	71±9	71±9	0.81	72±11	72±11	0.31
ECG, CXR, and echocardiography variables						
LBBB	6.9	7.7	0.52	9.6	9.7	0.96
LV hypertrophy	29	29	0.99	31	31	0.95
Pulmonary congestion CXR	31.2	34.3	0.18	49.1	46.8	0.35
LVEF	61±8.7	61±8.9	0.13	58.5±9.2	57.6±9.3	0.052
Clinical chemistry						
Albumin, g/dL	4.28±1.4	4.24±1.4	0.6	4.75±0.2.0	4.77±0.1.8	0.81
Sodium, mmol/L	140±3	140±3	0.91	139±3	139±3	0.87
Potassium, mmol/L	4±0.5	4±0.4	0.46	4.0±0.49	4.0±0.5	0.45
Hemoglobin, g/dL	14±1.9	14±1.9	0.64	14±2.0	14±1.9	0.11
Neutrophil count, 1000 cells/μL	4.2±1.5	4.2±1.4	0.57	4.8±2.1		0.82
eGFR, mL/min per 1.73 m^2	78±22	78±21	0.98	67±21	67±22	0.87
NT-proBNP, pg/mL	149±88	147±88	0.45	1573±2147	1603±2338	0.79
Medications						
ACE inhibitor	22	23	0.56	28	29	0.52
β-blocker	58	56.	0.49	60	64	0.09
Calcium channel blocker	45	46	0.59	34	37	0.33
Digitalis	5.1	5.2	0.94	22	22	0.85
Diuretic	79	78	0.68	88	86	0.29
Spironolactone	12	12	0.99	20	19	0.34
Aspirin	56	60	0.06	52	55	0.28
Lipid-lowering agents	30	34	0.06	28	31	0.14

Data are presented as mean±SD or %. ACE indicates angiotensin-converting enzyme; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CXR, chest radiograph; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LV, left ventricular; LVEF, LV ejection fraction; NYHA, New York Heart Association; TIA, transient ischemic attack. Other abbreviation as in Table 1.

investigated the effect of rosuvastatin in patients with moderate to severe HFrEF, a significant treatment interaction with NT-proBNP was observed.[15] Rosuvastatin had no effect on the primary end point (CV mortality, nonfatal myocardial infarction, and nonfatal stroke) in the overall cohort but improved outcomes in patients in the lowest tertile of NT-proBNP (<868 pg/mL). This was consistent with observations in ≈20 000 patients with a broad range of severity of

cardiovascular disease who had NT-proBNP measured in the Heart Protection Study.[23] Thus, although measurement of natriuretic peptide levels remains extremely useful in identifying patients with a cardiac cause of their symptoms, particularly those with HFpEF where diagnosis of diastolic dysfunction may be difficult using Doppler echocardiographic criteria, the assumption is that treatments are always more likely to benefit patients with higher baseline levels of natriuretic peptides and risk, should be carefully examined before using levels of natriuretic peptides to select patients for clinical trials.

Another interesting finding is that the nature of the relationship between mortality and the logarithm of NT-proBNP levels in the present study is similar to that reported in studies of HFrEF with similar severity of HF, even though the baseline levels of NT-proBNP tend to be 2 to 4 times greater in HFrEF.[2,15,17,20,24] For example, the median NT-proBNP of 339 pg/mL in the present study is similar to the median value of 409 pg/mL seen in the PEP-CHF trial, which randomized similar patients with HFpEF to the angiotensin-converting enzyme inhibitor perindopril.[15] In contrast, in the Valsartan Heart Failure Trial, the median baseline NT-proBNP was 903 pg/mL, and the natural logarithm of NT-proBNP was associated with an adjusted HR for all-cause mortality of 1.5 (95% CI, 1.3 to 1.6), similar to the HR of 1.6 (95% CI, 1.5 to 1.7) found in the present analysis. The difference in NT-proBNP levels between HFrEF and HFpEF may be related to lower LV diastolic wall stress in HFpEF due to smaller LV volumes and thicker LV walls that would be expected to produce smaller increases in natriuretic peptides.[25] Hence, despite the potential differences in the levels and mechanisms for the increase in natriuretic peptides in HFrEF and HFpEF, the prognostic information provided by NT-proBNP appears to be similar in the 2 types of HF and consistent with an overall linear relationship between the logarithms of the HRs and NT-proBNP.

A major limitation of this secondary analysis of data from I-PRESERVE is that the findings might be spurious and need to be confirmed in other samples. Furthermore, we used a somewhat arbitrary and retrospective level of NT-proBNP to classify patients into different risk groups and to test for the interaction. Additional studies are needed to confirm our results and find the best threshold to identify patients who benefit. Nevertheless, the present results suggest that one should not assume that patients at higher risk are always more likely to benefit from a treatment. However, the effect of treatment on absolute benefit may be small in patients already at low risk.

In conclusion, levels of NT-proBNP are elevated in HFpEF but to a lesser extent than in HFrEF. However, the prognostic information provided by NT-proBNP appears to be similar in the 2 types of HF. In this post hoc analysis of I-PRESERVE data, the use of irbesartan was associated with improved outcomes only in patients with HFpEF without substantially elevated NT-proBNP. This apparent benefit of irbesartan in lower-risk patients with HFpEF may indicate an effect of the drug earlier, but not later, in the natural history of the disease when structural changes might not be responsive to a therapeutic intervention. The strategy of using elevated plasma concentrations of natriuretic peptides as a patient selection criterion in trials of HFpEF should be reconsidered in the light of these results, which may help to set appropriate thresholds or abandon them all together.

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CLINICAL PERSPECTIVE

Natriuretic peptides are independent predictors of adverse outcomes in patients with heart failure (HF) and reduced ejection fraction, but data to support their role in HF and preserved ejection fraction are limited. Several recent HF trials have excluded patients with low natriuretic peptide levels to increase the likelihood of including patients with more severe HF and to increase the number of outcome events. This approach also assumes that the study intervention will have a greater effect in higher-risk patients, but this presumption is not well established. We tested this hypothesis in a post hoc analysis of 3480 patients in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Trial) who had a baseline measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP). Baseline NT-proBNP level was independently associated with an increased risk of all end points measured. Overall, irbesartan had no effect of any of the outcomes; however, its use was associated with improved outcomes in patients with NT-proBNP levels below, but not above, the median. After adjusting for 20 baseline covariates, irbesartan still had a beneficial effect on the primary outcome (hazard ratio, 0.74; 95% CI, 0.60 to 90; $P=0.003$), all-cause mortality (hazard ratio, 0.75; 95% CI, 0.56 to 0.99; $P=0.046$), and HF composite outcome (hazard ratio, 0.57; 95% CI, 0.41 to 0.80; $P=0.001$) in patients with NT-proBNP below the median. These findings may indicate a beneficial effect of irbesartan on early, but not later, high-risk stages of the disease and question the strategy of using elevated natriuretic peptide level as a patient selection criterion in HF with preserved ejection fraction trials. More studies are needed to support or contest this practice.

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Prognostic Value of Baseline Plasma Amino-Terminal Pro-Brain Natriuretic Peptide and Its Interactions With Irbesartan Treatment Effects in Patients With Heart Failure and Preserved Ejection Fraction: Findings From the I-PRESERVE Trial

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