Prognostic Value of N-Terminal Pro-B-Type Natriuretic Peptide Levels in Heart Failure Patients With and Without Atrial Fibrillation

See Editorial by Voors and Lam

BACKGROUND: Patients with heart failure (HF) and atrial fibrillation (AF) have higher circulating levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide) than HF patients without AF. There is uncertainty about the prognostic importance of a given concentration of NT-proBNP in HF patients with and without AF. We investigated this question in a large cohort of patients with HF and reduced ejection fraction.

METHODS AND RESULTS: We studied 14 737 patients with HF and reduced ejection fraction and a measurement of NT-proBNP at time of screening, enrolled in either the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) or the ATMOSPHERE trial (Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure), of whom 3575 (24%) had AF on their baseline ECG. Median (Q1, Q3) levels of NT-proBNP were 1817 pg/mL (1095–3266 pg/mL) in those with AF and 1271 pg/mL (703–2569 pg/mL) in those without (P<0.0001). Patients with AF were older (67 versus 62 years), had worse New York Heart Association class (III/IV; 36% versus 24%), and experienced fewer previous HF hospitalizations (52% versus 61%) or myocardial infarction (30% versus 46%); all P<0.001. We categorized patients with and without AF into 5 NT-proBNP bands: <400, 400 to 999 (reference), 1000 to 1999, 2000 to 2999, and ≥3000 pg/mL. For the primary composite outcome of cardiovascular death or HF hospitalization, event rates differed for patients with and without AF in the lowest band (<400 pg/mL; 8.2 versus 5.0 per 100 patient-years), but not for the higher bands (400–999 pg/mL, 7.4 versus 7.7 per 100 patient-years; 1000–1999 pg/mL, 9.8 versus 11.4 per 100 patient-year; 2000–2999 pg/mL, 13.5 versus 13.4 per 100 patient-years; ≥3000 pg/mL, 22.7 versus 23.0 per 100 patient-years). These findings were consistent whether NT-proBNP was examined as a categorical or continuous variable and before and after adjustment for other prognostic variables. We found similar results for the components of the composite outcome and all-cause mortality.

CONCLUSIONS: HF and reduced ejection fraction patients with AF had higher NT-proBNP than those without AF. However, above a concentration of 400 pg/mL (representing most patients in each group), NT-proBNP had similar predictive value for adverse cardiovascular outcomes, irrespective of AF status.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier NCT00853658 (ATMOSPHERE) and NCT01035255 (PARADIGM-HF).

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WHAT IS NEW?

- Contemporary heart failure trials require a higher enrollment BNP/NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration in patients with atrial fibrillation, compared with those without atrial fibrillation. The principal assumption behind this approach is that patients with atrial fibrillation are at a lower risk of cardiovascular events for a given level of BNP/NT-proBNP than patients without atrial fibrillation with the same BNP/NT-proBNP concentration.
- Our findings, obtained from several randomized, controlled heart failure trials, suggest that this is incorrect.

WHAT ARE THE CLINICAL IMPLICATIONS?

- These findings are important for future design of clinical trials in heart failure but also relevant to everyday clinical practice.
- Our findings are robust as they are derived from a very large data set and are clinically relevant as they now inform physicians that the increment in risk related to higher BNP/NT-proBNP concentrations is similar in all patients with heart failure and reduced ejection fraction, irrespective of rhythm.

Levels of natriuretic peptides increase in heart failure (HF) in response to raised myocardial wall stretch and are thought to represent a protective compensatory response, inhibiting the renin–angiotensin–aldosterone system, stimulating natriuresis and reducing vascular tone.[1,2]

Measurement of natriuretic peptides is recommended as part of the diagnostic work-up for HF, and they may also be used to monitor response to treatment and provide prognostic information.[3–6] Because higher levels are associated with higher rates of cardiovascular death and hospital admission for worsening HF, natriuretic peptides are also used to select higher-risk patients for inclusion in clinical trials. Many factors are known to influence the level of natriuretic peptides, including age, obesity, renal function, and atrial fibrillation (AF).[7–9] Levels of natriuretic peptides are, on average, higher in patients with AF, and the prognostic significance of a given concentration of B-type natriuretic peptide (BNP) or NT-proBNP (N-terminal pro-B-type natriuretic peptide) in patients with AF, compared with those without AF, is uncertain. Because of this uncertainty, recent clinical trials in patients with HF and reduced ejection fraction (HFrEF) have used different natriuretic peptide inclusion thresholds for individuals with and without AF, with a higher requirement for the former patients. It is hoped that this strategy will ensure patients with AF have event rates no less than in those without AF. To examine whether this approach has any validity, we compared the relationship between NT-proBNP concentration and outcomes in patients with and without AF using data from 2 contemporary trials in patients with HFrEF, each of which had similar enrollment criteria.

METHODS

The design, baseline characteristics, and primary results of the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and the ATMOSPHERE trial (Aliskiren Trial to Minimize Outcomes in Patients With Heart Failure Trial) are published.[10–14] Both trials were approved by the ethics committee at each study center. All patients provided written informed consent.

Study Patients

The inclusion criteria for PARADIGM-HF and ATMOSPHERE were similar and included New York Heart Association (NYHA) functional class II–IV status, ejection fraction of ≤35% (initially ≤40% for PARADIGM-HF but changed to ≤35% by amendment), and a plasma BNP of ≥150 pg/mL or NT-proBNP of ≥600 pg/mL. In both trials, patients who had been hospitalized for HF within the preceding 12 months could be enrolled with a lower natriuretic peptide concentration (BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL). Plasma NT-proBNP was measured in a core laboratory with the Roche Elecsys proBNP assay (Roche Diagnostics GmbH, Mannheim, Germany), with a coefficient of variation <2.5% at all levels tested.

Patients were required to be taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at a dose equivalent to enalapril 10 mg daily for at least 4 weeks before screening, along with a stable dose of a β-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist if indicated. The exclusion criteria included history of intolerance of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, symptomatic hypotension (or a systolic blood pressure <100 mm Hg at screening/<95 mm Hg at randomization), an estimated glomerular filtration rate <30 mL/min per 1.73 m^2 (<40 mL/min per 1.73 m^2 for ATMOSPHERE), a serum potassium concentration of >5.2 mmol/L at screening and >5.4 mmol/L at randomization in PARADIGM-HF and; >5.0 and >5.2 mmol/L, respectively, in ATMOSPHERE), or a history of angioedema.

Study Procedures

In both PARADIGM-HF and ATMOSPHERE, patients first received enalapril (5 or)10 mg BID (single-blind) and then sacubitril/valsartan (single-blind) for an additional 4 to 6 weeks in PARADIGM-HF and aliskiren plus enalapril in ATMOSPHERE. In PARADIGM-HF, patients tolerating both drugs at target doses were randomly assigned to enalapril 10 mg BID or sacubitril/valsartan 200 mg BID, and in ATMOSPHERE, patients who tolerated both drugs were

randomized in a 1:1:1 ratio to receive (1) combination of 5 or 10 mg enalapril BID and aliskiren 150 mg OD (combination group), (2) aliskiren 150 mg OD, (3) enalapril 5 or 10 mg BID. The dose of enalapril was selected based on its effect to reduce the risk of death compared with placebo in the SOLVD treatment trial (Studies of Left Ventricular Dysfunction).[15]

Baseline NT-proBNP

We examined the relationship between baseline NT-proBNP category (NT-proBNP bands) and outcomes using NT-proBNP as a continuous measure (modeled as a restricted cubic spline—see below). Baseline NT-proBNP was measured at time of screening in each of the 2 trials. We defined the following NT-proBNP bands at baseline: <400, 400 to 999 (reference group), 1000 to 1999, 2000 to 2999, and ≥3000 pg/mL and applied these bands separately in patients with and without AF.

Outcomes

In the present article, we focused on the primary end point of both trials, which was the first occurrence of cardiovascular death or HF hospitalization, as well as each of the components separately. We also report death from any cause, which was a secondary end point in PARADIGM-HF and a prespecified exploratory outcome in ATMOSPHERE.

Statistical Analysis

Baseline characteristics are presented as means with SDs for continuous variables and frequencies and percentages for categorical variables. Unadjusted and age-adjusted event rates are reported per 100 patient-years of follow-up according to AF status and NT-proBNP band. Cox proportional hazard models were applied to calculate hazard ratios and cumulative event curves according to the level of NT-proBNP with patients with 400 to 999 pg/mL as reference, in patients with and without AF, respectively. The adjusted Cox regression models included information on age, sex, race (white versus all other), geographical region, study drug, NYHA class, ejection fraction, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate, HF duration, ischemic cause, history of recent HF hospitalization, and history of myocardial infarction. Log (–log(survival)) curves were used to evaluate the proportional hazard assumption. The assumption of linearity of continuous variables (age) was tested by including a variable of age squared. These were found to valid unless otherwise specified. NT-proBNP as a continuous variable and the outcomes of interest, according to the presence of AF, adjusted for other prognostic variables, is shown with NT-proBNP modeled as a restricted cubic spline (NT-proBNP, 600 pg/mL is the reference value). Furthermore, we repeated analyses in each trial separately. BNP was only available for patients in PARADIGM-HF, and similar analyses for that natriuretic peptide in that trial are included in the Data Supplement. All *P* values are 2-sided, and a *P* value of <0.05 was considered significant. Analyses were performed using Stata version 14 (Stata Corp., College Station, TX) and SAS version 9.4 (SAS Institute, NC).

RESULTS

A total of 14 737 patients had a measurement of NT-proBNP at baseline, of whom 3575 (24%) had AF on their baseline ECG. Median (Q1, Q3) levels of NT-proBNP were 1817 pg/mL (1095, 3266) in those with AF and 1271 pg/mL (703, 2569) in those without AF (*P*<0.0001). Patients with AF were older (67 versus 62 years, respectively), were more often white (81% versus 60%), had worse functional status (NYHA class III/IV; 36% versus 24%) but were less likely to have a previous HF hospitalization (52% versus 61%), a history of myocardial infarction (30% versus 46%), and implantable cardioverter defibrillator (8% versus 13%), all *P*<0.001 (Table 1).

Clinical Outcomes According to NT-proBNP

The clinical outcomes of interest, according to the baseline NT-proBNP category, are summarized in Table 2. The rate of the composite outcome, each of its components, and all-cause death were significantly higher in patients with levels of NT-proBNP >1000 pg/mL than in patients with levels of NT-proBNP with 400 to 999 pg/mL as reference. There was a step-wise increase in the risk of the primary composite outcome across the 5 predefined NT-proBNP bands in each of the 2 groups of patients (with and without AF). The only exception was in patients with AF in the 2 lowest bands (<400 and 400–999 pg/mL) where rates and risk did not differ significantly between bands although there were very few patients with AF (and even fewer events) in the lowest NT-proBNP band. In these 2 lowest NT-proBNP bands, there was significant interaction between AF status and risk of the primary outcome and all-cause mortality.

In patients with NT-proBNP >3000 pg/mL, the rate of the primary composite outcome was 23.0 per 100 patient-year in patients without AF and 22.7 per 100 patient-year in those with AF; the adjusted hazard ratio, compared with individuals in the 400 to 999 pg/mL band, was 2.73 (2.46–3.03) and 2.91 (2.37–3.58), respectively (*P* value for interaction between the risk of the primary outcome and the presence or absence of AF, 0.125). No interaction between AF status and NT-proBNP band was found for the other outcomes or when each trial was analyzed separately (data not shown). For age-adjusted event rates, we found a significant difference according to AF status for the primary outcome and all-cause death in patients with NT-proBNP <400 pg/mL (*P*=0.002 both), but not for the outcomes of cardiovascular death and HF hospitalization. No significant differences in age-adjusted rates according to AF status were found in the higher NT-proBNP bands.

A similar pattern was seen for each of the components of the primary composite outcome and all-cause

Table 1. Baseline Characteristics According to the Presence of AF on Baseline ECG

	No AF on ECG, n=11 162	AF on ECG, n=3575	*P* Value
Age, mean, y	62±12	67±11	<0.001
Female sex, n (%)	2487 (22)	702 (20)	<0.001
White, n (%)	6729 (60)	2894 (81)	<0.001
Region, n (%)			<0.001
North America	657 (6)	109 (3)	
Western Europe	1977 (18)	432 (12)	
Eastern Europe	2776 (25)	910 (26)	
South America	2844 (26)	1874 (45)	
Asia	2908 (26)	524 (13)	
Ejection fraction, %	28.6±6.1	29.1±5.5	<0.001
Systolic blood pressure, mm Hg	122±17	123±16	0.0002
Heart rate/min	71±11	76±14	<0.001
Body mass index	27.4±5.4	29.1±5.5	<0.001
Current smoker, n (%)	1663 (15)	361 (10)	<0.001
NYHA class, n (%)			<0.001
I	480 (4)	71 (2)	
II	8088 (73)	2211 (62)	
III	2512 (23)	1246 (35)	
IV	73 (1)	43 (1)	
Laboratory measurements			
eGFR, mL/min per 1.73 m^2, median (Q1, Q3)	70 (57, 84)	66 (55, 80)	<0.001
CKD (eGFR<60 mL/min per 1.73 m^2)	3254 (29)	1238 (35)	<0.001
NT-proBNP pg/mL, median (Q1, Q3)	1271 (703, 2569)	1817 (1095, 3266)	<0.001
<400 pg/mL	886 (8)	90 (3)	
400–999 pg/mL	3543 (32)	676 (19)	
1000–1999 pg/mL	3087 (28)	1181 (33)	
2000–2999 pg/mL	1315 (12)	628 (18)	
≥3000 pg/mL	2331 (21)	1000 (28)	
Medical history, n (%)			
Prior HF hospitalization	6451 (61)	2159 (52)	<0.001
Myocardial infarction	5182 (46)	1053 (30)	<0.001
Hypertension	7138 (64)	2699 (76)	<0.001
Stroke	813 (7)	351 (10)	<0.001
COPD	1296 (12)	479 (13)	0.003
Diabetes mellitus	3632 (33)	1112 (31)	0.015
ICD	1452 (13)	269 (8)	<0.001
CRT	798 (7)	129 (4)	<0.001
Pharmacotherapy, n (%)			
β-blocker	10 323 (93)	3294 (92)	0.4999
Diuretic	8775 (79)	3051 (85)	<0.001
MRA	5269 (47)	1747 (49)	0.0833
Digoxin	2742 (25)	1841 (52)	<0.001
Amiodarone	1117 (10)	280 (8)	0.001
Statin	6471 (58)	1558 (44)	<0.001

AF indicates atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimate glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association functional class.

Table 2. Outcomes of Interest According to the Presence of AF at Baseline and Bands of NT-proBNP

Outcome/NT-proBNP Band (pg/ml)	No AF on ECG					AF on ECG					*P* for Interact.
	Events/ Patients	Event Rate Per 100 py	Age-Adj. Event Rate Per 100 py	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Events/ Patients	Event Rate Per 100 py	Age-Adj. Event Rate Per 100 py	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	
CV death or HF hosp.,	3153/11 162	11.7	11.8			1087/3575	12.8	12.8			0.125
≤400	138/886	5.0	4.2	0.66 (0.55–0.79)	0.65 (0.54–0.78)	20/90	8.2	6.7	1.11 (0.70–1.78)	1.11 (0.69–1.78)	
400–999	721/3542	7.7	7.7	1.00 (Ref.)	1.00 (Ref.)	136/676	7.4	7.3	1.00 (Ref.)	1.00 (Ref.)	
1000–1999	844/3087	11.4	11.4	1.48 (1.34–1.63)	1.42 (1.28–1.57)	298/1181	9.8	9.9	1.32 (1.08–1.61)	1.34 (1.09–1.65)	
2000–2999	434/1315	14.8	14.9	1.91 (1.70–2.15)	1.81 (1.60–2.04)	200/628	13.5	13.9	1.80 (1.45–2.24)	1.80 (1.44–2.25)	
≥3000	1016/2331	23.0	23.1	2.96 (2.69–3.26)	2.73 (2.46–3.03)	433/1000	22.7	23.3	2.96 (2.44–3.59)	2.91 (2.37–3.58)	
CV death	2042/11 162	7.0	7.1			730/3575	7.8	7.6			0.134
≤400	902/886	3.2	3.2	0.75 (0.60–0.94)	0.73 (0.58–0.91)	15/90	5.9	4.7	1.27 (0.74–2.20)	1.23 (0.71–2.13)	
400–999	413/3542	4.1	4.1	1.00 (Ref.)	1.00 (Ref.)	89/676	4.6	4.5	1.00 (Ref.)	1.00 (Ref.)	
1000–1999	513/3087	6.3	6.4	1.55 (1.36–1.76)	1.48 (1.30–1.69)	191/1181	5.8	5.8	1.28 (1.00–1.65)	1.24 (0.96–1.60)	
2000–2999	281/1315	8.6	8.7	2.10 (1.81–2.45)	1.92 (1.64–2.24)	138/628	8.5	8.6	1.89 (1.45–2.46)	1.77 (1.35–2.33)	
≥3000	745/2331	14.8	14.8	3.67 (3.25–4.14)	3.15 (2.77–3.59)	297/1000	13.2	13.5	2.98 (2.35–3.78)	2.68 (2.08–3.46)	
HF hospitalization	1798/111 62	6.7	6.7			630/3575	7.4	7.4			0.267
≤400	75/886	2.7	2.7	0.60 (0.47–0.77)	0.61 (0.47–0.78)	10/90	4.1	3.0	1.03 (0.53–1.99)	1.06 (0.55–2.06)	
400–999	433/3542	4.6	4.6	1.00 (Ref.)	1.00 (Ref.)	74/676	4.0	4.0	1.00 (Ref.)	1.00 (Ref.)	
1000–1999	493/3087	6.6	6.7	1.43 (1.25–1.62)	1.37 (1.21–1.57)	173/1181	5.7	5.8	1.39 (1.06–1.83)	1.45 (1.10–1.92)	
2000–2999	227/1315	7.7	7.8	1.65 (1.40–1.93)	1.61 (1.36–1.90)	116/628	7.7	8.0	1.88 (1.41–2.52)	1.88 (1.39–2.54)	
≥3000	570/2331	12.9	13.0	2.72 (2.40–3.08)	2.65 (2.32–3.03)	257/1000	13.5	14.1	3.10 (2.39–4.02)	3.17 (2.40–4.18)	
All-cause mortality	2439/11 162	8.3	8.5			881/3575	9.4	9.1			0.102
≤400	110/886	3.9	3.9	0.74 (0.60–0.91)	0.74 (0.60–0.92)	23/90	9.0	6.7	1.63 (1.04–2.55)	1.52 (0.96–2.41)	
400–999	508/3543	5.1	5.1	1.00 (Ref.)	1.00 (Ref.)	107/676	5.5	5.4	1.00 (Ref.)	1.00 (Ref.)	
1000–1999	623/3087	7.7	7.8	1.53 (1.36–1.72)	1.46 (1.30–1.65)	234/1181	7.1	7.0	1.30 (1.04–1.64)	1.23 (0.98–1.55)	
2000–2999	340/1315	10.4	10.5	2.07 (1.81–2.38)	1.89 (1.64–2.18)	167/628	10.3	10.4	1.90 (1.49–2.42)	1.72 (1.34–2.21)	
≥3000	858/2331	17.0	17.2	3.44 (3.09–3.85)	2.99 (2.65–3.36)	350/1000	15.5	15.5	2.91 (2.34–3.62)	2.52 (2.00–3.17)	

Adjusted for age, sex, race (white vs. all other), study drug, geographical region, New York Heart Association class, ejection fraction, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate (eGFR), HF duration, ischemic cause, history of recent HF hospitalization, and history of myocardial infarction. AF indicates atrial fibrillation; CI, confidence interval; CV, cardiovascular; HF hosp., heart failure hospitalization; HR, heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and py, patient-year.

mortality, with no significant interaction AF status and outcome for each NT-proBNP category (Table 2; Figure 1). The relation between NT-proBNP as a continuous variable and the outcomes of interest, according to the presence of AF, adjusted for other prognostic variables and with NT-proBNP of 600 pg/mL as the reference value is shown in Figure 2. Analyses of BNP in PARADIGM-HF showed very similar findings to those of NT-proBNP in PARADIGM-HF and ATMOSPHERE combined (Table I in the Data Supplement).

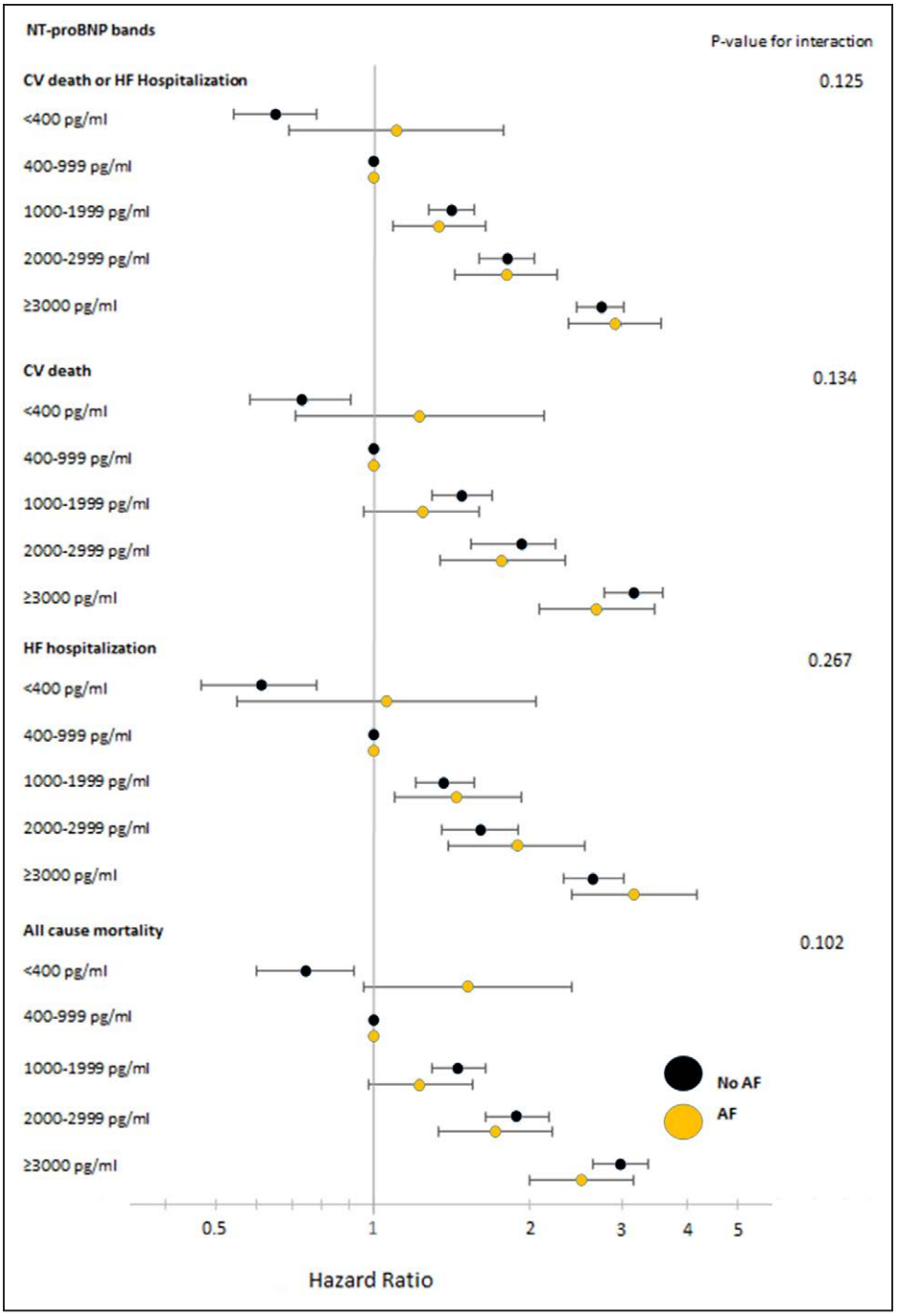

Figure 1. Forest plot of relation between baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide) and outcomes in patients with and without atrial fibrillation.
Adjusted for age, sex, race (white vs all other), study drug, geographical region, New York Heart Association class, ejection fraction, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate (eGFR), heart failure (HF) duration, ischemic cause, history of recent HF hospitalization, and history of myocardial infarction. AF indicates atrial fibrillation; and CV, cardiovascular.

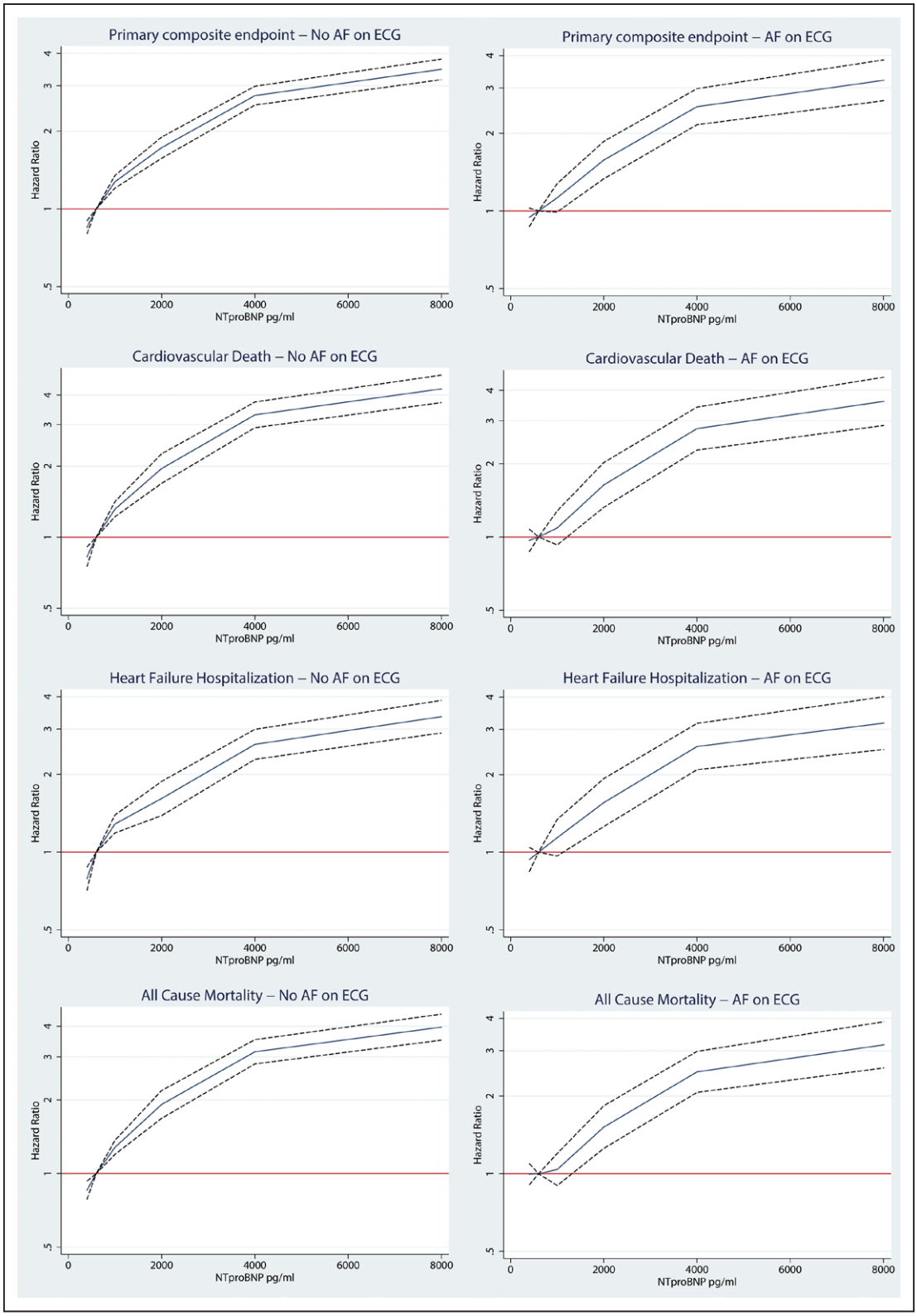

Figure 2. Restricted cubic splines of relation between baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide) and outcomes in patients with and without atrial fibrillation.

Interaction *P* values: Primary composite end point, *P*=0.1541; cardiovascular death, *P*=0.4349; heart failure hospitalization *P*=0.6869; all-cause mortality,*P*=0.4164. Adjusted for age, sex, race (white vs. all other), study drug, geographical region, New York Heart Association class, ejection fraction, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate, heart failure (HF) duration, ischemic cause, history of recent HF hospitalization, and history of myocardial infarction. AF indicates atrial fibrillation.

DISCUSSION

In this analysis, which included a large number of patients with HFrEF, we found that a given concentration of NT-proBNP was associated with a similar risk of cardiovascular death or hospitalization for HF in patients with and without AF. Patients with AF were less likely, however, to have a low NT-proBNP concentration. Our finding of similar risk related to NT-proBNP level was true whether comparing unadjusted outcomes or outcomes adjusted for other prognostic variables, some of which differed notably between patients with and without AF. These observations call into question the now common policy of requiring patients with AF to have a higher qualifying NT-proBNP (or BNP) for enrollment in clinical trials and the implicit assumption that a given natriuretic peptide concentration is not as predictive of an adverse outcome in patents with AF compared with those without. Our data show this not to be true, at least over the range from 400 pg/mL to 8000 pg/mL. Among individuals with a NT-proBNP of ≤400 pg/mL, patients without AF had lower events rates than those with AF (no clear differences were seen between patients with and without AF in any of the NT-proBNP bands >400 pg/mL). It is uncertain whether this apparent difference at NT-proBNP levels of <400 pg/mL is real or not and may just reflect the small numbers of patients (n=90) and events (n=20 patients with either cardiovascular death or HF hospitalization) in the AF group in this low NT-proBNP band. In any case, for clinical trials at least, this remaining uncertainty could be obviated simply by enrolling only patients with a NT-proBNP of >400 pg/mL.

There is a related question to consider. Do the same relationships apply for other natriuretic peptides? In a small study, in patients with more advanced HF (NYHA class III-IV), AF was an independent determinant of NT-proANP (N-terminal proatrial natriuretic peptide), but not of NT-proBNP levels, raising the possibility that atrial derived peptides might show different discrimination.[16] For BNP, we found the predictive value to be similar irrespective of AF status although only derived from patients in the PARADIGM-HF trial (Table I in the Data Supplement).

The explanation for our finding and why it contradicts conventional thinking is uncertain. Patients with AF had more adverse prognostic characteristics at baseline (eg, older age, worse NYHA class, and lower estimated glomerular filtration rate) and, for an equivalent level of NT-proBNP, their risk would have been greater than patients without AF had they been in sinus rhythm. In other words, their similar net risk to the overall risk in individuals without AF could have reflected a higher non–NT-proBNP–related risk and lower NT-proBNP–related risk. Apart from the unlikely scenario that these opposing risks would cancel each other out, adjusting for other prognostic factors did not meaningfully change the risk related to NT-proBNP in patients with AF (or in those without AF), probably reflecting the pre-eminence of natriuretic peptides as prognostic markers in HF. We used a separate reference group (NT-proBNP 400–999 pg/mL) in each of the 2 rhythm groups rather than a single reference group for all patients. Because the event rates were similar in this NT-proBNP band for each rhythm group, the use of 2 reference groups rather than 1 reference group did not change the interpretation of our findings. However, the relative risk for higher NT-proBNP bands within each rhythm stratum could have looked different had the event rate in 1 reference group been significantly higher or lower than in the other rhythm group.

We think our finding is important for clinical practice and, especially, for clinical trials in HFrEF. Physicians should not assume a higher natriuretic peptide concentration in a patient with AF merely reflects the presence of the arrhythmia and does not have the prognostic significance of the same level in a patient without AF—such thinking will underestimate the patients risk. Similarly, requirement for a higher entry natriuretic peptide threshold in patients with AF to enter a clinical trial, where the natriuretic peptide concentration is used as a means of ensuring a higher event rate, does not make sense and may result in a needlessly large screening-failure rate. These considerations may be different in HF and preserved ejection fraction where natriuretic peptides provide greater diagnostic security than in HFrEF as there is no investigative equivalent to a reduced EF in HF and preserved ejection fraction.[17]

Limitations

The current study has several limitations. It is a retrospective analysis, and the NT-proBNP bands used were not predefined. The fact that elevated BNP or NT-proBNP was required to get included in the study hampers the interpretation of the results in the lower bands. Our findings relate to HFrEF and whether the same is true for HF and preserved ejection fraction is not known. We only had data for BNP in PARADIGM-HF, which make these results less reliable.

Conclusions

In summary, above a concentration of 400 pg/mL, any given concentration of NT-proBNP had a similar predictive value for adverse outcomes in HFrEF patients with and without AF. Although NT-proBNP levels are, on average, higher in patients with AF, this does not diminish their prognostic import.

DISCLOSURES

Dr Jhund reports consulting and speakers fees from Novartis and research funding from Boehringer Ingelheim. Dr Mogensen reports speakers fees from Novo Nordisk and MSD. Drs Køber, Dickstein, and Abraham have received honoraria as steering committee members of ATMOSPHERE trial (Aliskiren Trial to

Minimize Outcomes in Patients With Heart Failure) from Novartis. Dr Zile reports consultant fees from Amgen, A-Z, Bayer, Bristol Myers Squibb, Capricor, Corvia, Eli Lilly, Giliad, Ironwood, Medtronic, Merck, Novartis, St. Jude Medical and research support from National Heart, Lung, and Blood Institute, Veterans Affairs, Department Of Defense, Medtronic and Novartis. Dr McMurray's employer, University of Glasgow, has received fees for his consulting or trial committee work with Abbvie, Amgen, AstraZeneca/Medimmune, Bayer, Bristol Myers Squibb, DalCor, GlaxoSmithKline, Merck, Novartis, Resverlogix, Sanofi-Aventis, and Stealth Therapeutics. Drs Desai and Solomon received honoraria as steering committee members of the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure). The other authors report no conflicts.

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FOOTNOTES

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Prognostic Value of N-Terminal Pro-B-Type Natriuretic Peptide Levels in Heart Failure Patients With and Without Atrial Fibrillation

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