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N-Terminal Pro-B-Type Natriuretic Peptide and Clinical Outcomes

Vericiguat Heart Failure With Reduced Ejection Fraction Study

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ABSTRACT

OBJECTIVES The purpose of this study was to examine the treatment effect of vericiguat in relation to N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at randomization.

BACKGROUND Vericiguat compared with placebo reduced the primary outcome of cardiovascular death (CVD) or heart failure hospitalization (HFH) in patients with HF with reduced ejection fraction (HFrEF) in the VICTORIA (A Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction) trial. Because an interaction existed between treatment and the primary outcome according to pre-specified quartiles of NT-proBNP at randomization, we examined this further.

METHODS This study evaluated the NT-proBNP relationship with the primary outcome in 4,805 of 5,050 patients as a risk-adjusted, log-transformed continuous variable. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented.

RESULTS Median NT-proBNP was 2,816 pg/ml (25th to 75th percentile: 1,556 to 5,314 pg/ml). The study treatment effect varied across the spectrum of NT-proBNP at randomization (with $\log^2$ transformation, p for interaction = 0.002). A significant association between treatment effects existed in patients with levels <4,000 pg/ml and remained evident up to 8,000 pg/ml. A 23% relative risk reduction occurred in the primary endpoint with NT-proBNP ≤4,000 pg/ml (HR: 0.77; 95% CI: 0.68 to 0.88). For NT-proBNP values ≤4,000 pg/ml (n = 3,100), the HR was 0.78 (95% CI: 0.67 to 0.90) for HFH and 0.75 (95% CI: 0.60 to 0.94) for CVD. For NT-proBNP ≤8,000 pg/ml (n = 4,133), the HR was 0.85 (95% CI: 0.76 to 0.95) for the primary outcome, 0.84 (95% CI: 0.75 to 0.95) for HFH, and 0.84 (95% CI: 0.71 to 0.99) for CVD. For NT-proBNP >8,000 pg/ml (n = 672), the HR was 1.16 (95% CI: 0.94 to 1.41) for the primary outcome.

CONCLUSIONS A reduction in the primary composite endpoint and its CVD and HFH components was observed in patients on vericiguat compared with subjects on placebo with NT-proBNP levels up to 8,000 pg/ml. This provided new insight into the benefit observed in high-risk patients with worsening HFrEF. (A Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction [HFrEF] [MK-1242-001] [VICTORIA]; NCT02861534)
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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CVD = cardiovascular death

HF = heart failure

HFH = heart failure hospitalization

HRrEF = heart failure with reduced ejection fraction

HR = hazard ratio

MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure

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

The measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a cornerstone for diagnosis, risk stratification, and follow-up of patients with heart failure (HF) (1). Accordingly, NT-proBNP levels have been widely used as an inclusion criterion for clinical trials and as surrogate metrics within studies to gauge the relationship between the treatment effect on this biomarker and overall outcomes (2). Because patient, trial, mechanism of treatment, or other factors may modulate the relationship between natriuretic peptides and outcomes, further understanding of these relationships is crucial for the interpretation of interventions and their impact on outcomes.

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The VICTORIA (A Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction) trial evaluated vericiguat compared with placebo in high-risk patients with HF and reduced ejection fractions (HFrEFs) who had a recent HF hospitalization (HFH) or intravenous diuretic therapy. The primary findings were a reduction in the primary composite outcome of cardiovascular death (CVD) or HFH with vericiguat compared with placebo (3). In a pre-specified subgroup analysis, a significant interaction was noted between NT-proBNP quartiles at randomization and the primary endpoint. Specifically, those patients in the highest quartile of NT-proBNP (>5,314 pg/ml) appeared to have less benefit from vericiguat compared with placebo; conversely, those in the lowest 3 quartiles derived greater benefit from vericiguat compared with placebo. Caution must be exercised in interpreting treatment effects from such subgroups because of the uncertainties about their biological plausibility versus the play of chance (4).

To further understand the NT-proBNP subgroup results, we explored the relationship of NT-proBNP across the spectrum of levels at randomization with the treatment effect of vericiguat compared with placebo in the VICTORIA trial. We also described the relationship of other baseline factors that potentially modified the interpretation of this pre-specified NT-proBNP subgroup interaction.

METHODS

STUDY PATIENTS. The design, baseline characteristics, and results of the VICTORIA trial were previously published (3,5,6). In brief, the trial included 5,050 patients with worsening chronic HF (New York Heart Association functional classes II to IV), a left ventricular EF <45%, elevated natriuretic peptide levels, and recent HF decompensation. Patients were randomly assigned in a 1:1 ratio to receive vericiguat or placebo. Patients in sinus rhythm had to have BNP ≥300 pg/ml or NT-proBNP ≥1,000 pg/ml; patients with atrial fibrillation had to have BNP ≥500 pg/ml or NT-proBNP ≥1,600 pg/ml. Guideline-based HF therapies were encouraged before inclusion, including sacubitril/valsartan. The trial protocol was approved by regulatory agencies in participating countries, as well as the ethics committees and institutional review boards at participating sites. All patients provided written informed consent.

NATRIURETIC PEPTIDE ASSESSMENT. Of the 5,050 participants in VICTORIA, 245 did not have an evaluable NT-proBNP at randomization, leaving a remaining 4,805 patients for analysis (Supplemental Table 1). Per protocol, NT-proBNP was measured by a central laboratory on the Roche Elecsys assay (Roche Diagnostics, Mannheim, Germany). Analytical range of the assay was 10 to 175,000 pg/ml.

CLINICAL OUTCOMES. The primary outcome of VICTORIA was the composite endpoint of time to CVD or first HFH. We also explored the individual components of the composite outcomes (CVD and HFH). All clinical outcomes observed up to the primary analysis cutoff date (June 18, 2019) were included.

STATISTICAL ANALYSIS. The distribution of NT-proBNP was right skewed, with values ranging from 10 to 175,000 pg/ml. The relationship of NT-proBNP (as a continuous variable) to the primary composite outcome was assessed using the restricted cubic spline with 4 knots (7) and was observed to be nonlinear ($p < 0.001$) (Supplemental Figure 1). We transformed NT-proBNP on a logarithmic scale (base 2), revealing a linear relationship with the log-hazard of the primary outcome. The relative risk change in this transformed variable was interpreted as per

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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doubling of NT-proBNP. To estimate these relative associations with the clinical outcomes, Cox proportional hazard models were used, and hazard ratios (HRs) and 95% confidence intervals (CIs) were reported, along with absolute risk reduction. We anticipated differences in the patient characteristics across the spectrum of NT-proBNP at randomization. Therefore, associations with clinical outcomes were stratified for region and/or race and reported as unadjusted and adjusted for the modified Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score (6,8). We also explored broader adjustment using an internally validated set of variables from VICTORIA for the primary composite endpoint and CVD, which contained 16 and 19 covariates, respectively (Supplemental Table 2A). A description of the patient characteristics that are in the VICTORIA prediction models but do not appear in **Table 1** are provided in Supplemental Table 2B. The interaction of the randomized study treatment assignment (vericiguat or placebo) with NT-proBNP at randomization was included in the models, and p values for the interactions were reported).

Cut points were approximated from the treatment effect across the spectrum of (log-transformed) NT-proBNP, in which the upper confidence limit of the treatment effect did not include 1.00 (i.e., 4,000 pg/ml) and below which the point estimate of the treatment effect was <1.00 (i.e., 8,000 pg/ml). These cut points were then used to summarize the relative treatment estimate (HR; 95% CI) above and below these values. To provide context to these findings, patient characteristics were summarized according to ≤4,000, >4,000 to 8,000, and >8,000 pg/ml. These characteristics are also provided according to quartiles of NT-proBNP in the Supplemental Appendix. Median (25th to 75th percentiles) for continuous variables and frequency (percentages) for categorical variables were used to summarize data.

Patients with missing values of NT-proBNP (n = 245) at randomization were excluded from the present study, and their data were not imputed (Supplemental Table 1). Data for patients with a missing MAGGIC score (71 of 4,805 patients) were not imputed, and these patients were excluded from the risk-adjusted analyses. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). A 2-sided test result with $p < 0.05$ was considered statistically significant.

RESULTS

TREATMENT EFFECT OF VERICIGUAT COMPARED WITH PLACEBO BY BASELINE NT-proBNP. The relationship between NT-proBNP as a continuous variable and the treatment effect of vericiguat on the primary composite outcome is shown in **Central Illustration A**. The histograms within this Figure depict the distribution of patients by NT-proBNP intervals of 1,200 pg/ml. Across the spectrum of NT-proBNP levels, there was an association of the treatment effect up to 8,000 pg/ml (Supplemental Figures 2A and 2B). This association of treatment efficacy with vericiguat, compared with placebo, on the primary outcome was further estimated at 4,000 pg/ml (HR: 0.90; 95% CI: 0.82 to 0.99) (Supplemental Figure 2A). The treatment effect on the primary outcome for patients with NT-proBNP ≤4,000 pg/ml and those with >4,000 pg/ml produced HRs of 0.77 (95% CI: 0.68 to 0.88) and 1.05 (95% CI: 0.92 to 1.20), respectively (**Table 2**). These and the following findings were confirmed after adjustment for prediction models developed in the VICTORIA trial (Supplemental Table 3). The individual components of the primary outcome were similarly affected (**Central Illustration B and C**, Supplemental Figures 3 and 4) in patients with NT-proBNP levels ≤4,000 pg/ml at randomization for CVD (HR: 0.75; 95% CI: 0.60 to 0.94) and HFH (HR: 0.78; 95% CI: 0.67 to 0.90) (**Table 2**). These HRs corresponded to absolute risk reductions of 6.8, 1.3, and 5.5 events per 100 patient-years for the primary composite endpoint, CVD, and HFH, respectively.

Further exploration of this relationship showed an association of the treatment effect with vericiguat on the primary outcome in NT-proBNP levels extended to 8,000 pg/ml. The components of the primary outcome were associated with a significant effect for CVD (HR: 0.84; 95% CI: 0.71 to 0.99) and HFH (HR: 0.84; 95% CI: 0.75 to 0.95) (**Table 2**). These HRs corresponded to absolute risk reductions of 5.4, 0.8, and 4.6 events per 100 patient-years for the primary composite endpoint, CVD, and HFH, respectively. When NT-proBNP values >8,000 pg/ml were analyzed, this association of treatment benefit was no longer evident for the primary outcome (HR: 1.16; 95% CI: 0.94 to 1.41), CVD (HR: 1.32; 95% CI: 1.01 to 1.71), or HFH (HR: 1.17; 95% CI: 0.92 to 1.48). When these outcomes for NT-proBNP values >8,000 pg/ml were adjusted using the VICTORIA prognostic model (Supplemental Table 3), the respective HRs were 1.10 (95% CI: 0.90 to 1.35) for the primary outcome, 1.27 (95% CI: 0.97 to 1.66) for CVD, and 1.11 (95% CI: 0.87 to 1.41) for HFH.

To provide clinical context, the patient characteristics according to NT-proBNP categories (≤4,000, >4,000 to 8,000, >8,000 pg/ml) at randomization are shown in **Table 1**. Patients with higher NT-

TABLE 1 Baseline Characteristics of Patients by NT-proBNP at Randomization

	NT-proBNP at Randomization (pg/ml)		
	≤4,000 (n = 3,100)	>4,000 to 8,000 (n = 1,033)	>8,000 (n = 672)
Age, yrs	67.0 (59.0–75.0)	70.0 (62.0–78.0)	70.0 (62.0–79.0)
Male	2,361 (76.2)	803 (77.7)	482 (71.7)
Race			
White	1,967 (63.5)	639 (61.9)	426 (63.4)
Black	148 (4.8)	57 (5.5)	27 (4.0)
Asian	730 (23.5)	237 (22.9)	151 (22.5)
Other	254 (8.2)	100 (9.7)	68 (10.1)
Geographic region			
Eastern Europe	1,023 (33.0)	367 (35.5)	212 (31.5)
Western Europe	501 (16.2)	173 (16.7)	134 (19.9)
Asia Pacific	756 (24.4)	246 (23.8)	159 (23.7)
Latin America	454 (14.6)	147 (14.2)	106 (15.8)
North America	366 (11.8)	100 (9.7)	61 (9.1)
Index event			
HF hospitalization within 3 months	1,972 (63.6)	757 (73.3)	486 (72.3)
HF hospitalization 3 to 6 months	562 (18.1)	156 (15.1)	103 (15.3)
IV diuretic for HF (without hospitalization) within 3 months	566 (18.3)	120 (11.6)	83 (12.4)
BMI, kg/m^2	27.6 (24.2–31.7)	25.9 (23.1–29.9)	25.4 (22.5–28.7)
Medical history			
Ejection fraction, %	30.0 (24.0–36.0)	27.0 (20.0–35.0)	26.0 (20.0–34.0)
Ejection fraction <40%	2,603 (84.1)	911 (88.4)	599 (89.5)
NYHA functional class at baseline			
I	1 (0.0)	0 (0.0)	1 (0.1)
II	1,998 (64.5)	546 (52.9)	290 (43.2)
III	1,075 (34.7)	469 (45.4)	361 (53.7)
IV	26 (0.8)	18 (1.7)	20 (3.0)
Systolic blood pressure, mm Hg	119.0 (109.0–131.0)	117.0 (107.5–130.0)	120.0 (108.0–133.0)
Diastolic blood pressure, mm Hg	73.0 (65.0–80.0)	71.0 (64.0–80.0)	72.0 (65.0–81.0)
Heart rate, beats/min	71.0 (63.0–80.0)	72.5 (64.0–82.0)	73.0 (65.0–84.0)
Atrial fibrillation	1,307 (42.2)	519 (50.2)	312 (46.4)
Diabetes mellitus	1,420 (45.8)	492 (47.6)	342 (50.9)
COPD	529 (17.1)	169 (16.4)	119 (17.7)
CAD	1,794 (57.9)	608 (58.9)	402 (59.8)
History of smoking	1,852 (59.7)	590 (57.1)	375 (55.8)
Time from diagnosis of any HF to randomization, yrs	3.3 (1.0–7.4)	3.3 (1.1–7.5)	3.0 (1.0–7.3)
Standard of care therapy			
ACE-I or ARB	2,358 (76.1)	747 (72.3)	435 (64.7)
Sacubitril/valsartan	460 (14.8)	129 (12.5)	95 (14.1)
Beta blocker	2,904 (93.7)	957 (92.6)	610 (90.8)
MRA	2,275 (73.4)	700 (67.8)	414 (61.6)
Triple therapy	1,993 (64.3)	571 (55.3)	310 (46.1)
ICD	854 (27.6)	291 (28.2)	179 (26.6)
Biventricular pacemaker	431 (13.9)	158 (15.3)	105 (15.6)

Continued on the next page

proBNP levels tended to be older, were in a higher New York Heart Association functional class, and had a lower body mass index, ejection fraction, and estimated glomerular filtration rates (Table 1). In addition, they were more likely to be enrolled earlier after index HFH. Although atrial fibrillation, baseline device, and beta-blocker use were similar across the NT-proBNP spectrum, lower rates of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists use were evident for patients within the upper strata of NT-proBNP values. The median MAGGIC risk score was lower among the cohort with NT-proBNP values ≤4,000 pg/ml than that in the other 2 groups.

These findings were in concert with those based on the pre-specified subgroup analysis of quartiles of NT-proBNP, which indicated higher risk patients in

TABLE 1 Continued

	NT-proBNP at Randomization (pg/ml)		
	≤4,000 (n = 3,100)	>4,000 to 8,000 (n = 1,033)	>8,000 (n = 672)
Laboratory results			
Hemoglobin, g/dl	13.7 (12.4–14.9)	13.0 (11.6–14.3)	12.5 (11.2–13.9)
Sodium, mEq/l	140.0 (138.0–142.0)	140.0 (138.0–142.0)	140.0 (138.0–142.0)
Potassium, mEq/l	4.5 (4.2–4.8)	4.5 (4.2–4.9)	4.4 (4.1–4.9)
eGFR, ml/min/1.73 m^2	63.6 (47.1–82.7)	51.5 (36.8–71.1)	42.4 (30.4–61.2)
≤30	176 (5.7)	141 (13.6)	161 (24.0)
>30 to ≤60	1,189 (38.4)	508 (49.2)	330 (49.1)
>60	1,707 (55.1)	378 (36.6)	179 (26.6)
Assigned study treatment			
Vericiguat	1,550 (50.0)	526 (50.9)	338 (50.3)
Placebo	1,550 (50.0)	507 (49.1)	334 (49.7)
MAGGIC risk score	22 (18–27)	26 (21–30)	27 (23–32)

Values are median (25th to 75th percentile) or n (%).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; IV = intravenous; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

the highest quartile (e.g., median MAGGIC risk score of 27). Patient characteristics and the treatment effect according to the components of the primary composite endpoint are available in Supplemental Tables 4A and 4B.

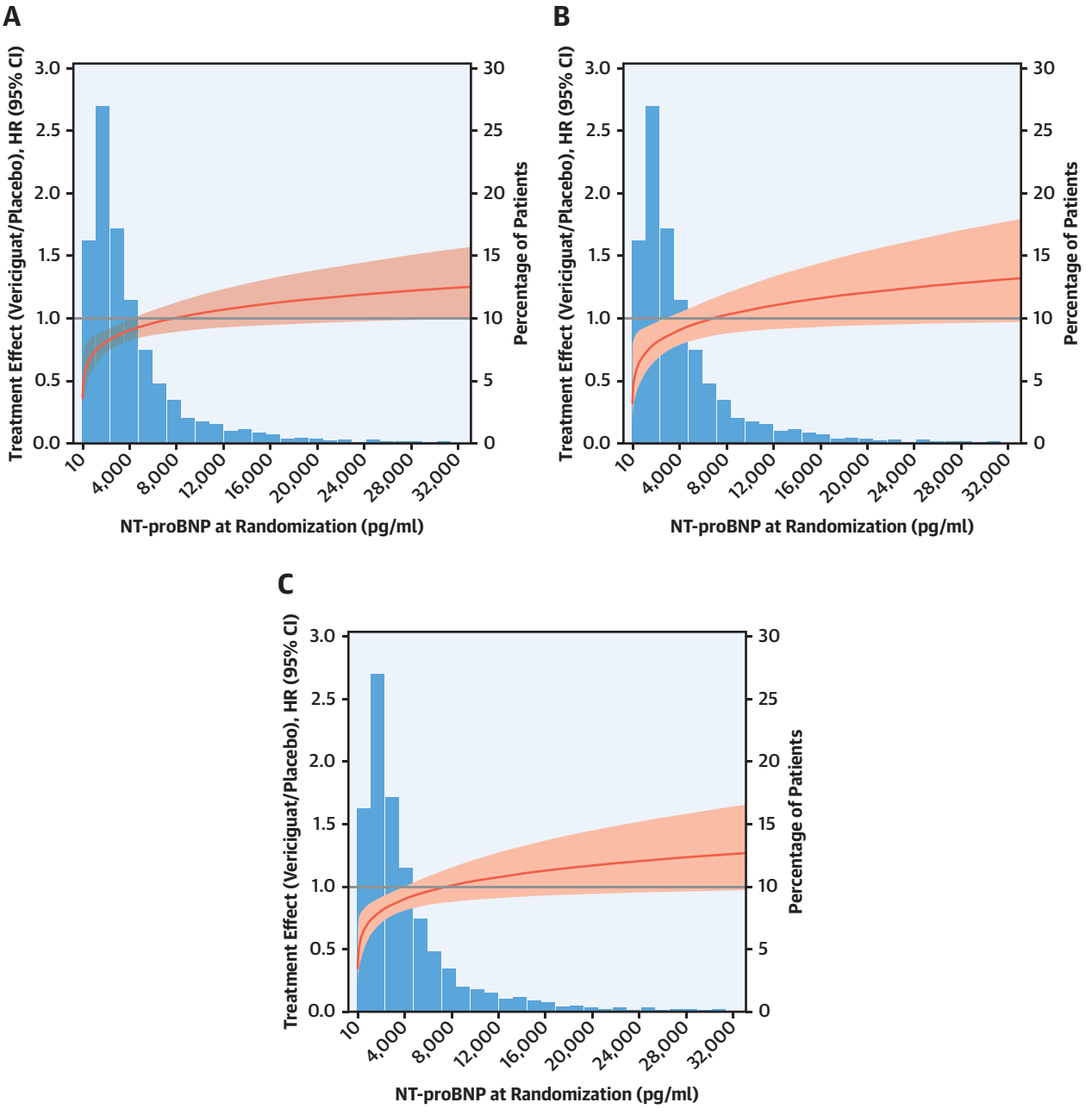
ASSOCIATION OF NT-proBNP WITH CLINICAL OUTCOMES. When the overall association between NT-proBNP values at randomization and the risk of the primary composite outcome was assessed, we observed an excess hazard per doubling of NT-proBNP with and without adjustment for the MAGGIC risk score (**Table 3**). This relationship was more pronounced in patients assigned to vericiguat compared with those assigned to placebo. Similar results were observed for CVD and HFH. These findings were confirmed after adjustment for prediction models developed in the VICTORIA trial (Supplemental Table 5).

DISCUSSION

The principal novel finding of the present study was that the treatment effect of vericiguat compared with placebo on the primary composite endpoint was greatest in patients with NT-proBNP levels <8,000 pg/ml at randomization, which was further amplified if these levels were <4,000 pg/ml. The benefit of vericiguat in this high-risk HF population appeared to be clinically meaningful in both relative and absolute terms and extended to both the CVD and HFH components of the primary outcome. Although patients with higher NT-proBNP levels within the range up to 8,000 pg/ml had several clinical features indicative of higher risk, the treatment effect associated with vericiguat compared with placebo persisted after risk adjustment for many of these factors. Our findings—using all the natriuretic peptide data as a continuous variable—provided further insight into that provided from the initial pre-specified NT-proBNP quartile subgroups and suggested the potential for a broader range of patients who could benefit from treatment. Moreover, there appeared to be amplification of that benefit for patients whose entry NT-proBNP levels were <4,000 pg/ml and who represented most of the study population. These findings might be useful in informing clinicians about how best to apply this new treatment in the growing population of patients with HFrEF with recent worsening of their status, despite receiving good guideline-based therapies.

Patients enrolled in the VICTORIA trial were at higher baseline risk for hospitalization or death compared with patients in contemporary clinical trials in HF, as evident by the median baseline NT-proBNP concentration of 2,816 pg/ml, and they were generalizable to the broader HFrEF population (9). In this trial population at such high risk for clinical events, NT-proBNP was predictive of the primary outcomes of CVD or first HFH, concordant with previous trials and other patient cohorts. This analysis also identified that this association between NT-proBNP and clinical

CENTRAL ILLUSTRATION Treatment Effect of Vericiguat Compared With Placebo



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Treatment effect of vericiguat compared with placebo across the range of N-terminal pro–B-type natriuretic peptide (NT-proBNP) at randomization for the **(A)** primary composite outcome, **(B)** cardiovascular death, or **(C)** heart failure hospitalization. Left-axis treatment effect expressed as hazard ratio (HR) **(red line)** with 95% confidence intervals (CIs) **(red shaded area)** adjusted for the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score. **Vertical shaded bars** indicate the number of patients within each NT-proBNP measurement bracket, expressed as a percentage on the right vertical axis. The presented values are from a back-transformation of log-transformed NT-proBNP, and the x-axis is truncated at 32,000 pg/ml for presentation only.

TABLE 2 Associations of the Study Treatment With the Primary Composite Endpoint According to NT-proBNP at Randomization Below/Above 4,000 and 8,000 pg/ml

	NT-proBNP at Randomization (pg/ml)							
	Placebo Events/ 100 Patient-Years	Vericiguat Events/ 100 Patient-Years	ARR	Treatment Effect (V vs. P)* HR (95% CI)	Placebo Events/ 100 Patient-Years	Vericiguat Events/ 100 Patient-Years	ARR	Treatment Effect (V vs. P)* HR (95% CI)
	≤4,000 (n = 3,100)				>4,000 (n = 1,705)			
CVD/HFH	28.4	21.6	6.8		61.4	64.7	−3.3	
Unadjusted				0.77 (0.67–0.88)				1.06 (0.93–1.21)
Adjusted				0.77 (0.68–0.88)				1.05 (0.92–1.20)
CVD	5.2	3.9	1.3		16.9	18.5	−1.6	
Unadjusted				0.75 (0.60–0.93)				1.12 (0.93–1.33)
Adjusted				0.75 (0.60–0.94)				1.10 (0.92–1.31)
HFH	23.2	17.7	5.5		44.6	46.2	−1.6	
Unadjusted				0.77 (0.67–0.89)				1.05 (0.90–1.23)
Adjusted				0.78 (0.67–0.90)				1.05 (0.90–1.22)
	≤8,000 (n = 4,133)				>8,000 (n = 672)			
CVD/HFH	33.7	28.3	5.4		74.5	87.2	−12.7	
Unadjusted				0.85 (0.76–0.94)				1.16 (0.95–1.42)
Adjusted				0.85 (0.76–0.95)				1.16 (0.94–1.41)
CVD	6.9	6.1	0.8		22.9	26.5	−3.6	
Unadjusted				0.85 (0.72–1.00)				1.34 (1.03–1.73)
Adjusted				0.84 (0.71–0.99)				1.32 (1.01–1.71)
HFH	26.8	22.2	4.6		51.6	60.7	−9.1	
Unadjusted				0.84 (0.75–0.94)				1.18 (0.93–1.49)
Adjusted				0.84 (0.75–0.95)				1.17 (0.92–1.48)

*All study treatment interactions were statistically significant ($p < 0.05$).

ARR = absolute risk reduction; CI = confidence interval; CVD = cardiovascular death; HFH = heart failure hospitalization; HR = hazard ratio; p = placebo; V = vericiguat; other abbreviation as in Table 1.

outcomes was not linear by revealing a much steeper increment in the relationship for values >4,000 pg/ml. This finding deserves consideration in future clinical trials or cohort studies that will estimate prognosis and evaluate new therapies.

A secondary analysis of the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial identified that NT-proBNP levels before and after run-in, as well as 1 month after

TABLE 3 Associations of Log-Transformed NT-proBNP at Randomization With Clinical Outcomes in Patients and According to Assigned Study Treatment

	Unadjusted HR (95% CI) per NT-proBNP Doubling (pg/ml)*	p Value†	p for Interaction‡	Adjusted HR (95% CI) per NT-proBNP Doubling (pg/ml)§	p Value†	p for Interaction‡
CVD/HFH						
All patients	1.43 (1.38–1.47)	<0.0001	0.001	1.36 (1.31–1.41)	<0.0001	0.002
Placebo	1.35 (1.29–1.41)			1.29 (1.23–1.35)		
Vericiguat	1.51 (1.43–1.58)			1.43 (1.36–1.51)		
CVD						
All patients	1.62 (1.54–1.70)	<0.0001	0.012	1.50 (1.43–1.58)	<0.0001	0.015
Placebo	1.52 (1.42–1.63)			1.41 (1.31–1.52)		
Vericiguat	1.72 (1.61–1.84)			1.60 (1.49–1.71)		
HFH						
All patients	1.35 (1.30–1.41)	<0.0001	0.003	1.29 (1.24–1.34)	<0.0001	0.005
Placebo	1.28 (1.21–1.35)			1.22 (1.15–1.29)		
Vericiguat	1.43 (1.36–1.51)			1.36 (1.29–1.44)		

*Unadjusted estimates in 4,805 patients. †HR (95% CI) and p value for log-transformed NT-proBNP as a main effect only in the model. ‡HR (95% CI) and p value for the interaction of log-transformed NT-proBNP at randomization with assigned study treatment. §Estimates adjusted for the MAGGIC Risk Score in 4,734 patients.

Abbreviations as in Tables 1 and 2.

randomization, were independently associated with clinical outcomes (10). However, there was no interaction between baseline NT-proBNP and treatment efficacy in that study. A subsequent Swedish registry in patients with HFrEF analyzed at hospital discharge or as outpatients showed median NT-proBNP levels of 2,640 pg/ml (75% of patients had a NT-proBNP of <5,914 pg/ml) (11). This study also demonstrated higher cardiovascular event rates, defined as cardiovascular hospitalization or CVD, with increasing NT-proBNP values.

The VICTORIA trial did not have a run-in phase, and the values at randomization were similar to the baseline values in other studies (e.g., GUIDE-IT [Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure]),which had a median baseline NT-proBNP of 2,653 pg/ml (12). This comparison was particularly relevant because the primary event rate of 35% in GUIDE-IT (using the same primary endpoint) identified a similarly high-risk population. Other contemporary trials, including DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and PARADIGM-HF, had median NT-proBNP values of 1,437 pg/ml and 1,615 pg/ml, respectively, and primary endpoint rates less than one-half of that observed in the VICTORIA trial (11).

STUDY STRENGTHS AND LIMITATIONS. We studied a large event-rich population with carefully adjudicated clinical outcomes and NT-proBNP values centrally measured in a core laboratory. Although we chose not to impute values for the 245 patients missing NT-proBNP levels at randomization, there were no substantive differences between those patients and the overall cohort, and their omission was unlikely to have affected our results (Supplemental Table 1). The present study was an extension of the pre-specified subgroup analysis of the primary outcomes by quartiles of NT-proBNP and allowed for the thorough examination of this relationship across the full spectrum of NT-proBNP, which was broad (10 to 175,000 pg/ml). The relationship among higher NT-proBNP levels, reduced vericiguat efficacy, and poorer outcomes might be related to diverse factors, including patient illness severity, adequacy of guideline-based therapy, activation of neuroendocrine pathways involved in HF pathophysiology, or blunting of guanylate cyclase responsiveness in advanced HF. This characterization of continuous NT-proBNP informed the additional subgroups of NT-proBNP and should be viewed as hypothesis-generating in the context of the overall trial results. Finally, we adjusted for known determinants of NT-proBNP, but as with all secondary analyses, there might be unmeasured confounders.

CONCLUSIONS

In patients enrolled in the VICTORIA trial, NT-proBNP at randomization was predictive of the primary and secondary outcomes. Patients with an NT-proBNP <8,000 pg/ml had both a reduction in the primary outcome and its 2 components, CVD and HFH, which identified a patient cohort who had vericiguat might be beneficial.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: For high-risk patients with HFrEF on guideline-based therapy who had a recent HF hospitalization or intravenous diuretic therapy, vericiguat appears to benefit those patients with NT-proBNP <8,000 pg/ml. This population, especially in those with NT-proBNP <4,000 pg/mml, had a reduction in both the primary outcome and its 2 components, CVD and HFH, thereby identifying a patient cohort who had vericiguat might be beneficial.

TRANSLATIONAL OUTLOOK: Although vericiguat is not yet approved for clinical use, this treatment may provide a useful additional therapeutic option in a high-risk population with HF.

REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776–803.

2. Vaduganathan M, Claggett B, Packer M, et al. Natriuretic peptides as biomarkers of treatment response in clinical trials of heart failure. J Am Coll Cardiol HF 2018;6:564–9.

3. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med 2020;382:1883–93.

4. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000;355:1064–9.

5. Armstrong PW, Roessig L, Patel MJ, et al. A multicenter, randomized, double-blind, placebo-controlled trial of the efficacy and safety of the oral soluble guanylate cyclase stimulator: the VICTORIA trial. J Am Coll Cardiol HF 2018;6:96–104.

6. Pieske B, Patel MJ, Westerhout CM, et al. Baseline features of the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) Trial. Eur J Heart Fail 2019;21:1596–604.

7. Harrell F. Regression Modeling Strategies with Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. 2nd edition. New York, NY: Springer; 2015.

8. Pocock SJ, Ariti CA, McMurray JJV, et al. Predicting survival in heart failure: risk score based on 39,372 patients from 30 studies. Eur Heart J 2013;34:1404–13.

9. Butler J, Anstrom KJ, Armstrong PW. Comparing the benefit of novel therapies across clinical trials: insights from the VICTORIA trial. Circulation 2020;142:717–9.

10. Zile MR, Claggett BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol 2016;68:2425–36.

11. Savarese G, Orsini N, Hage C, et al. Utilizing NT-proBNP for eligibility and enrichment in trials in HFpEF, HFmrEF, and HFeEF. J Am Coll Cardiol 2018;6:246–56.

12. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2017;318:713–20.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.