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ORIGINAL RESEARCH

# Effects of Sacubitril/Valsartan According to Natriuretic Peptide Levels in Patients Enrolled in PARADIGM-HF and PARAGON-HF

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## ABSTRACT

**BACKGROUND** Recent trials of new heart failure (HF) treatments suggest the effect of therapy may vary by N-terminal pro-B type natriuretic peptide (NT-proBNP) level.

**OBJECTIVES** The authors examined the efficacy of sacubitril/valsartan according to NT-proBNP levels in patients with reduced, mildly reduced, and preserved left ventricular ejection fraction (LVEF) enrolled in PARADIGM-HF (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting–Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) and PARAGON-HF (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Receptor Blockers Global Outcomes in HF with Preserved Ejection Fraction).

**METHODS** Individual patient data from PARADIGM-HF and PARAGON-HF were pooled and participants were divided into categories defined by quintiles of NT-proBNP level. The primary outcome examined was the composite of HF hospitalization or cardiovascular death.

**RESULTS** Among the 13,195 patients enrolled in both trials, 13,142 (99.6%) had a baseline NT-proBNP level measured. The rate of the primary outcome (per 100 person-years) increased with NT-proBNP levels: quintile 1, 5.9 (95% CI: 5.3-6.5); quintile 2, 7.5 (95% CI: 6.9-8.2); quintile 3, 9.0 (95% CI: 8.2-9.7); quintile 4, 12.0 (95% CI: 11.1-12.9); and quintile 5, 20.8 (95% CI: 19.6-22.2). The relative risk reduction in the primary outcome with sacubitril/valsartan was consistent across NT-proBNP levels: the HR in quintile 1 was 0.79 (95% CI: 0.65-0.96); quintile 2, 0.87 (95% CI: 0.72-1.04); quintile 3, 0.79 (95% CI: 0.66-0.93); quintile 4, 0.85 (95% CI: 0.73-0.99); and quintile 5, 0.86 (95% CI: 0.76-0.97; *P* for interaction = 0.86). The absolute risk reduction was greatest in NT-proBNP quintile 5; the number needed to treat for the primary outcome over the median follow-up of 31 months was 16 in quintile 5 vs 37 in quintile 1.

**CONCLUSIONS** The relative risk reductions with sacubitril/valsartan were consistent irrespective of NT-proBNP level in HF patients across the range of LVEF. Consequently, the absolute risk reductions were greatest in patients with higher NT-proBNP levels. (PARADIGM-HF; NCT01035255; and PARAGON-HF; NCT01920711). (JACC Heart Fail. 2025;■:■–■)


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**ABBREVIATIONS AND ACRONYMS**

**BNP** = B-type natriuretic peptide

**HF** = heart failure

**LVEF** = left ventricular ejection fraction

**NP** = natriuretic peptide

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

Natriuretic peptides (NPs) are commonly used in clinical practice to help diagnose heart failure (HF), assess prognosis, and evaluate response to treatment.[1,2] It has recently been reported that the benefits of the soluble guanylate cyclase stimulator vericiguat were attenuated in patients with a higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) level.[3,4] The latter observation raises the question as to whether high NP levels identify patients with HF so advanced that they might not respond to vericiguat and perhaps other treatments. This hypothesis is potentially supported by older findings from I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study) and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), although not by newer findings with cardiac-specific myosin activator omecamtiv mecarbil which appeared to have greater benefits in patients with higher NT-proBNP levels.[5,6] Alternatively, the attenuated effect of vericiguat in patients with high NP levels could result from crosstalk between the particulate and soluble guanylate cyclase pathways, which has been described in experimental animals and humans.[7,8] This finding with vericiguat also raises a question about whether the effect of sacubitril/valsartan varies according to NP level as neprilysin inhibition increases NPs (acting through particulate guanylate cyclase) and other vasoactive peptides some of which (eg, bradykinin) act through the nitric oxide-soluble guanylate cyclase pathway. To investigate this further, we examined the effect of sacubitril/valsartan according to baseline NT-proBNP level using pooled patient-level data from the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with Angiotensin-Converting-Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; NCT01035255) trial and the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; NCT01920711).[9,10] In this large data set, we describe patient characteristics according to NT-proBNP level across the range of left ventricular ejection fraction (LVEF), outcomes related to NT-proBNP level adjusted for baseline characteristics, and the relative and absolute risk reductions with a neprilysin inhibitor plus a renin-angiotensin blocker (ie, sacubitril/valsartan) compared to a renin-angiotensin blocker alone (ie, enalapril or valsartan).

## METHODS

The design and primary results of PARADIGM-HF and PARAGON-HF are already published.[9-11] Each trial was approved by local ethics committees and written informed consent was obtained from each patient.

**STUDY PATIENTS.** Briefly, PARADIGM-HF included 8,399 patients with an LVEF ≤40% (later changed to ≤35% by amendment). Patients were required to have NYHA functional class II-IV, and an NT-proBNP ≥600 pg/mL (or B-type natriuretic peptide [BNP] ≥150 pg/mL) or NT-proBNP ≥400 pg/mL (or BNP ≥100 pg/mL) if hospitalized for HF within the last 12 months. Patients were also required to be treated with a stable dose of a beta-blocker and an angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) equivalent to at least 10 mg of enalapril. Patients entered a single-blind run-in phase and received enalapril 10 mg twice daily for 2 weeks. If no unacceptable side effects occurred, they were switched to single-blind treatment with sacubitril/valsartan for an additional 4 to 6 weeks (49/51 mg twice daily, increasing to 97/103 mg twice daily). Thereafter, patients were randomized in a 1:1

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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 Author Center.

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ratio to double-blind treatment with either sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily. The primary outcome was the composite of HF hospitalization or cardiovascular death. The median follow-up was 27 months.

PARAGON-HF included 4,796 patients who were ≥50 years of age and who had an LVEF of 45% or higher. Patients were required to have signs and symptoms of HF, NYHA functional class II-IV, evidence of structural heart disease, and to be treated with a diuretic. For patients hospitalized for HF within 9 months and those not in atrial fibrillation (AF) on screening electrocardiography (ECG) were required to have an NT-proBNP ≥200 pg/mL, and those in AF were required to have an NT-proBNP level ≥600 pg/mL. For patients without hospitalization for HF within 9 months, those not in AF on screening ECG were required to have an NT-proBNP ≥300 pg/mL, and those in AF were required to have an NT-proBNP ≥900 pg/mL. Patients entered a single-blind run-in phase and received valsartan 40 mg or 80 mg twice daily for 1 to 2 weeks. If no unacceptable side effects occurred, they were switched to single-blind treatment with sacubitril/valsartan 49/51 mg twice daily for 2 to 4 weeks. Thereafter, patients were randomized in a 1:1 ratio to double-blind treatment with either sacubitril/valsartan 97/103 mg twice daily or valsartan 160 mg twice daily. The primary outcome was the composite of total (first and recurrent) hospitalizations for HF and cardiovascular death. The median follow-up was 35 months.

**NT-proBNP EVALUATION.** NT-proBNP was measured in both trials using samples collected at screening (before the run-in period), using the same assay (Roche Elecsys) in a central laboratory.[12,13] Patients without a baseline NT-proBNP measurement were excluded from this analysis.

**STUDY OUTCOMES.** For this analysis, the primary outcome used was the composite of time to the first hospitalization for HF or cardiovascular death. HF hospitalization, cardiovascular death, all-cause death, total (first and recurrent) HF hospitalizations, and the composite of total HF hospitalizations and cardiovascular death were also evaluated as secondary outcomes. All these events were centrally adjudicated by the same clinical events committee in both trials.

**STATISTICAL ANALYSES.** Baseline characteristics were summarized as mean ± SD or median (Q1-Q3) for continuous variables and counts and percentages for categorical variables according to the quintiles of NT-proBNP levels. Differences in baseline characteristics were tested using the Cochran-Armitage trend test for binary variables and the Jonckheere Terpstra test for continuous variables, respectively.

To evaluate the association between NT-proBNP levels and outcomes, time-to-event data were evaluated using the Kaplan-Meier estimator, and Cox proportional-hazards models, stratified by region and trial, and adjusted for randomized treatment, and HRs with 95% CIs were computed for the quintiles of NT-proBNP. Total (first and recurrent) events were evaluated with semiparametric proportional-rates models, stratified by region and trial, and adjusted for randomized treatment, and rate ratios with 95% CIs were computed. In addition, HRs and rate ratios stratified by region and trial and adjusted for randomized treatment, age, sex, race, body mass index (BMI), systolic blood pressure, heart rate, NYHA functional class III or IV, time from diagnosis of HF, prior HF hospitalization, LVEF, hypertension, history of myocardial infarction, history of stroke, AF rhythm on ECG at screening, and estimated glomerular filtration rate (eGFR) were reported.

To examine the effects of sacubitril/valsartan compared to enalapril or valsartan according to NT-proBNP levels, time-to-first event was evaluated with Cox proportional-hazards models and total events were evaluated with semiparametric proportional-rates models, respectively, and these models were stratified according to trial and region. In addition to the quintile categories of NT-proBNP, these estimates were obtained for patients with NT-proBNP <1,000 pg/mL or ≥1,000 pg/mL. The effect of randomized treatment across the range of NT-proBNP (log-transformed) levels as a continuous variable was modelled flexibly using restricted cubic splines with 3 knots (10th, 50th, and 90th percentile of log-transformed NT-proBNP). The effects of sacubitril/valsartan were also examined for subgroups of interest (males and females; nonobese and obese; no AF and AF on screening electrocardiography; eGFR ≥60 mL/min/1.73 $m^2$ and eGFR <60 mL/min/1.73 $m^2$). Regarding BMI, analysis for treatment effect was explored in more detailed subgroups (ie, <25.0 kg/$m^2$, 25.0-29.9 kg/$m^2$, 30-34.9 kg/$m^2$, and ≥35.0 kg/$m^2$). By applying a consistent relative risk reduction with sacubitril/valsartan (observed in the overall population) to event rates seen in the enalapril/valsartan treated population, differences in the incidence rate of the primary outcome were calculated continuously across the spectrum of log-transformed NT-proBNP. All analyses were conducted based on complete case analysis.

All analyses were conducted using STATA version 17.0.

**TABLE 1 Baseline Characteristics According to Categories Defined by Quintiles of NT-proBNP Level at Baseline**

| | Quintile 1 ≤620 pg/mL (n = 2,634) | Quintile 2 621-1,039 pg/mL (n = 2,627) | Quintile 3 1,040-1,654 pg/mL (n = 2,625) | Quintile 4 1,655-2,995 pg/mL (n = 2,628) | Quintile 5 ≥2,996 pg/mL (n = 2,628) | *P* Value |
|---|---|---|---|---|---|---|
| Age, y | 67.8 ± 10.6 | 65.9 ± 11.3 | 67.6 ± 10.9 | 67.7 ± 11.5 | 66.2 ± 11.8 | 0.14 |
| Region | | | | | | |
| North America | 246 (9.3) | 266 (10.1) | 224 (8.5) | 221 (8.4) | 193 (7.3) | 0.001 |
| Latin America | 281 (10.7) | 354 (13.5) | 334 (12.7) | 366 (13.9) | 466 (17.7) | <0.001 |
| Western Europe | 670 (25.4) | 706 (26.9) | 772 (29.4) | 688 (26.2) | 586 (22.3) | 0.010 |
| Central Europe | 1,002 (38.0) | 875 (33.3) | 881 (33.6) | 902 (34.3) | 868 (33.0) | 0.002 |
| Asia-Pacific | 435 (16.5) | 426 (16.2) | 414 (15.8) | 451 (17.2) | 515 (19.6) | 0.002 |
| Male | 1,484 (56.3) | 1,815 (69.1) | 1,778 (67.7) | 1,808 (68.8) | 1,975 (75.2) | <0.001 |
| Race | | | | | | |
| White | 2,016 (76.5) | 1,905 (72.5) | 1,950 (74.3) | 1,871 (71.2) | 1,666 (63.4) | <0.001 |
| Black | 83 (3.2) | 119 (4.5) | 102 (3.9) | 90 (3.4) | 132 (5.0) | 0.029 |
| Asian | 378 (14.4) | 402 (15.3) | 383 (14.6) | 437 (16.6) | 511 (19.4) | <0.001 |
| Other race or missing data | 157 (6.0) | 201 (7.7) | 190 (7.2) | 230 (8.8) | 319 (12.1) | <0.001 |
| Body-mass index, kg/m$^2$ | 30.5 ± 5.3 | 29.5 ± 5.5 | 29.3 ± 5.3 | 28.4 ± 5.2 | 26.8 ± 5.1 | <0.001 |
| Weight category | | | | | | |
| Underweight | 11 (0.4) | 25 (1.0) | 21 (0.8) | 37 (1.4) | 72 (2.7) | <0.001 |
| Normal | 380 (14.4) | 524 (20.0) | 515 (19.6) | 636 (24.2) | 947 (36.1) | <0.001 |
| Overweight | 915 (34.8) | 947 (36.1) | 1,016 (38.7) | 1,044 (39.8) | 991 (37.8) | 0.001 |
| Obese | 1,327 (50.4) | 1,130 (43.0) | 1,071 (40.8) | 907 (34.6) | 614 (23.4) | <0.001 |
| Vital signs | | | | | | |
| Systolic blood pressure, mm Hg | 128.6 ± 15.9 | 124.6 ± 15.7 | 124.2 ± 15.6 | 124.2 ± 16.1 | 121.8 ± 15.8 | <0.001 |
| Diastolic blood pressure, mm Hg | 74.4 ± 9.9 | 73.7 ± 10.2 | 74.0 ± 10.3 | 73.9 ± 10.4 | 73.2 ± 10.4 | <0.001 |
| Heart rate, beats/min | 69.2 ± 11.2 | 70.7 ± 11.8 | 71.8 ± 12.3 | 72.6 ± 12.4 | 74.1 ± 12.5 | <0.001 |
| HF characteristics | | | | | | |
| NYHA functional class III or IV | 508 (19.3) | 506 (19.3) | 558 (21.3) | 658 (25.1) | 782 (29.8) | <0.001 |
| Time from diagnosis of HF, y | | | | | | |
| ≤1 | 1,068 (40.7) | 910 (34.7) | 856 (32.6) | 817 (31.1) | 831 (31.6) | <0.001 |
| 1-5 | 908 (34.6) | 921 (35.1) | 971 (37.0) | 1,019 (38.8) | 1,064 (40.5) | <0.001 |
| ≥5 | 651 (24.8) | 793 (30.2) | 797 (30.4) | 792 (30.1) | 732 (27.9) | 0.029 |
| Prior HF hospitalization | 1,531 (58.1) | 1,383 (52.6) | 1,406 (53.6) | 1,531 (58.3) | 1,702 (64.8) | <0.001 |
| Ischemic cause | 1,263 (48.0) | 1,375 (52.3) | 1,326 (50.5) | 1,392 (53.0) | 1,385 (52.7) | 0.001 |
| LVEF | 49.0 ± 15.1 | 40.2 ± 14.7 | 39.7 ± 14.6 | 37.6 ± 14.1 | 31.7 ± 11.6 | <0.001 |
| Clinical history | | | | | | |
| Atrial fibrillation | 752 (28.6) | 938 (35.7) | 1,336 (50.9) | 1,386 (52.7) | 1,211 (46.1) | <0.001 |
| Myocardial infarction | 869 (33.0) | 1,042 (39.7) | 908 (34.6) | 933 (35.5) | 953 (36.3) | 0.42 |
| PCI or CABG | 830 (31.5) | 858 (32.7) | 819 (31.2) | 799 (30.4) | 636 (24.2) | <0.001 |
| Hypertension | 2,305 (87.5) | 2,075 (79.0) | 2,084 (79.4) | 2,110 (80.3) | 1,903 (72.4) | <0.001 |
| Diabetes | 1,095 (41.6) | 1,006 (38.3) | 1,006 (38.3) | 944 (35.9) | 898 (34.2) | <0.001 |
| Stroke | 213 (8.1) | 218 (8.3) | 266 (10.1) | 268 (10.2) | 264 (10.1) | 0.001 |
| COPD | 353 (13.4) | 328 (12.5) | 327 (12.5) | 357 (13.6) | 377 (14.3) | 0.16 |
| ECG findings | | | | | | |
| AF in screening ECG | 162 (6.2) | 521 (20.0) | 1,006 (38.5) | 1,091 (41.8) | 928 (35.5) | <0.001 |
| Heart rate in ECG, beats/min | 67.8 ± 12.6 | 70.4 ± 14.0 | 72.9 ± 14.8 | 74.2 ± 15.0 | 77.3 ± 16.5 | <0.001 |
| Heart rate without AF on screening ECG, beats/min | 66.9 ± 11.7 | 67.9 ± 12.3 | 69.6 ± 13.2 | 71.4 ± 13.6 | 75.4 ± 14.7 | <0.001 |
| Heart rate with AF on screening ECG, beats/min | 81.8 ± 16.7 | 80.5 ± 15.9 | 78.1 ± 15.7 | 78.2 ± 16.0 | 80.9 ± 18.7 | 0.95 |
| Laboratory values[a] | | | | | | |
| NT-proBNP, pg/mL | 424 (327-516) | 807 (703-918) | 1,307 (1,163-1,472) | 2,140 (1,877-2,513) | 5,017 (3,735-7,691) | <0.001 |
| In patients without AF on screening ECG | 420 (327-513) | 788 (698-900) | 1,293 (1,150-1,462) | 2,153 (1,894-2,523) | 5,238 (3,799-7,999) | <0.001 |
| In patients with AF on screening ECG | 479 (291-554) | 875 (738-959) | 1,328 (1,181-1,484) | 2,121 (1,852-2,486) | 4,718 (3,647-6,780) | <0.001 |
| eGFR, mL/min/1.73 m$^2$ | 69.9 ± 20.4 | 68.5 ± 19.4 | 66.8 ± 19.0 | 65.1 ± 18.9 | 62.6 ± 18.8 | <0.001 |
| eGFR <60 | 865 (32.9) | 919 (35.0) | 1,001 (38.3) | 1,100 (41.9) | 1,256 (47.9) | <0.001 |
| Serum creatinine, μmol/L | 90.3 ± 24.4 | 95.2 ± 24.5 | 96.3 ± 24.9 | 98.8 ± 25.4 | 105.0 ± 27.3 | <0.001 |
| Blood urea nitrogen, mmol/L | 7.2 ± 2.7 | 7.2 ± 2.8 | 7.5 ± 2.8 | 7.7 ± 2.9 | 8.2 ± 3.4 | <0.001 |
| Serum sodium, mmol/L | 140.9 ± 3.1 | 140.9 ± 3.0 | 141.1 ± 3.3 | 141.1 ± 3.2 | 141.2 ± 3.4 | <0.001 |
| Hemoglobin, g/L | 136.0 ± 15.0 | 139.2 ± 15.4 | 138.6 ± 15.6 | 137.6 ± 16.4 | 135.6 ± 16.5 | 0.12 |
| Anemia[b] | 544 (21.0) | 481 (18.6) | 514 (19.9) | 581 (22.5) | 772 (29.9) | <0.001 |

*Continued on the next page*

**TABLE 1 Continued**

| | Quintile 1 ≤620 pg/mL (n = 2,634) | Quintile 2 621-1,039 pg/mL (n = 2,627) | Quintile 3 1,040-1,654 pg/mL (n = 2,625) | Quintile 4 1,655-2,995 pg/mL (n = 2,628) | Quintile 5 ≥2,996 pg/mL (n = 2,628) | *P* Value |
|---|---|---|---|---|---|---|
| Treatment | | | | | | |
| Pretrial use of ACEI or ARB | 2,443 (92.7) | 2,472 (94.1) | 2,488 (94.8) | 2,499 (95.1) | 2,568 (97.7) | <0.001 |
| Beta-blocker | 2,182 (82.8) | 2,321 (88.4) | 2,345 (89.3) | 2,350 (89.4) | 2,394 (91.1) | <0.001 |
| Mineralocorticoid antagonist | 925 (35.1) | 1,149 (43.7) | 1,179 (44.9) | 1,229 (46.8) | 1,411 (53.7) | <0.001 |
| Loop diuretic agent | 662 (25.1) | 1,160 (44.2) | 1,248 (47.5) | 1,414 (53.8) | 1,847 (70.3) | <0.001 |
| Implantable cardioverter-defibrillator | 116 (4.4) | 285 (10.8) | 283 (10.8) | 281 (10.7) | 294 (11.2) | <0.001 |

Values are mean ± SD, n (%), or median (Q1-Q3), unless otherwise indicated. Body mass index was missing in 12 cases, blood pressure and heart rate in 1 case, NYHA functional class in 15 cases, time from diagnosis of HF in 12 cases, ischemic cause in 1 case, LVEF in 1 case, history of atrial fibrillation in 4 cases, history of stroke in 10 cases, COPD in 4 cases, electrocardiography data in 66 cases, eGFR and serum creatinine in 27 cases, blood urea nitrogen in 95 cases, serum sodium in 111 cases, and hemoglobin in 209 cases. [a]Laboratory data at screening are shown. [b]Hemoglobin <130 g/L in males, <120 g/L in females.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous catheter intervention.

## RESULTS

Among the 13,195 patients enrolled in PARADIGM-HF and PARAGON-HF, 14 in PARADIGM-HF and 39 in PARAGON-HF did not have a baseline NT-proBNP level measured, leaving 13,142 (99.6%) for analysis in this study. Of these, 6,570 patients were randomized to sacubitril/valsartan, and 6,572 patients were randomized to enalapril or valsartan. The median level of NT-proBNP at baseline was 1,307 pg/mL (Q1-Q3: 702-2,513 pg/mL); 1,615 pg/mL (Q1-Q3: 888-3,231 pg/mL) in PARADIGM-HF and 911 pg/mL (Q1-Q3: 464-1,613 pg/mL) in PARAGON-HF, respectively (Supplemental Figure 1). Patients were categorized by the quintile of NT-proBNP level; patients in quintile 1 had NT-proBNP level ≤620 pg/mL, those in quintile 2 621-1,039 pg/mL, those in quintile 3 1,040-1,654 pg/mL, those in quintile 4 1,655-2,995 pg/mL, and those in quintile 5 ≥2,996 pg/mL.

**PATIENT CHARACTERISTICS.** Many baseline characteristics including demographics, comorbidities, and functional status differed according to NT-proBNP level (Table 1). Patients with higher NT-proBNP levels were more often male, less frequently White (and more frequently Asian), and had a lower average BMI. Age was similar across quintiles of NT-proBNP level. Regarding clinical history, patients with higher NT-proBNP levels were more likely to have a history of AF (28.6% in quintile 1 vs 46.1% in quintile 5) and were more likely to have a history of stroke. Conversely, patients with higher NT-proBNP levels less often had a history of hypertension and diabetes mellitus.

Regarding HF characteristics, higher NT-proBNP levels were associated with higher NYHA functional class, longer duration of HF, and lower LVEF (49.0% in quintile 1 vs 31.7% in quintile 5). The median NT-proBNP level was higher in patients with AF on their ECG at screening (1,774 pg/mL [Q1-Q3: 1,178-2,998 pg/mL] vs compared 1,481 pg/mL [Q1-Q3: 747-2,586 pg/mL] in patients without AF). Only 6.2% of patients in quintile 1 had AF on their ECG compared to 20.0% in quintile 2, 38.5% in quintile 3, 41.8% in quintile 4, and 35.5% in quintile 5.

As NT-proBNP levels increased, eGFR values decreased. Patients with higher NT-proBNP also had lower systolic blood pressure and higher heart rates.

Pretrial use of an angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker, beta-blocker, mineralocorticoid receptor antagonist, loop diuretic, and implantable cardioverter-defibrillator was more common among patients with higher NT-proBNP.

**PRIMARY AND SECONDARY OUTCOMES ACCORDING TO NT-proBNP LEVELS.** The rate (per 100 patient-years) of the primary composite outcome of HF hospitalization or cardiovascular death increased with increasing NT-proBNP levels was 5.9 (95% CI: 5.3-6.5) in quintile 1; 7.5 (95% CI: 6.9-8.2) in quintile 2; 9.0 (95% CI: 8.2-9.7) in quintile 3; 12.0 (95% CI: 11.1-12.9) in quintile 4; and 20.8 (95% CI: 19.6-22.2) in quintile 5 (Table 2, Figure 1). The adjusted HR, with quintile 1 as the reference group, was 1.30 (95% CI: 1.13-1.49) for quintile 2, 1.56 (95% CI: 1.36-1.79) for quintile 3, 2.03 (95% CI: 1.77-2.32) for quintile 4, and 3.33 (95% CI: 2.91-3.81) for quintile 5. Similar trends were observed for the other outcomes.

**EFFECTS OF SACUBITRIL/VALSARTAN ON OUTCOMES ACCORDING TO BASELINE NT-proBNP LEVEL.** The benefit of sacubitril/valsartan, compared to enalapril or valsartan, was consistent across the quintile categories of NT-proBNP levels for all outcomes examined (Table 3). The HR for the primary composite outcome

**TABLE 2 Outcomes According to Quintile Categories of NT-proBNP Levels at Baseline**

| | Quintile 1 ≤620 pg/mL (n = 2,634) | Quintile 2 621-1,039 pg/mL (n = 2,627) | Quintile 3 1,040-1,654 pg/mL (n = 2,625) | Quintile 4 1,655-2,995 pg/mL (n = 2,628) | Quintile 5 ≥2,996 pg/mL (n = 2,628) |
|---|---|---|---|---|---|
| HF hospitalization or CV death | | | | | |
| Number of events (%) | 403 (15.3) | 468 (17.8) | 545 (20.8) | 685 (26.1) | 1,002 (38.1) |
| Rate (95% CI) | 5.9 (5.3-6.5) | 7.5 (6.9-8.2) | 9.0 (8.2-9.7) | 12.0 (11.1-12.9) | 20.8 (19.6-22.2) |
| Unadjusted HR (95% CI)[a] | Ref. | 1.27 (1.11-1.46) | 1.52 (1.33-1.73) | 2.02 (1.78-2.30) | 3.47 (3.07-3.93) |
| Adjusted HR (95% CI)[b] | Ref. | 1.30 (1.13-1.49) | 1.56 (1.36-1.79) | 2.03 (1.77-2.32) | 3.33 (2.91-3.81) |
| HF hospitalization | | | | | |
| Number of events (%) | 304 (11.5) | 306 (11.7) | 360 (13.7) | 448 (17.1) | 607 (23.1) |
| Rate (95% CI) | 4.4 (3.9-4.9) | 4.9 (4.4-5.5) | 5.9 (5.3-6.6) | 7.9 (7.2-8.6) | 12.6 (11.7-13.7) |
| Unadjusted HR (95% CI)[a] | Ref. | 1.17 (1.00-1.38) | 1.41 (1.21-1.65) | 1.90 (1.64-2.21) | 3.20 (2.76-3.71) |
| Adjusted HR (95% CI)[b] | Ref. | 1.21 (1.02-1.42) | 1.46 (1.24-1.72) | 1.93 (1.64-2.27) | 3.12 (2.65-3.68) |
| CV death | | | | | |
| Number of events (%) | 154 (5.9) | 224 (8.5) | 264 (10.1) | 352 (13.4) | 669 (25.5) |
| Rate (95% CI) | 2.1 (1.8-2.5) | 3.4 (3.0-3.9) | 4.0 (3.6-4.5) | 5.6 (5.0-6.2) | 12.3 (11.4-13.2) |
| Unadjusted HR (95% CI)[a] | Ref. | 1.45 (1.18-1.78) | 1.73 (1.41-2.11) | 2.32 (1.91-2.82) | 4.69 (3.90-5.64) |
| Adjusted HR (95% CI)[b] | Ref. | 1.45 (1.17-1.79) | 1.72 (1.39-2.11) | 2.24 (1.83-2.74) | 4.16 (3.41-5.07) |
| All-cause death | | | | | |
| Number of events (%) | 252 (9.6) | 315 (12.0) | 374 (14.3) | 493 (18.8) | 795 (30.3) |
| Rate (95% CI) | 3.4 (3.0-3.9) | 4.8 (4.3-5.3) | 5.7 (5.1-6.3) | 7.8 (7.2-8.6) | 14.6 (13.6-15.6) |
| Unadjusted HR (95% CI)[a] | Ref. | 1.34 (1.13-1.58) | 1.59 (1.36-1.88) | 2.17 (1.86-2.53) | 3.90 (3.36-4.54) |
| Adjusted HR (95% CI)[b] | Ref. | 1.31 (1.11-1.56) | 1.54 (1.30-1.83) | 2.03 (1.72-2.40) | 3.37 (2.86-3.97) |
| Total HF hospitalizations | | | | | |
| Number of events | 512 | 488 | 581 | 737 | 1,085 |
| Rate (95% CI) | 7.0 (6.1-8.1) | 7.4 (6.4-8.6) | 8.8 (7.8-10.1) | 11.7 (10.5-13.1) | 19.9 (18.1-21.9) |
| Unadjusted rate ratio (95% CI)[a] | Ref. | 1.15 (0.94-1.40) | 1.37 (1.14-1.66) | 1.85 (1.55-2.22) | 3.40 (2.85-4.06) |
| Adjusted rate ratio (95% CI)[b] | Ref. | 1.19 (0.98-1.46) | 1.43 (1.17-1.73) | 1.91 (1.58-2.31) | 3.37 (2.78-4.09) |
| Total HF hospitalizations and CV death | | | | | |
| Number of events | 666 | 712 | 845 | 1,089 | 1,754 |
| Rate (95% CI) | 9.1 (8.1-10.3) | 10.8 (9.7-12.1) | 12.9 (11.7-14.2) | 17.4 (15.9-19.0) | 32.1 (29.9-34.6) |
| Unadjusted rate ratio (95% CI)[a] | Ref. | 1.22 (1.03-1.44) | 1.46 (1.24-1.70) | 1.96 (1.69-2.28) | 3.73 (3.21-4.33) |
| Additional rate ratio (95% CI)[b] | Ref. | 1.25 (1.06-1.48) | 1.50 (1.27-1.76) | 1.99 (1.69-2.33) | 3.58 (3.05-4.21) |

Rates are given per 100 patient-years. [a]Baseline model adjusted for randomized treatment and stratified by region and trial. [b]Adjusted for randomized treatment, age, sex, race, body mass index, systolic blood pressure, heart rate, NYHA class III or IV, time from diagnosis of HF, prior HF hospitalization, left ventricular ejection fraction, hypertension, history of myocardial infarction, history of stroke, AF on electrocardiography at screening, and eGFR, and stratified by region and trial.

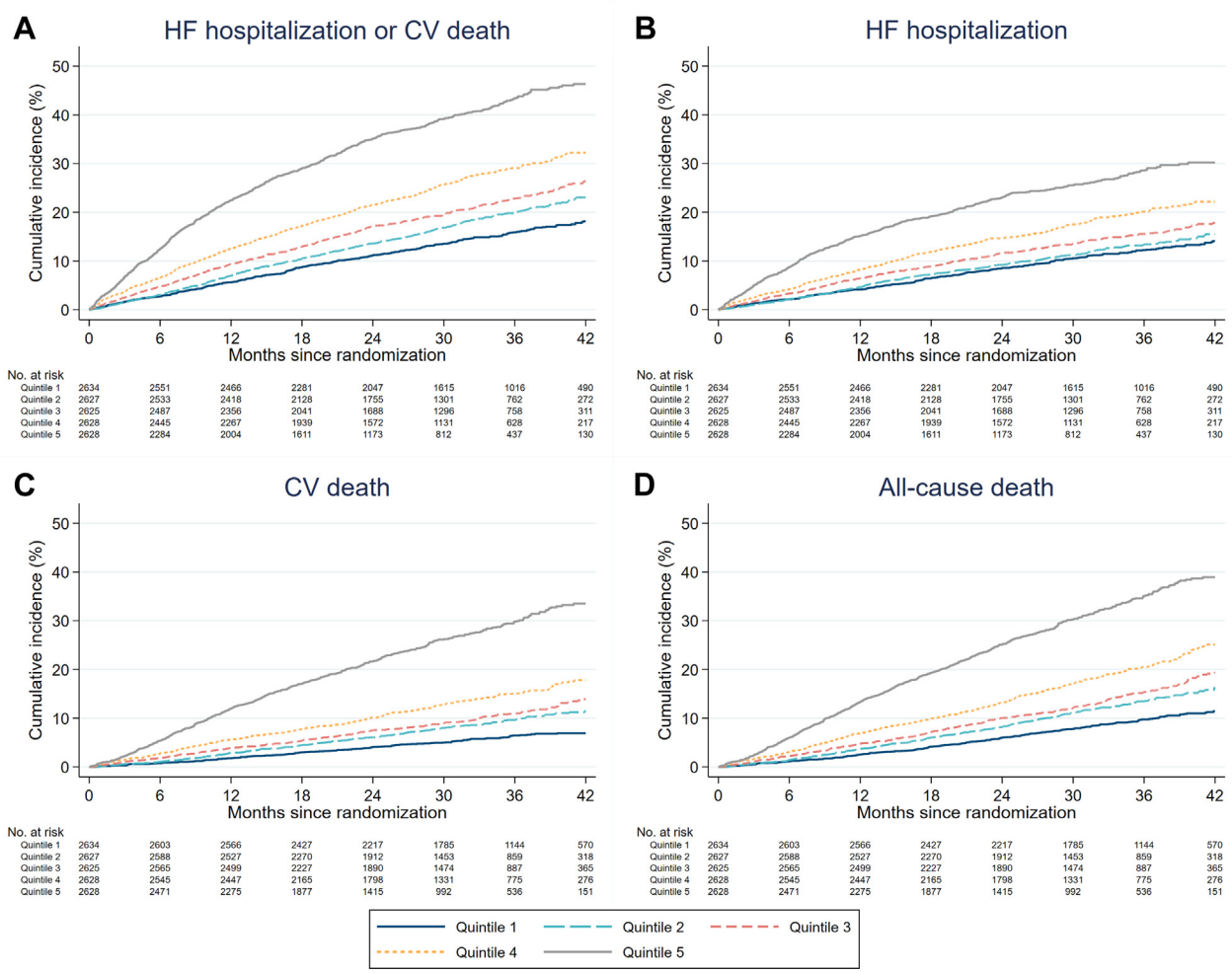
CV = cardiovascular; Ref. = Reference; other abbreviations as in Table 1.

in the overall pooled population was 0.84 (95% CI: 0.78-0.90), and it was 0.79 (95% CI: 0.65-0.96) in quintile 1; 0.87 (95% CI: 0.72-1.04) in quintile 2; 0.79 (95% CI: 0.66-0.93) in quintile 3; 0.85 (95% CI: 0.73-0.99) in quintile 4; and 0.86 (95% CI: 0.76-0.97) in quintile 5, with $P$ for interaction = 0.86. The consistent benefit was similarly observed if patients were divided according to NT-proBNP <1,000 pg/mL or ≥1,000 pg/mL (Supplemental Table 1). Examined as a continuous variable, there was no interaction between NT-proBNP and the effect of randomized treatment on the primary outcome ($P$ = 0.49) (Figure 2). The absolute rate difference between sacubitril/valsartan and enalapril or valsartan was greater in patients with higher NT-proBNP levels as a result of the higher event rate among people with a higher NT-proBNP level (Central Illustration). The number of patients needed to be treated (NNT) over the median trial duration of 31 months (Q1-Q3: 22-38 months) to prevent 1 patient from experiencing the primary endpoint was 37 (95% CI: 27-59) in quintile 1 and 16 (95% CI: 12-25) in quintile 5 of NT-proBNP.

The effects of sacubitril/valsartan on the other outcomes of interest were also consistent across quintiles of NT-proBNP ($P$ for interaction for all outcomes ≥0.5) (Table 3). The results were also consistent when NT-proBNP was modelled as a continuous variable ($P$ for interaction for all outcomes > 0.1) (Figure 2).

**EFFECTS OF SACUBITRIL/VALSARTAN ON HF HOSPITALIZATION OR CARDIOVASCULAR DEATH ACCORDING TO NT-proBNP LEVELS IN SUBGROUPS OF INTEREST.** The effect of sacubitril/valsartan, compared to enalapril

**FIGURE 1** Kaplan-Meier Curves for Each Outcome According to Quintiles of NT-proBNP




Kaplan-Meier curves according to quintiles of N-terminal pro-B-type natriuretic peptide (NT-proBNP) for the composite of hospitalization or cardiovascular (CV) death (A), heart failure (HF) hospitalization (B), CV death (C), and all-cause death (D).

or valsartan, on the primary outcome, according to NT-proBNP level in the interest subgroups (male vs female; no AF vs AF; obese vs nonobese; and eGFR ≥60 mL/min/1.73 $m^2$ vs eGFR <60 mL/min/1.73 $m^2$) are shown in Supplemental Table 2. There was no significant interaction between quintiles of NT-proBNP and the effect of randomized treatment on the primary outcome in each subgroup of interest (*P* for interaction for all outcomes >0.5). Even when analyzed in more detailed subgroups of BMI, the consistent benefit was similarly observed (Supplemental Table 3). The results were also consistent when NT-proBNP was modelled as a continuous variable (*P* for interaction for all outcomes >0.2) (**Figure 3**).

## DISCUSSION

As expected, in this pooled analysis of PARADIGM-HF and PARAGON-HF, demographics, comorbidities, and HF status varied according to NT-proBNP level at baseline. Also as expected, higher NT-proBNP levels were associated with a greater risk of clinical outcomes in the overall HF population, although this has rarely been demonstrated across such a wide range of LVEFs. NT-proBNP appears useful for risk stratification in patients HF, irrespective of LVEF phenotype, and those in the highest NT-proBNP quintile had a 3-times higher risk of HF hospitalization or cardiovascular death compared to those in the lowest quintile, even after adjustment for other prognostic

**TABLE 3 Effect of Sacubitril/Valsartan on Outcomes According to Quintile Categories of NT-proBNP Levels at Baseline**

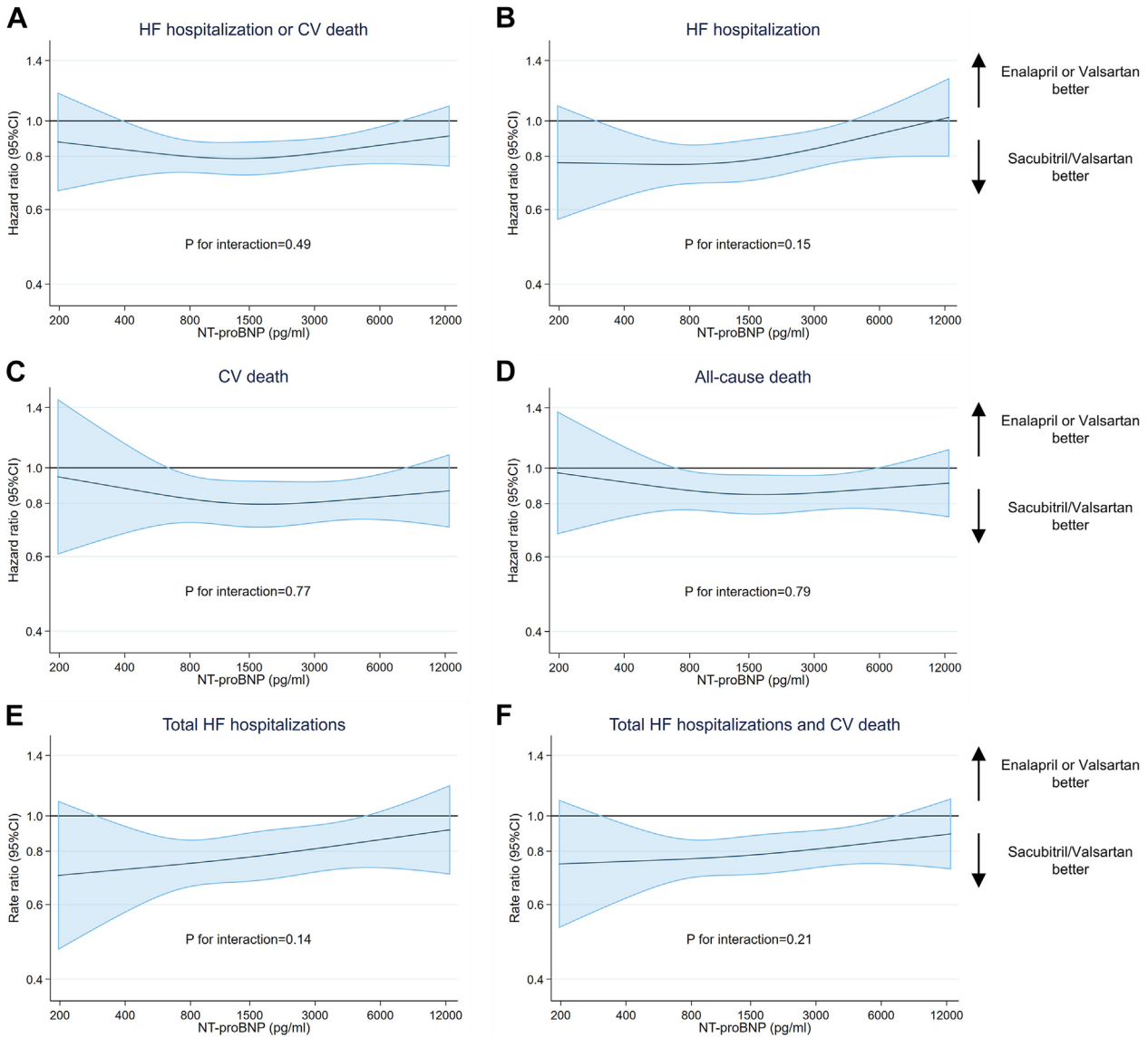
| | Quintile 1 ≤620 pg/mL | | Quintile 2 621-1,039 pg/mL | | Quintile 3 1,040-1,654 pg/mL | |
|---|---|---|---|---|---|---|
| | Sacubitril/Valsartan (n = 1,313) | Enalapril or Valsartan (n = 1,321) | Sacubitril/Valsartan (n = 1,317) | Enalapril or Valsartan (n = 1,310) | Sacubitril/Valsartan (n = 1,308) | Enalapril or Valsartan (n = 1,317) |
| HF hospitalization or CV death | | | | | | |
| Number of events (%) | 178 (13.6) | 225 (17.0) | 224 (17.0) | 244 (18.6) | 244 (18.7) | 301 (22.9) |
| Rate (95% CI) | 5.1 (4.4-5.9) | 6.6 (5.8-7.5) | 7.1 (6.2-8.1) | 8.0 (7.0-9.0) | 7.9 (7.0-9.0) | 10.0 (8.9-11.2) |
| HR (95% CI)[a] | 0.79 (0.65-0.96) | | 0.87 (0.72-1.04) | | 0.79 (0.66-0.93) | |
| HF hospitalization | | | | | | |
| Number of events (%) | 127 (9.7) | 177 (13.4) | 146 (11.1) | 160 (12.2) | 163 (12.5) | 197 (15.0) |
| Rate (95% CI) | 3.7 (3.1-4.4) | 5.2 (4.5-6.0) | 4.6 (3.9-5.4) | 5.2 (4.5-6.1) | 5.3 (4.5-6.2) | 6.5 (5.7-7.5) |
| HR (95% CI)[a] | 0.72 (0.57-0. 90) | | 0.84 (0.67-1.06) | | 0.80 (0.65-0.98) | |
| CV death | | | | | | |
| Number of events (%) | 68 (5.2) | 86 (6.5) | 108 (8.2) | 116 (8.9) | 114 (8.7) | 150 (11.4) |
| Rate (95% CI) | 1.9 (1.5-2.4) | 2.3 (1.9-2.9) | 3.2 (2.7-3.9) | 3.6 (3.0-4.3) | 3.5 (2.9-4.2) | 4.6 (3.9-5.4) |
| HR (95% CI)[a] | 0.78 (0.57-1.08) | | 0.90 (0.69-1.17) | | 0.76 (0.59-0.97) | |
| All-cause death | | | | | | |
| Number of events (%) | 114 (8.7) | 138 (10.5) | 154 (11.7) | 161 (12.3) | 171 (13.1) | 203 (15.4) |
| Rate (95% CI) | 3.1 (2.6-3.7) | 3.8 (3.2-4.4) | 4.6 (3.9-5.4) | 5.0 (4.2-5.8) | 5.2 (4.5-6.0) | 6.2 (5.4-7.1) |
| HR (95% CI)[a] | 0.82 (0.64-1.05) | | 0.92 (0.74-1.15) | | 0.84 (0.68-1.03) | |
| Total HF hospitalizations | | | | | | |
| Number of events | 212 | 300 | 235 | 253 | 248 | 333 |
| Rate (95% CI) | 5.8 (4.6-7.4) | 8.2 (6.9-9.8) | 7.0 (5.8-8.6) | 7.8 (6.3-9.7) | 7.5 (6.3-9.1) | 10.2 (8.6-12.1) |
| Rate ratio (95% CI)[a] | 0.73 (0.55-0.98) | | 0.85 (0.63-1.14) | | 0.73 (0.57-0.94) | |
| Total HF hospitalizations and CV death | | | | | | |
| Number of events | 280 | 386 | 343 | 369 | 362 | 483 |
| Rate (95% CI) | 7.7 (6.4-9.3) | 10.5 (9.0-12.3) | 10.2 (8.8-12.0) | 11.4 (9.7-13.4) | 11.0 (9.5-12.8) | 14.8 (12.9-17.0) |
| Rate ratio (95% CI)[a] | 0.75 (0.58-0.95) | | 0.86 (0.69-1.09) | | 0.74 (0.60-0.91) | |

**TABLE 3 Continued**

| | Quintile 4 1,655-2,995 pg/mL | | Quintile 5 ≥2,996 pg/mL | | |
|---|---|---|---|---|---|
| | Sacubitril/Valsartan (n = 1,326) | Enalapril or Valsartan (n = 1,302) | Sacubitril/Valsartan (n = 1,306) | Enalapril or Valsartan (n = 1,322) | *P* Value for Interaction |
| HF hospitalization or CV death | | | | | |
| Number of events (%) | 321 (24.2) | 364 (28.0) | 468 (35.8) | 534 (40.4) | |
| Rate (95% CI) | 11.1 (9.9-12.3) | 13.0 (11.7-14.4) | 19.2 (17.6-21.1) | 22.5 (20.6-24.4) | |
| HR (95% CI)[a] | 0.85 (0.73-0.99) | | 0.86 (0.76-0.97) | | 0.86 |
| HF hospitalization | | | | | |
| Number of events (%) | 209 (15.8) | 239 (18.4) | 293 (22.4) | 314 (23.8) | |
| Rate (95% CI) | 7.2 (6.3-8.2) | 8.5 (7.5-9.7) | 12.1 (10.7-13.5) | 13.2 (11.8-14.7) | |
| HR (95% CI)[a] | 0.85 (0.71-1.02) | | 0.91 (0.77-1.06) | | 0.54 |
| CV death | | | | | |
| Number of events (%) | 164 (12.4) | 188 (14.4) | 307 (23.5) | 362 (27.4) | |
| Rate (95% CI) | 5.2 (4.5-6.1) | 6.0 (5.2-6.9) | 11.2 (10.0-12.6) | 13.3 (12.0-14.7) | |
| HR (95% CI)[a] | 0.85 (0.69-1.05) | | 0.85 (0.73-1.00) | | 0.86 |
| All-cause death | | | | | |
| Number of events (%) | 237 (17.9) | 256 (19.7) | 373 (28.6) | 422 (31.9) | |
| Rate (95% CI) | 7.5 (6.6-8.5) | 8.2 (7.2-9.2) | 13.6 (12.3-15.1) | 15.5 (14.1-17.0) | |
| HR (95% CI)[a] | 0.92 (0.77-1.10) | | 0.89 (0.77-1.02) | | 0.93 |
| Total HF hospitalizations | | | | | |
| Number of events | 328 | 409 | 511 | 574 | |
| Rate (95% CI) | 10.4 (8.9-12.2) | 13.1 (11.2-15.3) | 18.7 (16.2-21.7) | 21.1 (18.6-24.0) | |
| Rate ratio (95% CI)[a] | 0.81 (0.65-1.01) | | 0.88 (0.73-1.07) | | 0.69 |
| Total HF hospitalizations and CV death | | | | | |
| Number of events | 492 | 597 | 818 | 936 | |
| Rate (95% CI) | 15.6 (13.8-17.7) | 19.1 (16.9-21.7) | 29.9 (26.8-33.5) | 34.4 (31.2-37.9) | |
| Rate ratio (95% CI)[a] | 0.82 (0.69-0.98) | | 0.87 (0.75-1.01) | | 0.59 |

Rates are given per 100 patient years. [a]Stratified by region and trial.
Abbreviations as in Tables 1 and 2.

**FIGURE 2** **Treatment Effect of Sacubitril/Valsartan on Outcomes Across the Range of NT-proBNP Levels at Baseline**

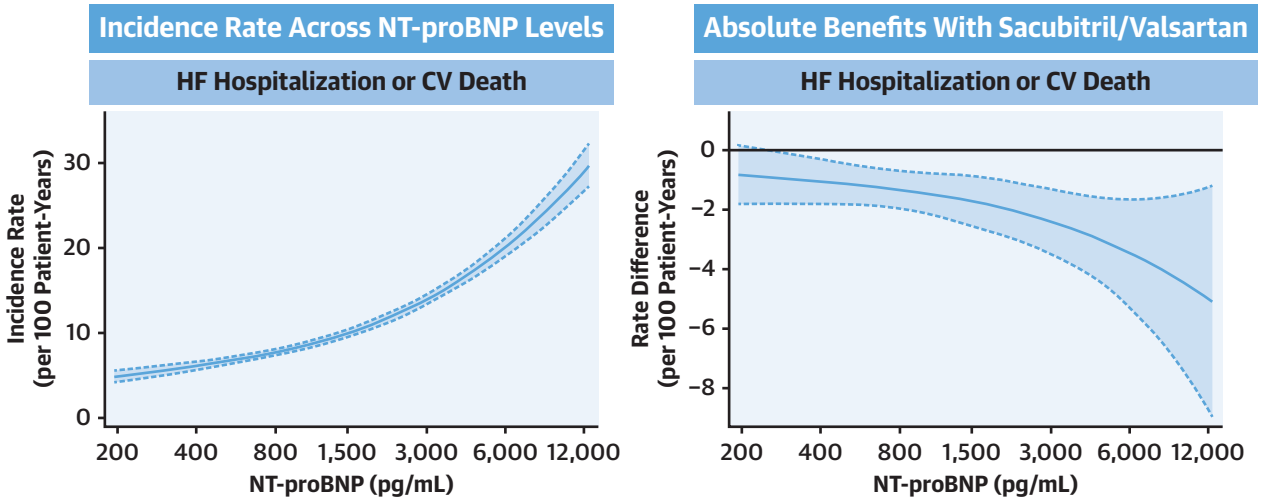



Effect of sacubitril/valsartan on the composite of HF hospitalization or CV death (A), HF hospitalization (B), CV death (C), all-cause death (D), total (first and recurrent) HF hospitalizations (E), composite of total HF hospitalizations and CV death (F), across the range of NT-proBNP levels at baseline. The range of NT-proBNP levels shown is between the 2nd and 98th percentile. Abbreviations as in **Figure 1**.

variables, including LVEF. Of more interest, the relative risk reductions of all outcomes with sacubitril/valsartan were consistent across NT-proBNP levels at baseline. Consequently, there was a greater absolute risk reduction in patients with higher NT-proBNP levels. Finally, the benefits of sacubitril/valsartan were similar irrespective of NT-proBNP concentration in the subgroups defined by baseline characteristics known to influence NT-proBNP level.[1,2,14-19]

As described in the introduction, an interaction has been described between NT-proBNP and the effect of 2 recently developed therapies for HF. Among patients with HFrEF and LVEF ≤35% enrolled in GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility

**CENTRAL ILLUSTRATION** **Incidence Rate and Rate Differences With Sacubitril/Valsartan Treatment for the Composite of HF Hospitalization or CV Death Across the Range of NT-proBNP Levels at Baseline**

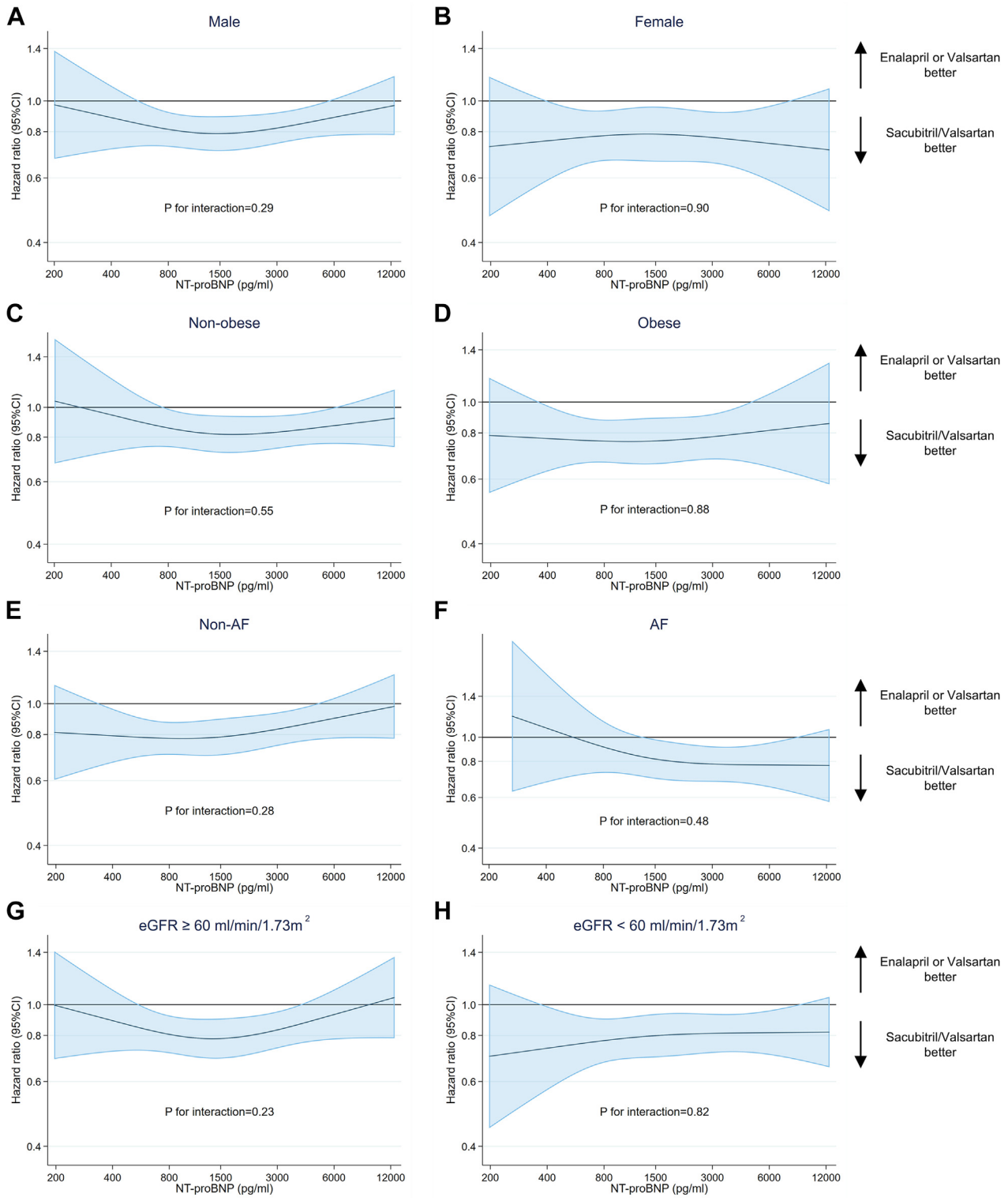



**Kondo T, et al. JACC Heart Fail. 2025;■(■):■-■.**

Incidence rates for the composite of heart failure (HF) hospitalization or cardiovascular (CV) death were calculated in patients with HF with reduced ejection fraction/HF with mildly reduced ejection fraction/HF with preserved ejection fraction across the range of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at baseline. Rate differences for the incidence rate of the composite of HF hospitalization or CV death are calculated by applying a consistent relative risk reduction with sacubitril/valsartan (observed in the overall population) to participants in the control group across the range of NT-proBNP levels at baseline. The range of NT-proBNP levels shown is between the 2nd and 98th percentile.

in Heart Failure), the median NT-proBNP was 1,998 pg/mL (Q1-Q3: 993-4,079 pg/mL). There was an interaction between baseline NT-proBNP level and the relative risk reduction in the primary endpoint (a worsening HF event or cardiovascular death) due to treatment with omecamtiv mecarbil, with a greater effect in patients with a higher NT-proBNP (*P* for interaction = 0.005 for NT-proBNP analyzed as a continuous variable).[4] Conversely, among patients with LVEF <45% participating in VICTORIA, the median NT-proBNP was 2,816 pg/mL (Q1-Q3: 1,556-5,314 pg/mL) and the relative risk reduction in the primary endpoint (hospitalization for HF or cardiovascular death) with vericiguat was less in patients with a higher NT-proBNP (*P* for interaction = 0.002 for NT-proBNP analyzed as a continuous variable).[3] Some support for the hypothesis that higher baseline NT-proBNP levels might identify "treatment non-responders" comes from analyses of TOPCAT (median NT pro-BNP 900 pg/mL [Q1-Q3: 557-1,920 pg/mL]) with spironolactone and I-PRESERVE (median NT pro-BNP 339 pg/mL [Q1-Q3: 133-964 pg/mL]) with irbesartan although these trials did not show a significant effect of treatment overall meaning interpretation of subgroup findings and interactions is even more difficult than usual.[5,6] No such interaction between NT-proBNP level and treatment effect was seen in the present study (where the median NT pro-BNP was 1,307 pg/mL [Q1-Q3: 702-2,513 pg/mL]) and the relative risk reduction with sacubitril/valsartan was consistent across the full range of LVEF in patients with HF in PARADIGM-HF and PARAGON-HF. Because of this, the absolute risk reduction was larger in patients with a higher NT-proBNP level who were at greater risk and the resulting NNT over the trial duration in the highest NT-proBNP quintile was only 16 for the primary outcome compared to an NNT of 37 for patients with the lowest NT-proBNP quintile. The only other similar finding we know of is with sodium-glucose cotransporter 2 inhibitors, specifically in analyses of the DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure), DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure), and the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Preserved Ejection Fraction) trials.[20-23] These observations are important for clinical practice as more severely ill patients (with higher NT-proBNP levels) tend to receive less guideline-

**FIGURE 3** **Effect of Sacubitril/Valsartan on the Primary Outcome (HF Hospitalization or CV Death) Across the Range of NT-ProBNP Level in Subgroups of Interest**




Effects of sacubitril/valsartan on the composite of HF hospitalization or CV death in males (A), females (B), nonobese (C), obese (D), no-atrial fibrillation (no-AF) (E), in AF (F), in eGFR ≥60 mL/min/1.73 $m^2$ (G), and in eGFR <60 mL/min/1.73 $m^2$ (H) across the range of NT-proBNP levels at baseline. The range of NT-proBNP levels shown is between the 2nd and 98th percentile. eGFR = estimated glomerular filtration rate; other abbreviations as in Figure 1.

recommended therapy yet have, potentially, the most to gain from treatment.

**STUDY LIMITATIONS.** Patients enrolled in these clinical trials were selected according to specific inclusion and exclusion criteria; therefore, our results may not be generalizable to all patients with HF in the general population. The analysis of NT-proBNP and outcomes by quintiles was determined post hoc. There were different NT-proBNP enrollment thresholds for patients with AF or prior HF hospitalization which may have affected the relationship between NT-proBNP level and outcome. As all patients had to have an entry NT-proBNP level above at least 200 pg/mL, we cannot be sure about the effect of sacubitril/valsartan in patients with an NT-proBNP concentration below this cutoff. NT-proBNP levels were higher in VICTORIA than in other trials although overlapped substantially with GALACTIC-HF. Moreover, a qualitatively similar interaction between NT-proBNP level and the effect of omecamtiv mecarbil was seen for participants enrolled in the inpatient setting (where NT-proBNP levels were much higher) and the outpatient setting. In addition, although PIONEER-HF was small and not a morbidity/mortality trial, sacubitril/valsartan improved clinical outcomes in patients with a median baseline NT-proBNP of 4,821 pg/mL (Q1-Q3: 3,109-8,767 pg/mL).[24]

## CONCLUSIONS

In patients with HF across the range of LVEF, higher NT-proBNP levels were associated with many adverse prognostic features, including lower BMI, worse symptoms, AF, and renal impairment. Among these patients, higher NT-proBNP levels were also associated with higher risks of HF hospitalization and cardiovascular death. The benefits of sacubitril/valsartan on these outcomes were consistent regardless of NT-proBNP levels, with greater absolute benefits in patients with higher NT-proBNP levels.

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

The effects of sacubitril/valsartan were consistent irrespective of NT-proBNP level in patients with HF across the range of LVEF, with greater absolute risk reduction in patients with higher NT-proBNP levels who were at greater risk.

### TRANSLATIONAL OUTLOOK:

The effect of some HF drugs varies according to NP level; but this is not the case for sacubitril/valsartan. Future drugs added for HF treatment should be evaluated for whether their efficacy differs according to NP levels.

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**KEY WORDS** clinical trial, heart failure, natriuretic peptide, outcomes, sacubitril/valsartan

**APPENDIX** For supplemental tables and a figure, please see the online version of this paper.