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CLINICAL RESEARCH

# Ejection Fraction, Biomarkers, and Outcomes and Impact of Vericiguat on Outcomes Across EF in VICTORIA

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## ABSTRACT

**BACKGROUND** Vericiguat reduced the risk of cardiovascular death (CVD) or hospitalization for heart failure (HF) in patients with worsening HF and reduced left ventricular ejection fraction (LVEF).

**OBJECTIVES** The authors assessed the association of LVEF with biomarker levels, risk of outcome, and whether the effect of vericiguat was homogeneous across LVEF in the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure With Reduced Ejection Fraction) trial.

**METHODS** Patients were grouped by LVEF tertiles (≤24%, 25%-33%, and >33%). Patient characteristics, clinical outcomes, and efficacy and safety of vericiguat were examined by tertile. Prespecified biomarkers including N-terminal pro-B-type natriuretic peptide, cardiac troponin T, growth differentiation factor 15, interleukin 6, high-sensitivity C-reactive protein, and cystatin C were examined.

**RESULTS** The mean LVEF was 29% ± 8% (range: 5%-45%). A pattern of higher N-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactive protein, and interleukin 6 was evident in patients in the lowest LVEF tertile vs the other tertiles. Patients with lower LVEF experienced higher rates of the composite outcome (41.7%, 36.3%, and 33.4% for LVEF ≤24, 25-33, and >33; $P < 0.001$). There was no significant treatment effect heterogeneity of vericiguat across LVEF groups (adjusted HR from lowest to highest tertiles: 0.79 [95% CI: 0.68-0.94]; 0.95 [95% CI: 0.82-1.11]; 0.94 [95% CI: 0.79-1.11]; $P$ for interaction = 0.222), although the HR was numerically lower in the lowest tertile. There was also no heterogeneity of effect for CVD and HF hospitalization individually ($P$ interaction for CVD = 0.964; HF hospitalization = 0.438). Discontinuation of treatment because of adverse events, symptomatic hypotension, or syncope was consistent across the range of LVEF.

**CONCLUSIONS** Patients with lower LVEF had a distinctive biomarker profile and a higher risk for adverse clinical outcomes vs those with a higher LVEF. There was no significant interaction for the benefit of vericiguat across LVEF tertiles, although the largest signal for benefit in both the primary outcome and HF hospitalizations was noted in tertile 1 (LVEF ≤24%). (Vericiguat Global Study in Subjects with Heart Failure With Reduced Ejection Fraction [VICTORIA]; NCT02861534) (J Am Coll Cardiol HF 2023;11:583-592) © 2023 by the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**ARNI** = angiotensin receptor/neprilysin inhibitor

**CVD** = cardiovascular death

**GDF** = growth differentiation factor

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**hsCRP** = high-sensitivity C-reactive protein

**IL** = interleukin

**LVEF** = left ventricular ejection fraction

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

Left ventricular ejection fraction (LVEF) is commonly used in trials to categorize patients with heart failure (HF) into those with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Previous HFrEF trials have used an LVEF inclusion threshold of either ≤40% or ≤35%, although preserved LVEF is generally defined as ≥50%.[1-6] This classification has resulted in an LVEF evidence gap leading to attempts to designate a cohort of patients with an LVEF between 40% and 50% as mildly reduced HF. The VICTORIA (Vericiguat Global Study in Subjects With Heart Failure with Reduced Ejection Fraction) trial demonstrated that in patients with HFrEF and a recent worsening event, treatment with the soluble guanylate cyclase stimulator vericiguat added to comprehensive background medical therapy reduced the combined endpoint of cardiovascular death (CVD) or HF hospitalization.[7] This trial was distinct in that it extended the inclusion criteria for LVEF to 45% and required that patients have unusually high N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in conjunction with a recent worsening HF event. In this context, 2 recent trials evaluating a sodium-glucose cotransporter 2 inhibitor and an angiotensin receptor/neprilysin inhibitor (ARNI) suggested that improvement in outcomes may extend across a wider spectrum of LVEF in patients with HFrEF.[8-11] Additionally, although the association of treatment benefit with patient-specific biomarker profiles is often used to guide therapy, monitor disease severity, and characterize the pathophysiology of HF, their relationship to LVEF is not well established. The aim of the current study was to examine the efficacy and safety of vericiguat across the spectrum of LVEF in HFrEF. We also evaluated the natural history, clinical outcomes according to LVEF, and potential mechanistic insights provided by a panel of biomarkers acquired at randomization.

## METHODS

**STUDY DESIGN AND PATIENTS.** In brief, VICTORIA (Vericiguat Global Study in Subjects with Heart Failure With Reduced Ejection Fraction; NCT02861534) was a multinational, randomized, double-blind, placebo-controlled trial that enrolled 5,050 patients with chronic HF (New York Heart Association functional class II-IV) with reduced LVEF (<45%) and an elevated NT-proBNP level. All patients enrolled were required to have evidence of worsening HF defined as hospitalization within 6 months before randomization or outpatient intravenous diuretic therapy within the previous 3 months. Patients were randomly assigned to receive vericiguat (target dose: 10 mg daily) or a matching placebo. LVEF was measured within 12 months of enrollment. Ejection fraction was determined at the sites for all participants and recorded on case report forms as numbers. The median duration of follow-up was 11 months.

The protocol was approved by participating ethics committees and Institutional Review Boards; all patients provided written informed consent. The VICTORIA trial design and primary results have been published previously.[7,12,13]

**OUTCOMES.** The primary outcome was a composite of CVD or first HF hospitalization. The secondary outcomes included the components of the primary outcome, first HF hospitalizations, a composite of all-cause death or first HF hospitalization, and all-cause death. Prespecified safety outcomes of clinical interest included symptomatic hypotension and syncope. Biomarkers including high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, high-sensitivity troponin T, cystatin C, and growth differentiation factor (GDF)-15 were acquired at baseline and measured using standard techniques at the Inova Heart and Vascular Institute (Falls Church, Virginia, USA) and the University of Maryland (Baltimore, Maryland, USA).

**STATISTICAL ANALYSIS.** Patients were divided into 3 subgroups based on tertiles of baseline LVEF: ≤24%, 25% to 33%, and >33%. Continuous variables were described using median (25th-75th

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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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**TABLE 1 Baseline Characteristics According to LVEF**

| | Overall (N = 5,036) | LVEF ≤24% (n = 1,472) | LVEF 25%-33% (n = 1,871) | LVEF 34%-45% (n = 1,693) | *P* Value |
|---|---|---|---|---|---|
| Age, y | 69.0 (60.0-76.0) | 65.0 (56.0-73.0) | 69.0 (60.0-76.0) | 71.0 (63.0-79.0) | <0.001 |
| Female | 1,205 (23.9) | 284 (19.3) | 444 (23.7) | 477 (28.2) | <0.001 |
| Race/ethnicity | | | | | <0.001 |
| Asian | 1,130 (22.4) | 306 (20.8) | 429 (22.9) | 395 (23.3) | |
| Black | 248 (4.9) | 125 (8.5) | 77 (4.1) | 46 (2.7) | |
| Other | 428 (8.5) | 182 (12.4) | 163 (8.7) | 83 (4.9) | |
| White | 3,229 (64.1) | 859 (58.4) | 1,201 (64.2) | 1,169 (69.0) | |
| Region | | | | | <0.001 |
| Asia Pacific | 1,181 (23.5) | 315 (21.4) | 440 (23.5) | 426 (25.2) | |
| Eastern Europe | 1,689 (33.5) | 489 (33.2) | 636 (34.0) | 564 (33.3) | |
| Latin and South America | 723 (14.4) | 237 (16.1) | 276 (14.8) | 210 (12.4) | |
| North America | 558 (11.1) | 220 (14.9) | 182 (9.7) | 156 (9.2) | |
| Western Europe | 885 (17.6) | 211 (14.3) | 337 (18.0) | 337 (19.9) | |
| Index event | | | | | <0.001 |
| HF hospitalization 3-6 mo | 869 (17.3) | 257 (17.5) | 342 (18.3) | 270 (15.9) | |
| HF hospitalization <3 mo | 3,367 (66.9) | 1,072 (72.8) | 1,245 (66.5) | 1,050 (62.0) | |
| IV diuretic for HF <3 mo | 800 (15.9) | 143 (9.7) | 284 (15.2) | 373 (22.0) | |
| BMI, kg/m$^2$ | 26.9 (23.7-30.9) | 26.5 (23.6-30.1) | 26.8 (23.7-30.9) | 27.3 (23.8-31.4) | 0.004 |
| MAGGIC risk score | 24 (19-28) | 25 (21-30) | 24 (20-28) | 22 (17-27) | <0.001 |
| NYHA functional class | | | | | <0.001 |
| I/II | 2,972 (59.0) | 819 (55.7) | 1,103 (59.0) | 1,050 (62.0) | |
| III/IV | 2,062 (41.0) | 652 (44.3) | 767 (41.0) | 643 (38.0) | |
| Medical history | | | | | |
| Diabetes | 2,361 (46.9) | 665 (45.2) | 878 (46.9) | 818 (48.3) | 0.078 |
| Hypertension | 3,984 (79.1) | 1,076 (73.1) | 1,476 (78.9) | 1,432 (84.6) | <0.001 |
| Hyperlipidemia | 2,886 (57.3) | 816 (55.4) | 1,057 (56.5) | 1,013 (59.8) | 0.011 |
| Anemia | 1,067 (21.2) | 256 (17.4) | 410 (21.9) | 401 (23.7) | <0.001 |
| COPD | 864 (17.2) | 226 (15.4) | 322 (17.2) | 316 (18.7) | 0.014 |
| PAD | 629 (12.5) | 134 (9.1) | 233 (12.5) | 262 (15.5) | <0.001 |
| Atrial fibrillation | 2,262 (44.9) | 590 (40.1) | 823 (44.0) | 849 (50.1) | <0.001 |
| History of MI | 2,115 (42.0) | 561 (38.1) | 822 (43.9) | 732 (43.2) | 0.005 |
| History of stroke | 572 (11.4) | 170 (11.5) | 212 (11.3) | 190 (11.2) | 0.775 |
| Prior PCI | 1,673 (33.2) | 429 (29.1) | 654 (35.0) | 590 (34.8) | <0.001 |
| Tobacco use | 2,965 (58.9) | 926 (62.9) | 1,084 (57.9) | 955 (56.4) | <0.001 |
| Vitals | | | | | |
| Systolic BP, mm Hg | 119 (109-131) | 114 (106-125) | 118 (109-129) | 124 (113-136) | <0.001 |
| Diastolic BP, mm Hg | 72 (65-80) | 72 (65-80) | 72 (65-80) | 73 (65-80) | 0.578 |
| Heart rate, beats/min | 72 (64-81) | 73 (65-83) | 72 (64-81) | 70 (63-80) | <0.001 |
| Medications/devices | | | | | |
| ACE inhibitor or ARB | 3,693 (73.4) | 1,039 (70.7) | 1,363 (73.0) | 1,291 (76.3) | <0.001 |
| ARNI | 729 (14.5) | 261 (17.8) | 286 (15.3) | 182 (10.8) | <0.001 |
| Beta-blocker | 4,680 (93.1) | 1,366 (92.9) | 1,743 (93.4) | 1,571 (92.9) | 0.961 |
| MRA | 3,537 (70.3) | 1,161 (79.0) | 1,336 (71.6) | 1,040 (61.5) | <0.001 |
| Triple therapy | 3,002 (59.7) | 976 (66.4) | 1,142 (61.2) | 884 (52.3) | <0.001 |
| ICD | 1,395 (27.7) | 543 (36.9) | 571 (30.6) | 281 (16.6) | <0.001 |
| Biventricular pacemaker | 736 (14.6) | 264 (18.0) | 281 (15.1) | 191 (11.3) | <0.001 |

*Continued on the next page*

percentiles) and tested for trends across LVEF levels using Spearman correlations. Categoric variables were presented as frequencies (%) and tested for trends using trend or Cochran-Mantel-Haenszel tests where appropriate. Biomarkers according to LVEF at baseline were presented as medians (25th-75th percentile). The rates of CVD and/or HF hospitalization across tertiles of LVEF were calculated as both frequencies divided by total patients per group and the number of events per 100 patient-years of follow-up.

The relationships between baseline LVEF (tertiles and continuous) and clinical outcomes were evaluated using Cox proportional hazards models. These

**TABLE 1 Continued**

| | Overall (N = 5,036) | LVEF ≤24% (n = 1,472) | LVEF 25%-33% (n = 1,871) | LVEF 34%-45% (n = 1,693) | *P* Value |
|---|---|---|---|---|---|
| Labs at randomization | | | | | |
| Hemoglobin, g/dL | 13.4 (12.1-14.7) | 13.8 (12.5-14.9) | 13.3 (12.0-14.7) | 13.1 (11.8-14.5) | <0.001 |
| Creatinine, mg/dL | 1.2 (0.9-1.6) | 1.2 (0.9-1.5) | 1.2 (0.9-1.6) | 1.2 (0.9-1.6) | 0.037 |
| Sodium, mEq/L | 140 (138-142) | 140 (138-142) | 140 (138-142) | 141 (139-142) | <0.001 |
| Potassium, mEq/L | 4.5 (4.2-4.8) | 4.5 (4.1-4.8) | 4.5 (4.2-4.8) | 4.5 (4.2-4.8) | 0.129 |
| eGFR, mL/min/1.73 $m^2$ | 58.4 (41.3-77.2) | 61.0 (44.4-81.3) | 58.4 (39.9-76.5) | 55.6 (39.5-74.8) | <0.001 |
| Randomized arm | | | | | 0.629 |
| Placebo | 2,520 (50.0) | 751 (51.0) | 921 (49.2) | 848 (50.1) | |
| Vericiguat | 2,516 (50.0) | 721 (49.0) | 950 (50.8) | 845 (49.9) | |

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

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; BMI = body mass index; BP = blood pressure; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; IV = intravenous; LVEF = left ventricular ejection fraction; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PAD = peripheral artery disease; PCI = percutaneous coronary intervention.

relationships were also adjusted for the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) score. The proportional hazards assumption was checked graphically using a standardized score process and found to be appropriately met. When baseline LVEF was examined as tertiles, LVEF of 34% to −45% was used as a reference, and HRs with 95% CIs were reported for the other 2 groups. When baseline LVEF was examined as a continuous variable, the restricted cubic spline method with 4 knots was used to test the linearity assumption, and log HRs were plotted (Supplemental Figure 1). The unadjusted and adjusted HRs with 95% CIs per 5-point increase in baseline LVEF were calculated for all clinical outcomes.

The effect of vericiguat on the primary and secondary outcomes across LVEF levels was assessed using a Cox proportional hazards model by including the assigned study treatment, LVEF (both tertiles and continuous), and their interaction. The unadjusted and adjusted HRs with 95% CIs comparing vericiguat with placebo within each LVEF level and the interaction *P* value are presented. A sensitivity analysis of the effect of vericiguat across LVEF levels (tertiles

**TABLE 2 Clinical Outcomes According to LVEF**

| | Overall (N = 5,036) | | | | | | LVEF ≤24% (n = 1,472) | |
|---|---|---|---|---|---|---|---|---|
| | Events | Event per 100 p-y | HR Every 5% Decrease | *P* Value | aHR[a] per 5% Decrease | *P* Value | Events | Event per 100 p-y |
| Primary outcome | 1,860 (36.9) | 35.6 | 1.07 (1.04-1.10) | <0.001 | 1.03 (1.00-1.06) | 0.038 | 614 (41.7) | 42.0 |
| CV death | 851 (16.9) | 13.4 | 1.11 (1.07-1.16) | <0.001 | 1.05 (1.01-1.09) | 0.025 | 313 (21.3) | 17.2 |
| HFH | 1,431 (28.4) | 27.4 | 1.08 (1.04-1.11) | <0.001 | 1.03 (1.00-1.07) | 0.045 | 464 (31.5) | 31.8 |

**TABLE 2 Continued**

| | LVEF 25%-33% (n = 1,871) | | LVEF 34%-45% (n = 1,693) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Events | Event per 100 p-y | Events | Event per 100 p-y | HR | *P* Value | aHR[a] per 5% Decrease | *P* Value |
| Primary outcome | 680 (36.3) | 35.2 | 566 (33.4) | 30.8 | I vs III: 1.34 (1.20-1.51) | <0.001 | I vs III: 1.13 (1.01-1.28) | 0.039 |
| | | | | | II vs III: 1.13 (1.01-1.27) | 0.030 | II vs III: 1.04 (0.93-1.17) | 0.474 |
| CV death | 302 (16.1) | 12.9 | 236 (13.9) | 10.7 | I vs III: 1.60 (1.35-1.90) | <0.001 | I vs III: 1.25 (1.05-1.49) | 0.012 |
| | | | | | II vs III: 1.20 (1.01-1.42) | 0.038 | II vs III: 1.06 (0.89-1.26) | 0.506 |
| HFH | 535 (28.6) | 27.8 | 432 (25.5) | 23.5 | I vs III: 1.33 (1.16-1.51) | <0.001 | I vs III: 1.13 (0.98-1.29) | 0.089 |
| | | | | | II vs III: 1.17 (1.03-1.32) | 0.017 | II vs III: 1.07 (0.94-1.22) | 0.277 |

Values are n (%) or HR (95% CI), unless otherwise indicated. [a]Adjusted for MAGGIC score.

aHR = adjusted HR; CV = cardiovascular; HFH = heart failure hospitalization; p-y = patient-years; other abbreviation as in Table 1.

**TABLE 3 Baseline Biomarkers According to LVEF at Randomization**

| | Overall (N = 5,036) | LVEF ≤24% (n = 1,472) | LVEF 25%-33% (n = 1,871) | LVEF 34%-45% (n = 1,693) | *P* Value |
|---|---|---|---|---|---|
| NT-proBNP, pg/mL | 2,816 (1,556-5,312) (n = 4,805) | 3,442 (1,847-6,356) (n = 1,401) | 2,876 (1,544-5,336) (n = 1,785) | 2,464 (1,396-4,525) (n = 1,608) | <0.001 |
| hs-cTnT, ng/L | 29.6 (18.8-48.6) (n = 4,614) | 29.6 (18.9-49.1) (n = 1,372) | 30.1 (19.1-49.9) (n = 1,697) | 29.2 (18.2-47.0) (n = 1,533) | 0.369 |
| GDF-15, pg/mL | 3,047 (1,917-5,145) (n = 4,395) | 3,166 (1,915-5,466) (n = 1,313) | 3,007 (1,871-5,144) (n = 1,609) | 3,009 (1,969-4,859) (n = 1,462) | 0.053 |
| hsCRP, mg/L | 3.9 (1.5-9.4) (n = 4,519) | 4.4 (1.7-11.7) (n = 1,341) | 3.8 (1.5-9.3) (n = 1,662) | 3.6 (1.3-8.6) (n = 1,504) | <0.001 |
| IL-6, pg/mL | 6.8 (4.6-11.2) (n = 4,577) | 7.4 (4.8-12.7) (n = 1,364) | 6.7 (4.6-10.8) (n = 1,688) | 6.5 (4.4-10.1) (n = 1,513) | <0.001 |
| Cystatin C, mg/L | 1.3 (1.1-1.8) (n = 4,506) | 1.3 (1.0-1.7) (n = 1,337) | 1.3 (1.1-1.8) (n = 1,657) | 1.4 (1.1-1.8) (n = 1,500) | <0.001 |

Values are median (25th-75th percentile).

GDF = growth differentiation factor; hsCRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; IL = interleukin; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide.

and continuous) was also examined using additive regression models (the Lin and Ying semiparametric models[14]) at an absolute level; the absolute hazard differences (per 100 patient-years) with 95% CIs were reported.

Safety outcomes were summarized as frequencies and event rates according to both the LVEF level and study treatment. In addition, a separate analysis was conducted for patients with LVEF of 41% to 45%. Missing LVEF values (n = 14) were not imputed because such patients were excluded from this analysis. All analyses were based on the intention-to-treat principle, and all analyses were performed using SAS version 9.4 (SAS Institute, Inc). A 2-sided test result with $P < 0.05$ was considered statistically significant.

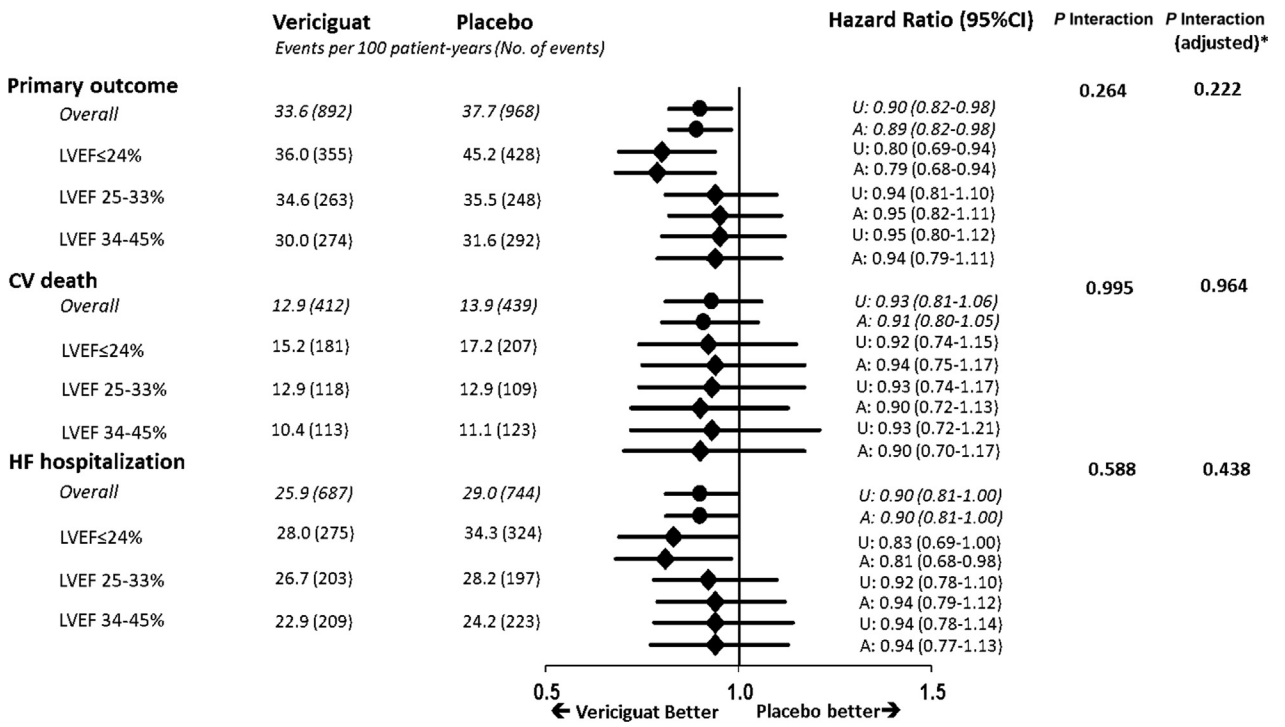
## RESULTS

**BASELINE CHARACTERISTICS.** Of the 5,050 patients enrolled, LVEF was available in 5,036 patients and ranged from 5% to 45%. The SD LVEF was 29% ± 8%, and the median time from the measurement of LVEF to randomization was 36 days (25th-75th percentile: 15-94 days). Table 1 shows the baseline characteristics of the patients stratified according to baseline LVEF. Patients in the lower tertiles of LVEF were more often younger and male; had a lower body mass index; and were less likely to have a history of diabetes, hypertension, anemia, chronic obstructive pulmonary disease, or myocardial infarction. A higher proportion of patients in the lowest tertile of LVEF were on diuretic agents and received cardiac resynchronization therapy or an implantable cardioverter-defibrillator.

**CLINICAL OUTCOMES ACCORDING TO BASELINE LVEF.** In Table 2, the overall primary clinical outcome and each of its components are expressed as both observed event rates and events per 100 patient-years and categorized according to tertiles of LVEF. A clear pattern of significantly higher rates of the primary outcome and both CVD and HF hospitalization were evident in patients with LVEF ≤24%. In parallel with this finding, for the middle and highest LVEF tertiles, the rates of these events progressively and significantly declined. When LVEF was examined as a continuous variable, the linearity of the relationship of LVEF at baseline on the primary composite can be seen in Supplemental Figure 1. It is notable that for each 5-point decrease in LVEF, there was a 7% higher risk of the primary outcome (HR: 1.07 [95% CI: 1.04-1.10]). Similar findings were evident for CVD (HR: 1.11 [95% CI: 1.07-1.16]) and HF hospitalizations (HR: 1.08 [95% CI: 1.04-1.11]). After adjusting for the MAGGIC score, a similar pattern was observed for the primary outcome (HR: 1.03 [95% CI: 1.00-1.06]), CVD (HR: 1.05 [95% CI: 1.01-1.09]), and HF hospitalization (HR: 1.03 [95% CI: 1.00-1.07]).

**BIOMARKER PROFILE ACCORDING TO LVEF AT RANDOMIZATION.** In Table 3, the biomarker data acquired at randomization are shown for the overall population and according to the LVEF tertiles. Elevations were evident in cardiac troponin (about twice the upper limit of normal), GDF-15 (about 4-fold above normal), IL-6 (about 1.5-fold above the upper limit of normal), and marginally elevated levels of hsCRP and cystatin C. When examining these biomarkers according to LVEF categories, patients in the lowest LVEF tertile had significantly higher NT-proBNP ($P < 0.01$), hsCRP ($P < 0.01$), and IL-6 levels ($P < 0.01$) and a trend toward higher GDF-15 levels ($P = 0.053$) compared with those in the other LVEF tertiles. There was no significant difference in high-sensitivity cardiac troponin T values among the different tertiles ($P = 0.369$). A small increase in cystatin C was noted in the highest LVEF tertile.

**FIGURE 1** Clinical Outcomes and Effect of Vericiguat According to Baseline LVEF



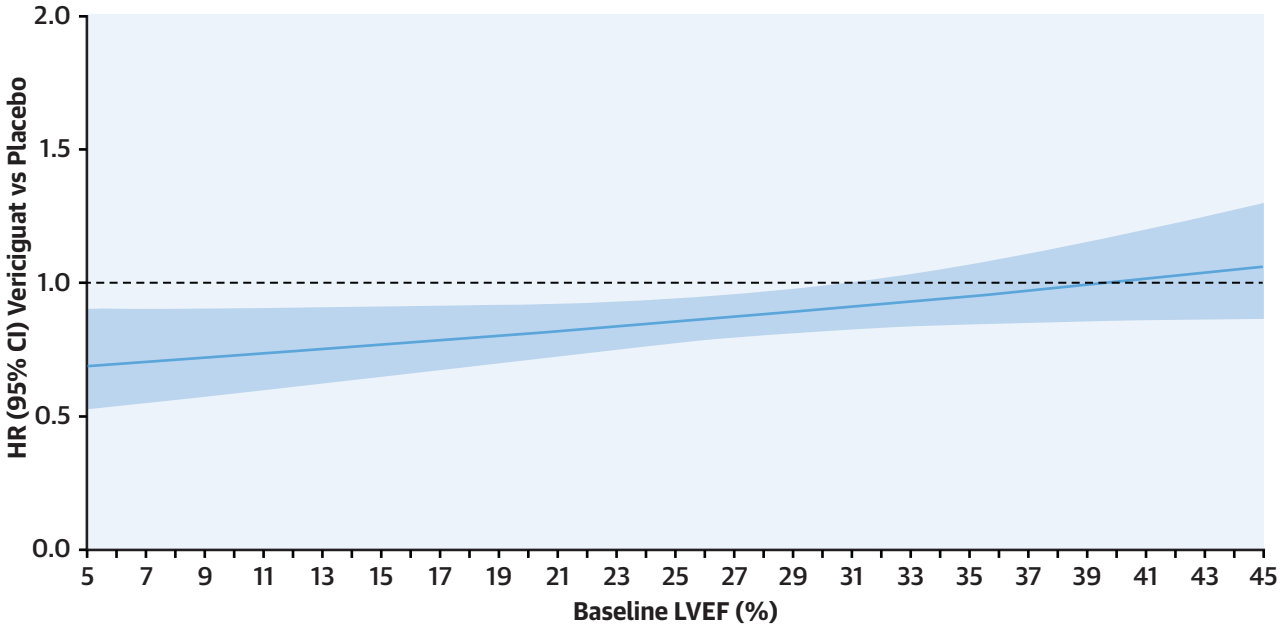

The effect of vericiguat on the clinical outcomes did not vary significantly by baseline left ventricular ejection fraction (LVEF) tertile. *Adjusted for MAGGIC score.
A = adjusted; CV = cardiovascular; HF = heart failure; MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure; U = unadjusted.

**IMPACT OF VERICIGUAT ON THE OUTCOME ACROSS THE SPECTRUM OF LVEF.** When the treatment effect was examined according to tertiles of baseline LVEF, no significant statistical heterogeneity was noted for the primary outcome (unadjusted HR from lowest to highest tertile: 0.80 [95% CI: 0.69-0.94], 0.94 [95% CI: 0.81-1.10], and 0.95 [95% CI: 0.80-1.12]; *P* interaction = 0.264). Similar results were observed for CVD and HF hospitalization (**Figure 1**). When these associations were adjusted for the MAGGIC score, the results did not change materially. Similar results were also seen when the effect of LVEF was analyzed as a continuous variable (*P* interaction = 0.089 for primary endpoint [**Central Illustration**]; *P* interaction = 0.776 for CVD [Supplemental Figure 2]; *P* interaction = 0.128 for HF hospitalization [Supplemental Figure 3]).

When the treatment effect of vericiguat was assessed on an absolute scale, no significant statistical heterogeneity was observed with the primary endpoint or its components when LVEF was in 3 categories (all *P* interaction >0.05 after adjustment for the MAGGIC risk score) (Supplemental Table 1). When these associations were examined using LVEF on a continuous scale, the absolute benefit of vericiguat for CVD/HFH was observed as LVEF decreased (*P* interaction = 0.048 after adjustment for MAGGIC risk score). When the subset of patients with LVEF of 41% to 45% was examined, no significant improvement was observed in the primary outcome (HR: 0.89 [95% CI: 0.63-1.27]) (Supplemental Table 2).

**IMPACT OF VERICIGUAT ON SAFETY OUTCOMES ACROSS THE SPECTRUM OF LVEF.** **Table 4** shows the discontinuation and safety outcomes according to both LVEF and study treatment. No significant difference was observed in the proportion of patients who discontinued the treatment for any reason (44.1%, 37.1%, and 35.1%) or those who discontinued because of an adverse event (7.2%, 6.0%, and 7.0%) between the 2 groups in any of the LVEF categories. Patients with a lower baseline LVEF experienced higher rates of symptomatic hypotension (9.2%, 8.6%, and 7.9% in LVEF tertiles ≤24%, 25%-33%, and

**CENTRAL ILLUSTRATION** **Treatment Effect of Vericiguat on Primary Endpoint (Cardiovascular Death or Heart Failure Hospitalization) According to Baseline LVEF (Continuous *P* Interaction = 0.089, Adjusted for MAGGIC Score)**

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The effect of vericiguat on the primary outcome did not vary significantly by baseline continuous left ventricular ejection fraction (LVEF). However, the largest signal for benefit was noted in patients with lower LVEF. MAGGIC = Meta-Analysis Global Group in Chronic Heart Failure.

>33%; $P < 0.001$) and syncope (4.0%, 4.1%, and 3.1% in LVEF tertiles ≤24%, 25%-33%, and >33%; $P < 0.001$). However, no difference in the proportion of patients experiencing syncope or symptomatic hypotension was noted between the treatment groups in each LVEF category. The results remained similar for patients with LVEF of 41% to 45% (Supplemental Table 3).

## DISCUSSION

In this post hoc analysis of 5,036 patients enrolled in the VICTORIA trial, several key findings were observed. First, the baseline characteristics of patients varied significantly by baseline LVEF. Patients in lower tertiles were more often males and younger; had a lower burden of comorbidities such as diabetes and hypertension; and were less likely to have a history of previous myocardial infarction or percutaneous coronary intervention, suggesting that they had a nonischemic etiology of HF. Second, for each 5-point decrease in LVEF, there was a 7% higher risk of the primary outcome. Third, biomarkers such as NT-proBNP, cardiac troponin, GDF-15, IL-6, hsCRP, and cystatin C were markedly elevated in the overall population. Furthermore, compared with the upper tertiles, those in the lowest tertile had higher NT-proBNP, hsCRP, and IL-6. Fourth, the effect of vericiguat on the primary outcome of CVD or HF hospitalization and its components did not vary significantly by baseline LVEF tertile, although the largest signal for benefit in both the primary outcome and HF hospitalizations was noted in tertile 1 (LVEF ≤24%). Furthermore, in a subgroup analysis of patients with a baseline LVEF of 41% to 45%, administering vericiguat showed no significant improvement in the primary composite outcome or its components. Lastly, treatment with vericiguat was safe across all 3 tertiles of LVEF with no significantly increased risk of hypotension, syncope, or discontinuation.

The difference in the clinical profile across the LVEF spectrum in the VICTORIA trial is largely similar to previous studies that comprehensively profiled the treatment effect according to LVEF in patients with HFrEF. Both the PARADIGM-HF (Comparison of Angiotensin Neprilysin Inhibitor With Angiotensin

**TABLE 4 Safety Outcomes According to LVEF and Study Treatment**

| | Overall (N = 5,036) | | | | LVEF ≤24% (n = 1,472) | | | |
|---|---|---|---|---|---|---|---|---|
| | All Events (N = 5,036) | Vericiguat Events (n = 2,516) | Placebo Events (n = 2,520) | *P* Value | All Events (N = 1,472) | Vericiguat Events (n = 721) | Placebo Events (n = 751) | *P* Value |
| Any discontinuation | 1,937 (38.5) | 961 (38.1) | 976 (38.8) | 0.632 | 649 (44.1) | 319 (44.2) | 330 (43.9) | 0.907 |
| Discontinuation due to AE | 337 (6.7) | 177 (7.0) | 160 (6.4) | 0.330 | 106 (7.2) | 55 (7.6) | 51 (6.8) | 0.534 |
| Symptomatic hypotension | 427 (8.5) | 229 (9.1) | 198 (7.9) | 0.115 | 134 (9.2) | 71 (9.9) | 63 (8.4) | 0.334 |
| Syncope | 188 (3.7) | 101 (4.0) | 87 (3.5) | 0.295 | 58 (4.0) | 30 (4.2) | 28 (3.8) | 0.673 |

**TABLE 4 Continued**

| | LVEF 25%-33% (n = 1,871) | | | | LVEF 34%-45% (n = 1,693) | | | |
|---|---|---|---|---|---|---|---|---|
| | All Events (N = 1,871) | Vericiguat Events (n = 950) | Placebo Events (n = 921) | *P* Value | All Events (N = 1,693) | Vericiguat Events (n = 845) | Placebo Events (n = 848) | *P* Value |
| Any discontinuation | 694 (37.1) | 360 (37.9) | 334 (36.3) | 0.466 | 594 (35.1) | 297 (35.2) | 297 (35.0) | 0.957 |
| Discontinuation due to AE | 112 (6.0) | 63 (6.6) | 49 (5.3) | 0.232 | 119 (7.0) | 59 (7.0) | 60 (7.1) | 0.940 |
| Symptomatic hypotension | 160 (8.6) | 89 (9.4) | 71 (7.7) | 0.199 | 133 (7.9) | 69 (8.2) | 64 (7.6) | 0.641 |
| Syncope | 77 (4.1) | 42 (4.4) | 35 (3.8) | 0.499 | 53 (3.1) | 29 (3.4) | 24 (2.8) | 0.480 |

Values are n (%), unless otherwise noted. *P* values are chi-square comparisons between vericiguat and placebo.
AE = adverse event; other abbreviation as in Table 1.

Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trials reported that patients in lower LVEF tertiles had fewer comorbidities such as diabetes and a history of myocardial infarction and had higher NT-proBNP, just like in the VICTORIA trial.[8,9] Although in the previous trials patients in the lower LVEF tertiles were more likely to be treated with background HF therapy such as angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, and diuretics, no such difference was observed in the VICTORIA trial.

Post hoc analyses of previous HFrEF trials have shown that LVEF is a strong predictor of clinical outcomes in patients with HFrEF. In the DAPA-HF trial, each 5% decrease in LVEF was associated with an 18% increase in the risk of worsening HF or CVD.[8] Among patients enrolled in the PARADIGM-HF trial, each 5% decrease in LVEF was associated with a 9% higher risk of HF hospitalization or CVD, and in the CHARM (Candesartan in Heart Failure Reduction in Mortality) program, each 10% reduction in LVEF was associated with a 45% greater risk of this outcome.[9,15] Similar results were observed in the current study, confirming that LVEF is a strong predictor of outcomes. Of note, previous studies enrolled stable ambulatory HF patients, and data on acutely ill patients including a broader population spectrum of LVEF are limited.

Previous pharmacologic clinical trials in patients with HFrEF, such as the ones studying ARNI, beta-blockers, and mineralocorticoid receptor antagonist, have demonstrated a consistent reduction in the primary outcome across the spectrum of LVEF.[2-4,6,16-18] Combined analysis of the PARAGON-HF (Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) and PARADIGM-HF trials showed that sacubitril/valsartan reduced the composite of first HF hospitalization and CVD across all LVEF subgroups in HFrEF (HR: 0.77 [95% CI: 0.63-0.94]; HR: 0.81 [95% CI: 0.71-0.92]; HR: 0.81 [95% CI: 0.69-0.94] for LVEF ≤22.5%, >22.5%-32.5%, and 32.5%-42.5%, respectively) compared with renin-angiotensin-aldosterone system inhibitors.[9,19] Similarly, the DAPA-HF and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction) trials showed a benefit across the LVEF spectrum with dapagliflozin (HR: 0.75 [95% CI: 0.59-0.95]; HR: 0.75 [95% CI: 0.57-0.98]; HR: 0.67 [95% CI: 0.51-0.89]; HR: 0.83 [95% CI: 0.63-1.09] for LVEF <26%, 26%-30%, 31%-35%, and >35%, respectively) and empagliflozin (HR: 0.70 [95% CI: 0.53-0.93]; HR: 0.99 [95% CI: 0.76-1.31] for LVEF ≤30% and ≥30%) for the composite of HF hospitalization or CVD across the spectrum of LVEF, respectively.[8,20,21] We also observed similar results with vericiguat improving the primary outcome of CVD or HF hospitalization across the spectrum of LVEF.

As a result of HFrEF trials including patients with LVEF <35% or <40% and HFpEF trials including patients with LVEF ≥45% or ≥50%, there remains a knowledge gap regarding the effect of therapies in patients with HF with mildly reduced EF, particularly those with an LVEF in the range of 40% to 49%. The clinical characteristics of patients with LVEF in this range is intermediate between HFrEF and HFpEF.[22-24] A few studies have included patients across the LVEF spectrum, and secondary analyses of these studies provide some insight into the treatment of patients with an ejection fraction of 40% to 49%. In the CHARM program, patients with an LVEF of 40% to 49% experienced a significant reduction in CVD or HF hospitalization, in line with patients who had lower LVEFs.[15] Similarly, in the combined analysis of PARADIGM-HF and PARAGON-HF, sacubitril/valsartan was found to be effective in reducing adverse clinical outcomes in patients with mildly reduced ejection fraction.[9] The VICTORIA trial included patients with an LVEF <45%, and in the current post hoc study, patients with an LVEF of 40% to 45% were studied separately. We found no significant reduction in the primary outcome or its components in this population. This further suggests that the beneficial effects of vericiguat may be most prominent in patients with lower LVEF.

Patients with lower LVEF exhibited a distinctive biomarker profile with notably higher NT-proBNP. Lower LVEF was also associated with increased inflammatory markers (hsCRP and IL-6). Of note, these biomarkers may not be cardiac specific, making it difficult to discern whether differences found in this study are the cause or consequence of HF.

**STUDY LIMITATIONS.** The results of this study should be interpreted in light of some underlying limitations. First, this is a post hoc analysis, and the nonrandomized distribution of participants in each LVEF category could contribute to bias. Second, possible variations in the sites and time of measurement of LVEF before randomization could have potentially led to some inaccuracies in the classification of patients at the time of enrollment. Third, interaction analysis regarding the effect of vericiguat based on LVEF should be considered cautiously because the analysis may have limited power. It is possible that patients with lower LVEF may have a greater benefit, especially because they have a higher absolute baseline risk, which is suggested by our sensitivity analysis.

## CONCLUSIONS

Patients with lower LVEF exhibited differences in circulating biomarker profiles compared with those with higher LVEF and also had a higher risk for adverse clinical outcomes. The effect of vericiguat on the primary outcome (CVD or HF hospitalization) and its components did not vary significantly by baseline LVEF tertile, although the largest signal for benefit in both the primary outcome and HF hospitalizations was noted in tertile 1 (LVEF ≤24%). Vericiguat was safe and did not cause an increase in the risk of syncope or symptomatic hypotension in any of the LVEF tertiles.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In this post hoc analysis of the VICTORIA trial, we found that patients with lower LVEF had a distinctive biomarker profile and a higher risk for adverse clinical outcomes vs those with higher LVEF. The effect of vericiguat on CVD or HF hospitalization did not vary significantly by baseline LVEF tertile; however, the largest signal for benefit was noted in patients with LVEF ≤24%.

**TRANSLATIONAL OUTLOOK:** Future studies should investigate biomarker profiles associated with different HF phenotypes and whether these biomarker profiles are the cause or consequence of heart failure.

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**KEY WORDS** biomarkers, clinical outcomes, heart failure with reduced ejection fraction, left ventricular ejection fraction, vericiguat

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