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ORIGINAL RESEARCH

Blood Pressure and Safety Events With Vericiguat in the VICTORIA Trial

Carolyn S. P. Lam, MBBS, PhD; Hillary Mulder, MS; Yuri Lopatin, MD, PhD; Jose B. Vazquez-Tanus, MD; David Siu, MD; Justin Ezekowitz, MBBCH, MSc; Burkert Pieske, MD; Christopher M. O'Connor, MD; Lothar Roessig, MD; Mahesh J. Patel, MD; Kevin J. Anstrom, PhD; Adrian F. Hernandez, MD, MHS; Paul W. Armstrong, MD; on behalf of the VICTORIA Study Group*

BACKGROUND: Although safety and tolerability of vericiguat were established in the VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial in patients with heart failure with reduced ejection fraction, some subgroups may be more susceptible to symptomatic hypotension, such as older patients, those with lower baseline systolic blood pressure (SBP), or those concurrently taking angiotensin receptor neprilysin inhibitors. We described the SBP trajectories over time and compared the occurrence of symptomatic hypotension or syncope by treatment arm in potentially vulnerable subgroups in VICTORIA. We also evaluated the relation between the efficacy of vericiguat and baseline SBP.

METHODS AND RESULTS: Among patients receiving at least 1 dose of the study drug (n=5034), potentially vulnerable subgroups were those >75 years old (n=1395), those with baseline SBP 100–110 mm Hg (n=1344), and those taking angiotensin receptor neprilysin inhibitors (n=730). SBP trajectory was plotted as mean change from baseline over time. The treatment effect on time to symptomatic hypotension or syncope was evaluated overall and by subgroup, and the primary efficacy composite outcome (heart failure hospitalization or cardiovascular death) across baseline SBP was examined using Cox proportional hazards models. SBP trajectories showed a small initial decline in SBP with vericiguat in those >75 years old (versus younger patients), as well as those receiving angiotensin receptor neprilysin inhibitors (versus none), with SBP returning to baseline thereafter. Patients with SBP <110 mm Hg at baseline showed a trend to increasing SBP over time, which was similar in both treatment arms. Safety event rates were generally low and similar between treatment arms within each subgroup. In Cox proportional hazards analysis, there were similar numbers of safety events with vericiguat versus placebo (adjusted hazard ratio [HR], 1.18; 95% CI, 0.99–1.39; *P*=0.059).
No difference existed between treatment arms in landmark analysis beginning after the titration phase (ie, post 4 weeks) (adjusted HR, 1.14; 95% CI, 0.93–1.38; P=0.20). The benefit of vericiguat compared with placebo on the primary composite efficacy outcome was similar across the spectrum of baseline SBP (P for interaction=0.32).

CONCLUSIONS: These data demonstrate the safety of vericiguat in a broad population of patients with worsening heart failure with reduced ejection fraction, even among those predisposed to hypotension. Vericiguat's efficacy persisted regardless of baseline SBP.

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Key Words: blood pressure ■ heart failure ■ heart failure with reduced ejection fraction ■ safety events ■ vericiguat

Among patients with heart failure with reduced ejection fraction (HFrEF), concerns about hypotension often limit the use of potentially life-saving medications. In the CHAMP-HF (Change the Management of Patients with Heart Failure) registry, lower systolic blood pressure (SBP) was an independent

Correspondence to: Paul W. Armstrong, MD, 4-120 Katz Group Centre for Pharmacy and Health Research, University of Alberta, Edmonton, AB Canada T6G 2E1. E-mail: parmstro@ualberta.ca

*A complete list of the VICTORIA Study Group members can be found in the Supplemental Material.

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CLINICAL PERSPECTIVE

What Is New?

- Consistent with the safety and tolerability of vericiguat observed in the overall VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial, there were no excessive reductions in blood pressure with vericiguat across subgroups representing potentially vulnerable patients predisposed to blood pressure decreases, such as older patients, those with lower baseline blood pressure, and patients receiving concurrent angiotensin receptor neprilysin inhibitors.
- The benefit of vericiguat was consistent across baseline systolic blood pressure (*P* for interaction=0.32).

What Are the Clinical Implications?

- Along with prior evidence of benefit with vericiguat regardless of age and background therapy, our findings indicate the favorable benefit-to-risk ratio of vericiguat extends to patients potentially predisposed to blood pressure decreases.

Nonstandard Abbreviations and Acronyms

ARNI	angiotensin receptor neprilysin inhibitors
CHAMP-HF	Change the Management of Patients with Heart Failure
HFrEF	heart failure with reduced ejection fraction
SBP	systolic blood pressure
SGLT2i	sodium glucose cotransporter-2 inhibitors
VICTORIA	Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction

predictor of underuse or under-dosing of neurohormonal antagonists in eligible patients.[1] Although hypotensive patients should be evaluated for dehydration/overdiuresis with consideration of reducing or removing medications causing hypotension without survival benefit, it should also be emphasized that application of guideline-directed medical therapies has been shown to improve clinical outcomes in HFrEF despite lowering SBP. Physicians must therefore balance the risk of hypotension with the expected longer-term therapeutic benefits because withholding effective therapies for this reason may contribute to poor prognosis among patients with HFrEF. Indeed, even when SBP is not limiting, further data from CHAMP-HF suggest a reluctance of physicians to prescribe or up-titrate beneficial, but potentially hypotensive-inducing agents, in the absence of other contraindications.[2] Newer effective therapies in HFrEF that may lower SBP, such as angiotensin receptor-neprilysin inhibitors (ARNI),[3] further complicate management of patients with HFrEF given their advanced age, frequent comorbidities, and multiple concomitant medications.

Recently, the VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial randomized 5050 patients within 6 months of worsening HFrEF to the soluble guanylate cyclase stimulator vericiguat or placebo on top of high use of contemporary guideline-directed medical therapy and showed that vericiguat significantly reduced the risk for the primary outcome of HF hospitalization or cardiovascular death over a median follow-up of 10.8 months (hazard ratio [HR], 0.90; 95% CI, 0.82–0.98).[4] Prespecified adverse events of interest were symptomatic hypotension and syncope, which occurred in 9.1% versus 7.9% (*P*=0.12), and 4.0% versus 3.5% (*P*=0.30) of the vericiguat versus placebo groups, respectively. Although these safety and tolerability results were reassuring for the use of vericiguat in the overall studied population, it seems likely that there may be some patients who are more prone than others to blood pressure decreases, symptomatic hypotension, or syncope. Potentially vulnerable subgroups may be older patients, those with lower baseline SBP, or those concurrently taking vasoactive medications. Specifically, because neprilysin inhibition may also augment the guanylate cyclase-cyclic guanosine monophosphate pathway, the effect of the combined use of ARNI and vericiguat on SBP is of particular interest.[5,6] Accordingly, we aimed to describe the SBP trajectories during treatment and compared the occurrence of symptomatic hypotension or syncope in patients receiving vericiguat compared with placebo, with particular emphasis on potentially vulnerable subgroups. We also evaluated the relation between the efficacy of vericiguat and baseline SBP.

METHODS

Data will be made available as outlined in the VICTORIA data sharing charter (https://thecvc.ca/victoria/data-sharing/).

Trial Overview

Briefly, VICTORIA (NCT02861534) was a multicenter, international, randomized, placebo-controlled trial that investigated the efficacy and safety of vericiguat, on

top of evidence-based therapy, in patients with chronic HFrEF (EF <45%, New York Heart Association class II–IV) and a recent (<6 months) worsening HF event.[7] Patients with SBP <100 mm Hg and those on long-acting nitrates or phosphodiesterase type 5 inhibitors were excluded and the use of any intravenous treatment within 24 hours before randomization was prohibited. After a screening phase of up to 30 days, eligible patients were randomized 1:1 to start on a 2.5 mg dose of vericiguat or matching placebo, then up-titrated to 5 mg and subsequently to the target dose of 10 mg once daily of vericiguat or matching placebo in a blinded fashion. There was no run-in phase in VICTORIA. The up-titration protocol was based on mean SBP and clinical symptoms were assessed at 2-week intervals, with a 4-week total titration phase. Patients were then evaluated every 4 months until study completion. At every subsequent visit, additional efforts were taken at the discretion of the investigator to maximize the likelihood of titration to the 10 mg target dose, based on mean SBP measurement and safety considerations. Prespecified adverse events of clinical interest were symptomatic hypotension and syncope (both nonserious and serious adverse events), for which patients were monitored through the course of the study, with all events of hypotension captured via electronic or paper reporting. The primary outcome was a composite of HF hospitalization or cardiovascular death; the secondary end points were HF hospitalization alone, cardiovascular death alone, a composite of all-cause mortality or HF hospitalization, and all-cause death alone. The trial protocol was approved by institutional review boards or ethics committees at the participating sites and all the patients provided informed consent.

Potentially Vulnerable Subgroups

Potentially vulnerable subgroups were defined as follows: (1) age >75 years old, (2) SBP 100 to 110 mm Hg, and (3) baseline therapy with ARNI. Our selected age cutoff of 75 years and SBP cutoff of 110 mm Hg corresponded to the oldest age and lowest SBP categories in prior analyses of newer HFrEF therapies.[8–10] Given potential synergistic effects of sacubitril and vericiguat on particulate and soluble guanylate cyclase, respectively, the subgroup comparison by baseline ARNI use was prespecified and enrollment of patients receiving baseline ARNI was actively encouraged throughout the trial.[7] Although the efficacy outcomes by age group (above and below 75 years old) and baseline ARNI use have been reported,[4] the subgroup analyses of safety events have not.

Further subgroups of interest included patients with NT-proBNP (N-terminal pro-B-type natriuretic peptide above and below 4000 pg/mL and 8000 pg/mL, because treatment heterogeneity by baseline NT-proBNP had been previously observed in VICTORIA,[4] with cut points from the treatment effect across the spectrum of (log-transformed) NT-proBNP at 4000 pg/mL and 8000 pg/mL.[11] Finally, recognizing that sodium glucose cotransporter-2 inhibitors (SGLT2i) will be increasingly used in HFrEF, we also examined the small subgroup of patients receiving SGLT2i at baseline (n=122 [2.4%]). Patients with nonmissing information for each criterion were included in these subgroup analyses.

Statistical Analysis

Patients were included in these analyses if they received at least 1 dose of the study drug (n=5034). Baseline characteristics were summarized for each vulnerable subgroup and compared with the rest of the population not meeting the individual subgroup criteria, with continuous variables presented as medians with 25th and 75th percentiles and categorical variables presented as counts (percentages). Characteristics were compared between groups using 2-sample *t* tests or Wilcoxon rank sum tests for continuous variables and chi-square or Fisher's exact test for categorical variables. SBP trajectory for each subgroup was plotted as mean change from baseline over time with the corresponding standard errors. SBP measurements obtained before the date of the first dose and 14 days after the last dose of study medication were included.

The treatment effect on time to symptomatic hypotension or syncope was evaluated overall and by subgroup. The number of events and incidence rates are presented within each treatment arm and subgroup for the composite safety outcome and symptomatic hypotension and syncope individually. Incidence rates are calculated as the number of events per 100 patient-years of follow-up. Evaluation of the treatment effect and modification of the treatment effect by subgroup were performed using Cox proportional hazards models for the 3 outcomes (composite of symptomatic hypotension and syncope and individual components). Adjusted models were evaluated using the following list of covariates: age, sex, race, SBP, ARNI use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, New York Heart Association class, estimated glomerular filtration rate, and NT-proBNP. Continuous covariates used for determining subgroups were included categorically when necessary. The proportional hazards assumption was assessed using weighted Schoenfeld residuals, with no major violations found. Hazard ratios (HRs) with 95% CIs comparing vericiguat with placebo, overall, and within subgroups, are presented. For models assessing the interaction between treatment and subgroup, the *P* value for the interaction is also presented.

To assess the incidence of symptomatic hypotension or syncope after dose titration by randomized treatment, a landmark analysis was performed for

patients who reached the 4-week (post-titration) visit without an event of symptomatic hypotension or syncope. Day 0 for assessing events began at 4 weeks post randomization. Treatment effect was assessed using a Cox proportional hazards model. In order to reduce the potential for any bias incurred in performing a landmark analysis, the model was adjusted for potential confounders (urate, region/race, and implantable cardiac defibrillator for syncope; SBP, QT interval, chloride, calcium, region/race, implantable cardiac defibrillator, randomized while hospitalized, and history of diabetes, atrial flutter, and hyperlipidemia for symptomatic hypotension). We used backward selection with a 0.05 cutoff, starting with a list of ≈65 baseline characteristics, for each of the 3 end points (composite safety end point and the components). The proportional hazards assumption was assessed, with no major violations found. The HRs (95% CI) comparing vericiguat with placebo and associated *P* value for each outcome are presented.

Finally, the effect of vericiguat compared with placebo on the primary efficacy composite outcome (HF hospitalization or cardiovascular death) was examined across the spectrum of baseline SBP using a Cox proportional hazards model. The relation between baseline SBP and HF hospitalization/cardiovascular death was assessed for nonlinearity using natural cubic splines, and the relation was found to be nonlinear. The final model included randomized treatment, SBP using natural cubic splines, and the interaction between treatment and SBP. HRs (95% CI) for the treatment effect were estimated at 1 mm Hg intervals of SBP from 100 to 160 mm Hg.

All analyses were conducted by the Duke Clinical Research Institute (Durham, NC) using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Characteristics by Vulnerable Subgroups

Among a total of 5034 patients with recent worsening HF who received at least 1 dose of study drug, mean age was 67.3±12.2 years and mean SBP was 121.4±15.7 mm Hg, with distribution as shown in Figure S1. There were 1395 (27.6%) patients >75 years old and 1344 (26.6%) with SBP 100 to 110 mm Hg.

Baseline characteristics according to the location of patients in the 3 aforementioned vulnerable subgroups are shown in Table 1. Compared with younger patients, those >75 years old were more likely to be female and White with comorbidities (atrial fibrillation, hypertension, hyperlipidemia, anemia) and a history of cardiovascular disease (coronary artery disease, stroke, peripheral artery disease); have higher baseline SBP, lower glomerular filtration rate, and higher NT-proBNP; and were less likely to be on guideline-directed triple therapy at baseline. Compared with patients with higher baseline SBP, those with SBP <110 mm Hg were slightly younger, more often Asian, more likely to be within 3 months of HF hospitalization, and more likely to be receiving guideline-directed triple therapy, with higher baseline NT-proBNP. Guideline-directed triple therapy was commonly used, with 730 (14.5%) patients receiving ARNI at baseline. Compared with patients not receiving ARNI, those receiving ARNI at baseline were younger, more likely to be male and Asian with a similar comorbidity burden but lower baseline SBP, and more likely to have received triple therapy and devices.

Dose Achieved and Treatment Adherence

Treatment dose achieved after standardized up-titration by protocol (based on mean SBP and clinical symptoms) was as follows. Among patients >75 years old, the proportion of patients achieving the 10 mg target dose of study drug was similar for vericiguat (78%) and placebo (78%); this was also similar to the proportion of younger patients achieving the target dose of vericiguat (79%). Among patients with baseline SBP 100 to 110 mm Hg, the proportion of patients achieving the 10 mg target dose of study drug was similar for vericiguat (60%) and placebo (62%); however, a higher proportion of patients with higher baseline SBP (≥110 mm Hg) achieved the target dose of vericiguat (86%) and placebo (87%). Among patients receiving ARNI, the proportion of patients achieving the 10 mg target dose of study drug was slightly lower for vericiguat (69%) than placebo (73%); however, a higher proportion of patients not receiving ARNI achieved the target 10 mg dose of vericiguat (81%) and placebo (82%).

Treatment adherence rates were similarly high in all subgroups over the duration of the study: 95.6% for patients >75 years old (versus 94.9% in younger patients), 94.2% in those with baseline SBP <110 mm Hg (versus 95.4% in those with higher SBP), and 94.6% in those receiving baseline ARNI therapy (versus 95.2% in those not receiving ARNI).

SBP Trajectory by Vulnerable Subgroups

As previously reported in the overall VICTORIA cohort,[4] SBP declined slightly more in the vericiguat than placebo group over the first 16 weeks before returning to baseline (Figure 1A). Compared with younger patients, the initial decline in SBP with vericiguat was more pronounced in those >75 years old, with SBP still returning to baseline thereafter (Figure 1B and 1C). A similar SBP trajectory was observed in patients >85 years old, compared with those above and below 65 years of age, whereas a smaller difference between treatment arms was observed (Figure S2A).

Table 1. Baseline Characteristics by Age, Baseline SBP, and Use of ARNI

Characteristic	Age >75 y			SBP <110 mm Hg			Use of ARNI at baseline		
	Yes (N=1395)	No (N=3639)	*P* value	Yes (N=1344)	No (N=3690)	*P* value	Yes (N=730)	No (N=4303)	*P* value
Age, y	80.0 (78.0, 84.0)	64.0 (57.0, 70.0)	<0.001	68.0 (58.0, 76.0)	69.0 (61.0, 77.0)	<0.001	67.0 (58.0, 75.0)	69.0 (60.0, 77.0)	<0.001
Female sex	398 (28.5%)	808 (22.2%)	<0.001	314 (23.4%)	892 (24.2%)	0.55	152 (20.8%)	1053 (24.5%)	0.033
Race*			<0.001			<0.001			<0.001
Asian	273 (19.6%)	858 (23.6%)		381 (28.4%)	750 (20.3%)		204 (27.9%)	927 (21.5%)	
Black	21 (1.5%)	228 (6.3%)		80 (6.0%)	169 (4.6%)		39 (5.3%)	210 (4.9%)	
Other	97 (7.0%)	332 (9.1%)		122 (9.1%)	307 (8.3%)		23 (3.2%)	406 (9.4%)	
White	1004 (72.0%)	2220 (61.0%)		760 (56.6%)	2464 (66.8%)		464 (63.6%)	2759 (64.1%)	
Region			<0.001			<0.001			<0.001
Asia Pacific	316 (22.7%)	865 (23.8%)		402 (29.9%)	779 (21.1%)		212 (29.0%)	969 (22.5%)	
Eastern Europe	362 (25.9%)	1330 (36.5%)		341 (25.4%)	1351 (36.6%)		87 (11.9%)	1605 (37.3%)	
Latin and South America	212 (15.2%)	512 (14.1%)		179 (13.3%)	545 (14.8%)		64 (8.8%)	660 (15.3%)	
North America	131 (9.4%)	422 (11.6%)		179 (13.3%)	374 (10.1%)		147 (20.1%)	406 (9.4%)	
Western Europe	374 (26.8%)	510 (14.0%)		243 (18.1%)	641 (17.4%)		220 (30.1%)	663 (15.4%)	
Index event			<0.001			<0.001			0.27
HF hospitalization 3–6 mo	258 (18.5%)	604 (16.6%)		208 (15.5%)	654 (17.7%)		138 (18.9%)	724 (16.8%)	
HF hospitalization within 3 mo	880 (63.1%)	2491 (68.5%)		955 (71.1%)	2416 (65.5%)		486 (66.6%)	2885 (67.0%)	
Intravenous diuretic for HF (without hospitalization) within 3 mo	257 (18.4%)	544 (14.9%)		181 (13.5%)	620 (16.8%)		106 (14.5%)	694 (16.1%)	
Body mass index, kg/m^2	25.2 (22.6–28.6)	27.5 (24.2–31.8)	<0.001	26.0 (23.0–29.7)	27.2 (24.0– 31.3)	<0.001	27.4 (24.3– 31.8)	26.8 (23.6–30.7)	<0.001
Ejection fraction, %	31.0 (25.0–38.0)	28.0 (21.0–35.0)	<0.001	25.0 (20.0–32.0)	30.0 (25.0–36.0)	<0.001	27.0 (20.0–33.5)	30.0 (23.0–35.0)	<0.001
New York Heart Association class			0.27			0.20			0.60
I	1 (0.1%)	1 (0.0%)		0 (0.0%)	2 (0.1%)		0 (0.0%)	2 (0.0%)	
II	805 (57.7%)	2160 (59.4%)		773 (57.5%)	2192 (59.4%)		427 (58.6%)	2538 (59.0%)	
III	575 (41.2%)	1424 (39.2%)		547 (40.7%)	1452 (39.4%)		296 (40.6%)	1702 (39.6%)	
IV	14 (1.0%)	52 (1.4%)		24 (1.8%)	42 (1.1%)		6 (0.8%)	60 (1.4%)	
Medical history									
Atrial fibrillation	817 (58.6%)	1445 (39.7%)	<0.001	619 (46.1%)	1643 (44.5%)	0.33	327 (44.8%)	1934 (44.9%)	0.94
Diabetes	592 (42.4%)	1772 (48.7%)	<0.001	590 (43.9%)	1774 (48.1%)	0.009	348 (47.7%)	2016 (46.9%)	0.68
Hypertension	1192 (85.4%)	2795 (76.8%)	<0.001	893 (66.4%)	3094 (83.8%)	<0.001	567 (77.7%)	3419 (79.5%)	0.27
Hyperlipidemia	860 (61.6%)	2027 (55.7%)	<0.001	720 (53.6%)	2167 (58.7%)	0.001	435 (59.6%)	2451 (57.0%)	0.18

(*Continued*)

Table 1. Continued

Characteristic	Age >75 y			SBP <110 mm Hg			Use of ARNI at baseline		
	Yes (N=1395)	No (N=3639)	*P* value	Yes (N=1344)	No (N=3690)	*P* value	Yes (N=730)	No (N=4303)	*P* value
Anemia	421 (30.2%)	647 (17.8%)	<0.001	282 (21.0%)	786 (21.3%)	0.81	156 (21.4%)	912 (21.2%)	0.92
History of coronary artery disease	896 (64.2%)	1959 (53.8%)	<0.001	707 (52.6%)	2148 (58.2%)	<0.001	397 (54.4%)	2458 (57.1%)	0.17
History of Stroke	186 (13.3%)	391 (10.7%)	0.010	144 (10.7%)	433 (11.7%)	0.32	89 (12.2%)	488 (11.3%)	0.50
History of peripheral artery disease	226 (16.2%)	404 (11.1%)	<0.001	124 (9.2%)	506 (13.7%)	<0.001	91 (12.5%)	539 (12.5%)	0.96
Vitals									
SBP, mm Hg	120.0 (110.0–133.0)	118.0 (108.0–130.0)	<0.001	105.0 (102.0–107.0)	124.0 (117.0–136.0)	<0.001	116.0 (107.0–126.0)	119.0 (109.0–132.0)	<0.001
Diastolic blood pressure, mm Hg	69.0 (61.0–76.0)	74.0 (67.0–81.0)	<0.001	65.5 (60.0–71.0)	75.0 (68.0–82.0)	<0.001	71.0 (64.0–79.0)	73.0 (65.0–80.0)	0.002
Heart rate, beats per minute	70.0 (62.0–79.0)	72.2 (64.0–82.0)	<0.001	72.0 (64.0–81.0)	72.0 (64.0–81.0)	0.52	70.0 (63.0–79.0)	72.0 (64.0–81.0)	<0.001
Standard of care medications and devices									
Angiotensin-converting enzyme or angiotensin receptor blocker	998 (71.6%)	2698 (74.1%)	0.07	942 (70.1%)	2754 (74.6%)	0.001	27 (3.7%)	3669 (85.3%)	<0.001
Beta blocker	1281 (91.9%)	3404 (93.5%)	0.039	1249 (93.0%)	3436 (93.1%)	0.89	664 (91.0%)	4021 (93.4%)	0.014
ARNI	172 (12.3%)	558 (15.3%)	0.007	239 (17.8%)	491 (13.3%)	<0.001	730 (100.0%)	0 (0.0%)	<0.001
Mineralocorticoid receptor antagonist	786 (56.4%)	2755 (75.7%)	<0.001	1047 (78.0%)	2494 (67.6%)	<0.001	525 (71.9%)	3016 (70.1%)	0.32
Triple therapy	638 (45.7%)	2367 (65.0%)	<0.001	862 (64.1%)	2143 (58.1%)	<0.001	482 (66.0%)	2523 (58.6%)	<0.001
Biventricular pacemaker	263 (18.9%)	475 (13.1%)	<0.001	232 (17.3%)	506 (13.7%)	0.002	131 (17.9%)	607 (14.1%)	0.007
Implantable cardioverter defibrillator	359 (25.8%)	1039 (28.6%)	0.047	445 (33.1%)	953 (25.8%)	<0.001	309 (42.3%)	1089 (25.3%)	<0.001
Laboratory results									
Creatinine, mg/dL	1.4 (1.1–1.8)	1.1 (0.9–1.5)	<0.001	1.2 (0.9–1.6)	1.2 (0.9–1.6)	0.57	1.2 (1.0–1.6)	1.2 (0.9–1.6)	0.009
Estimated glomerular filtration rate, mL/min per 1.73 m^2	47.0 (33.9–60.6)	62.8 (45.7–83.2)	<0.001	58.6 (40.7–78.5)	58.3 (41.4–76.7)	0.74	55.6 (41.4–74.5)	58.7 (41.2–77.7)	0.10
N-terminal pro-B-type natriuretic peptide, pg/mL	3460 (1914–6234)	2611 (1452–5001)	<0.001	3228 (1824–5587)	2708 (1470–5233)	<0.001	2718 (1554–5033)	2833 (1555–5358)	0.28

Data presented as median (25th, 75th) or number (%), unless otherwise indicated. ARNI indicates angiotensin receptor neprilysin inhibitors; ; HF, heart failure; and SBP, systolic blood pressure.
*Race was reported by the patient.

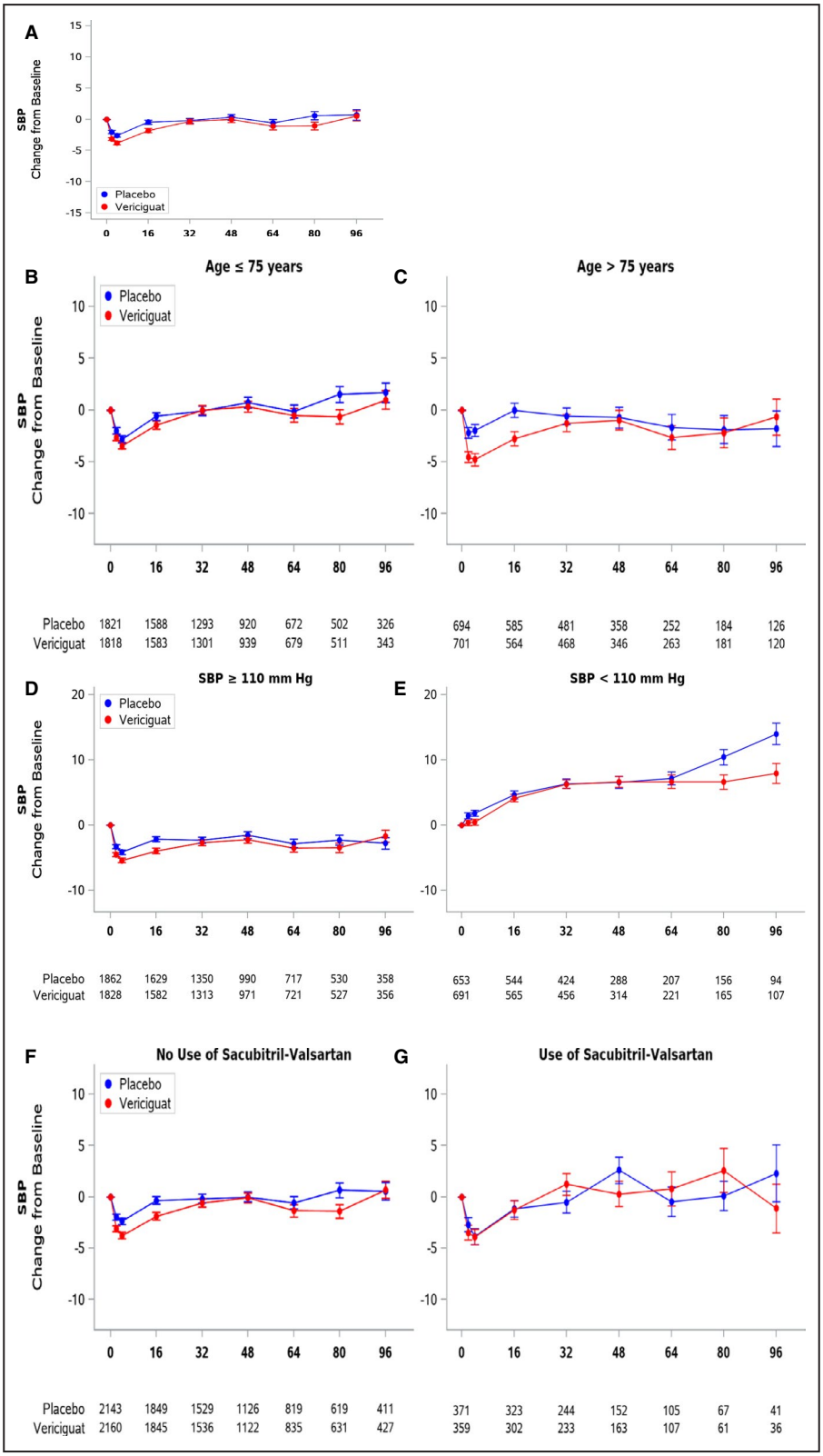

Figure 1. SBP trajectory (mean ±1 SE) over time in the entire VICTORIA population (A), and by subgroups of age below (B) or above (C) 75 years; SBP above (D) or below (E) 110 mm Hg; and those not receiving (F) or receiving (G) ARNI at baseline.
ARNI indicates angiotensin receptor neprilysin inhibitors; SBP: systolic blood pressure; and VICTORIA: Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction.

Compared with patients with higher baseline SBP, those with SBP <110 mm Hg at baseline showed a trend to increasing SBP over time, which was similar in both treatment arms (Figure 1D and 1E). Compared with patients not receiving ARNI, those receiving ARNI at baseline showed a similar SBP trajectory, with no difference between treatment arms (Figure 1F and 1G). Likewise, the SBP trajectories were similar between patients receiving (versus not receiving) any renin-angiotensin blockade, maximal doses of renin-angiotensin system inhibitors, and guideline-directed triple therapy (Figure S3).

Occurrence of Symptomatic Hypotension and Syncope

In adjusted Cox proportional hazards analysis for time to the composite of symptomatic hypotension or syncope in the overall cohort (Figure 2A through 2C) there was no significant difference in hazard rates for vericiguat compared with placebo (adjusted HR, 1.18; 95% CI, 0.99–1.39; *P*=0.059) (Figure 2A). There was no significant difference in the rates of symptomatic hypotension alone (adjusted HR, 1.17; 95% CI, 0.96–1.42; *P*=0.13) (Figure 2B) or syncope alone (adjusted HR, 1.16; 95% CI, 0.86–1.55; *P*=0.33) (Figure 2C) between treatment arms. Treatment discontinuation rates were also similar between treatment arms, regardless of occurrence of syncope or symptomatic hypotension (Table S1). Patients experiencing symptomatic hypotension or syncope were at increased risk of the primary outcome (adjusted HR, 1.55; 95% CI, 1.31–1.82). In landmark analysis beginning after the titration phase (ie, post 4 weeks) (Figure 2D through 2F), there was no difference in the occurrence of symptomatic hypotension or syncope between vericiguat- and placebo-treated patients, either before (unadjusted HR, 1.13; 95% CI, 0.93–1.37; *P*=0.22) or after multivariable adjustment (adjusted HR, 1.14; 95% CI, 0.93–1.38; *P*=0.20) (Figure 2D). Similarly, there was no difference in the rates of symptomatic hypotension alone (unadjusted HR, 1.09; 95% CI, 0.86–1.38, *P*=0.47; adjusted HR, 1.13; 95% CI, 0.89–1.43; *P*=0.32) (Figure 2E) or syncope alone (unadjusted HR, 1.17; 95% CI, 0.86–1.59; *P*=0.32; adjusted HR, 1.20; 95% CI, 0.88–1.64; *P*=0.26) (Figure 2F) between treatment arms.

When analyzed by subgroups (Table 2), event rates were similar between treatment arms within each subgroup.

Efficacy of Vericiguat According to Baseline SBP

Although the benefit of vericiguat compared with placebo on the primary composite outcome (HF hospitalization or cardiovascular death) appeared more pronounced in younger patients,[4] when we examined the effect of vericiguat compared with placebo on the primary composite outcome across the spectrum of baseline SBP (Figure 3), there was no evidence of treatment heterogeneity (*P* for interaction=0.32).

Further Subgroup Analyses

We also examined SBP trajectory, as well as occurrence of symptomatic hypotension and syncope according to NT-proBNP cut points above and below 4000 pg/mL and 8000 pg/mL (Figure S4, Table S2). The rates of symptomatic hypotension and syncope were similar between treatment arms in each NT-proBNP strata, with no difference between NT-proBNP subgroups.

Patients receiving SGLT2i at baseline (n=122) were younger (median [25th, 75th percentile] age 64 [58, 74] versus 69 [60, 77] years), more likely to be male (86% versus 76%), more likely to have a history of diabetes (98% versus 46%), had lower baseline SBP (115 [106–131] versus 119 [109–131] mm Hg), and more concurrent ARNI use (21% versus 14%) but similar overall use of triple therapy (63% versus 60%) compared with patients not receiving SGLT2i. In the small group of patients receiving SGLT2i at baseline, the proportion of patients achieving the 10 mg target dose of study drug was slightly lower for vericiguat (74%) than placebo (85%) but similar to the proportion of patients not receiving SGLT2i who achieved the target 10 mg dose of vericiguat (79%) and placebo (81%). SBP trajectories showed that patients receiving SGLT2i at baseline appeared to have lower SBP compared with those who were not, although CIs were wide (Figure S5). Symptomatic hypotension and syncope event rates were numerically higher in those receiving SGLT2i at baseline compared with those who were not; however, numbers of events were small and the differences were not statistically significant (Table S3).

DISCUSSION

Consistent with the safety and tolerability of vericiguat observed in the overall VICTORIA trial, we did not observe excessive blood pressure decreases with vericiguat across a large number of subgroups representing potentially vulnerable patients predisposed to blood pressure decreases. These subgroups included older patients, those with lower baseline SBP, as well as patients receiving concurrent ARNI therapy. There was a small numerical increase in occurrence of symptomatic hypotension or syncope early during dose titration but no difference in rates of symptomatic hypotension or syncope from 4 weeks onwards. The rates of symptomatic hypotension and rates of syncope

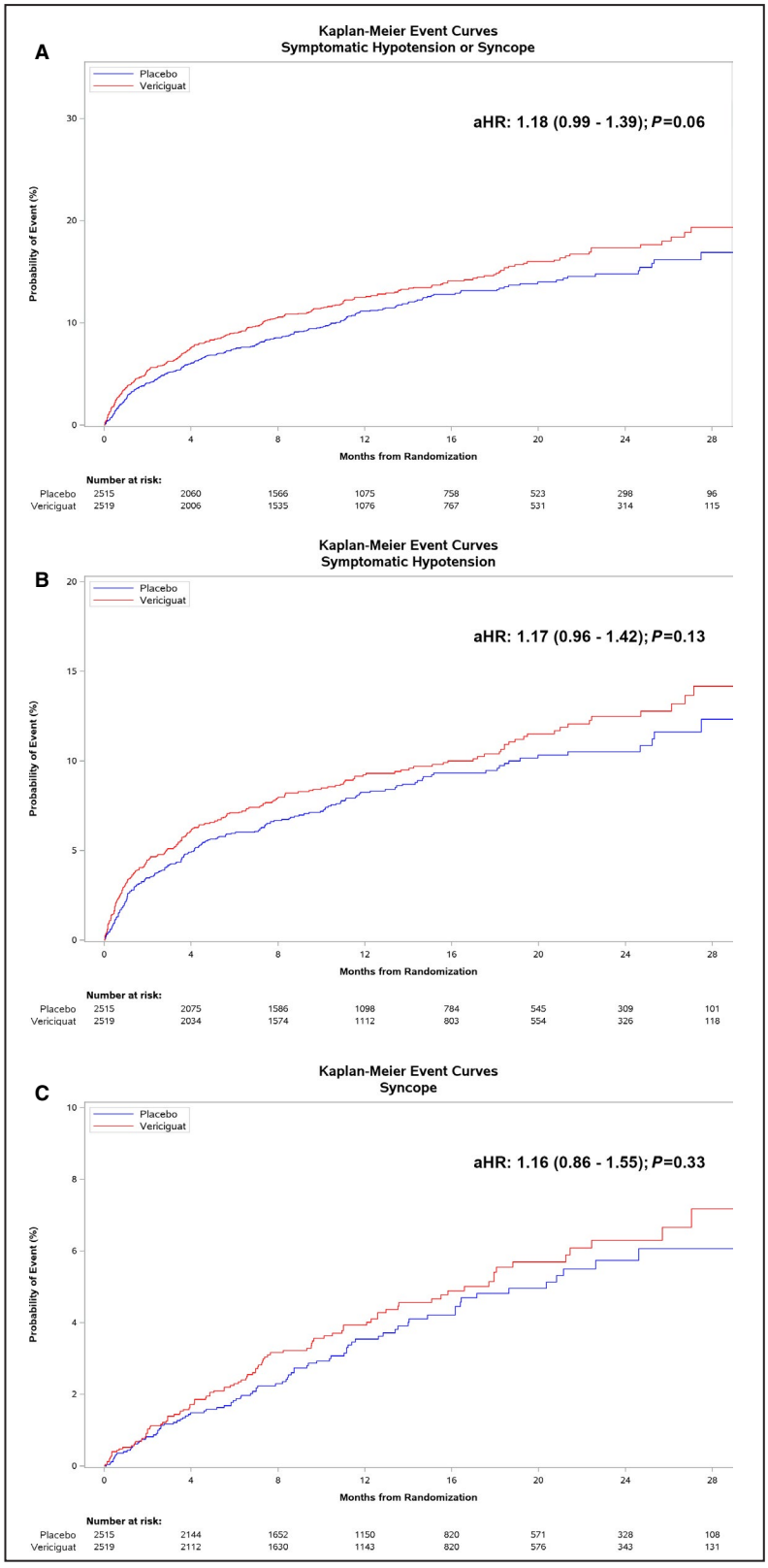

Figure 2. Kaplan-Meier event curves for time from randomization to (A) symptomatic hypotension or syncope, (B) symptomatic hypotension alone, and (C) syncope alone, and (D) landmark analysis in the post-titration phase (ie, after 4 weeks) of time to symptomatic hypotension or syncope, (E) symptomatic hypotension alone, (F) and syncope alone. aHR indicates adjusted hazard ratio.

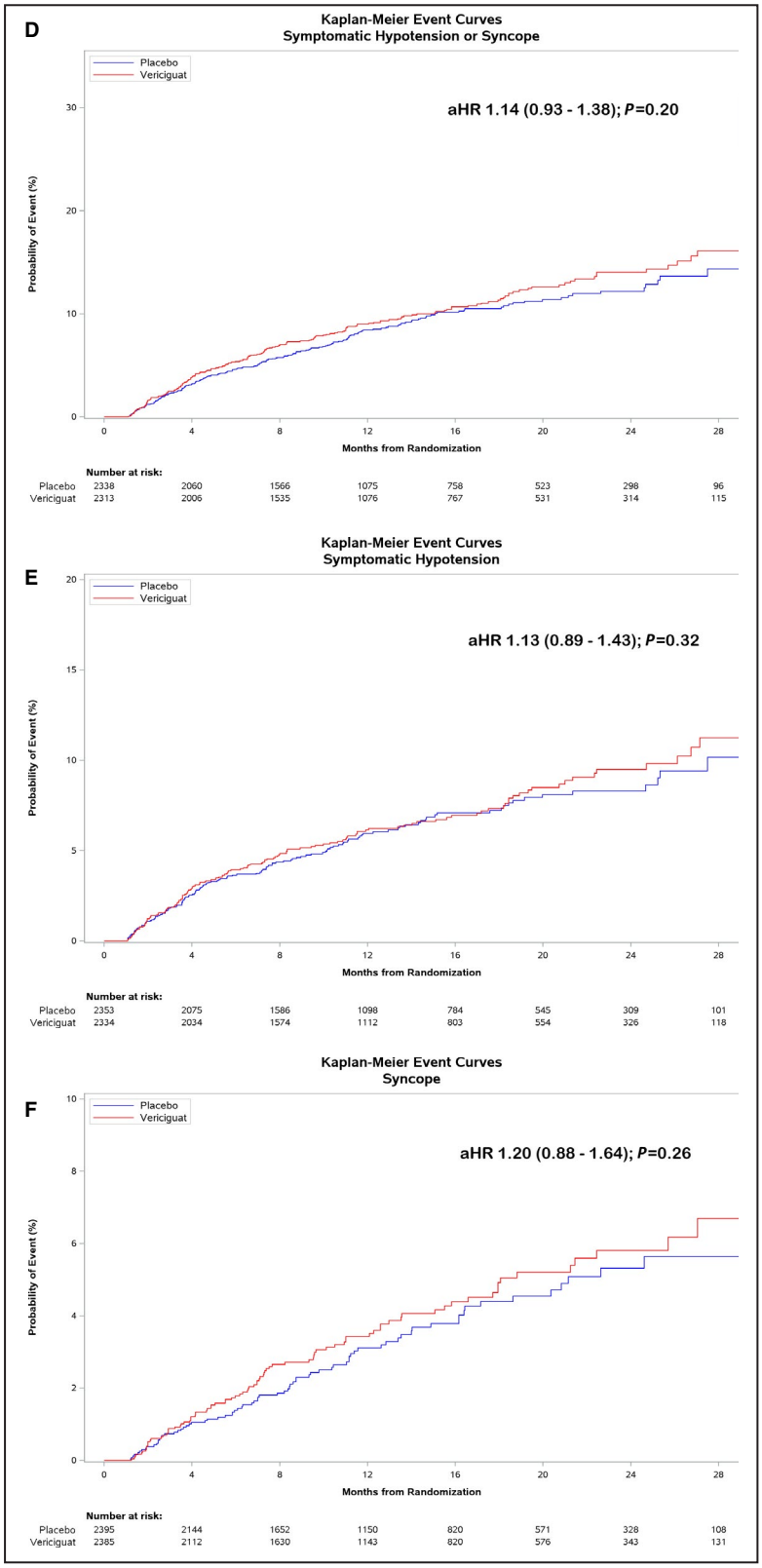

Figure 2. (Continued)

were generally low and similar between randomized treatment arms across specified subgroups. Along with prior evidence of benefit with vericiguat regardless of age and background therapy, as well as this new evidence of the consistency of benefit across baseline SBP, our findings indicate the favorable benefit to risk

Table 2. Treatment Effect on Time to Symptomatic Hypotension or Syncope by Vulnerable Subgroups

	Vericiguat Rate (Events)*	Placebo Rate (Events)*	Unadjusted		Adjusted	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Symptomatic hypotension or syncope						
Age ≤75 y	12.03 (222)	9.61 (179)	1.26 (1.03–1.53)	0.28	1.23 (1.01–1.51)	0.42
Age >75 y	13.35 (90)	12.99 (88)	1.03 (0.77–1.39)		1.06 (0.78–1.44)	
SBP ≥110 mm Hg	10.08 (193)	9.13 (178)	1.11 (0.91–1.36)	0.36	1.11 (0.90–1.37)	0.33
SBP <110 mm Hg	19.66 (119)	15.05 (89)	1.30 (0.99–1.71)		1.32 (0.99–1.75)	
No use of ARNI	11.61 (258)	9.55 (212)	1.22 (1.02–1.46)	0.48	1.23 (1.02–1.49)	0.24
Use of ARNI	18.09 (54)	17.23 (55)	1.05 (0.72–1.53)		0.95 (0.64–1.41)	
Symptomatic hypotension						
Age ≤75 y	8.88 (168)	6.84 (130)	1.30 (1.04–1.64)	0.08	1.27 (1.00–1.61)	0.20
Age >75 y	8.85 (61)	9.96 (68)	0.90 (0.64–1.27)		0.96 (0.67–1.37)	
SBP ≥110 mm Hg	7.14 (140)	6.34 (126)	1.14 (0.89–1.44)	0.82	1.13 (0.88–1.45)	0.70
SBP <110 mm Hg	14.36 (89)	12.06 (72)	1.19 (0.87–1.62)		1.23 (0.89–1.69)	
No use of ARNI	8.12 (185)	6.87 (155)	1.19 (0.96–1.47)	0.73	1.21 (0.97–1.51)	0.48
Use of ARNI	14.53 (44)	13.20 (43)	1.10 (0.72–1.67)		1.01 (0.65–1.57)	
Syncope						
Age ≤75 y	3.53 (69)	3.13 (61)	1.13 (0.80–1.60)	0.72	1.15 (0.81–1.63)	0.94
Age >75 y	4.50 (32)	3.55 (26)	1.27 (0.76–2.13)		1.18 (0.69–2.02)	
SBP ≥110 mm Hg	3.30 (66)	3.08 (63)	1.08 (0.76–1.52)	0.41	1.09 (0.77–1.55)	0.52
SBP <110 mm Hg	5.26 (35)	3.78 (24)	1.40 (0.83–2.35)		1.35 (0.79–2.30)	
No use of ARNI	3.77 (88)	3.00 (70)	1.26 (0.92–1.73)	0.25	1.29 (0.93–1.77)	0.10
Use of ARNI	3.91 (13)	4.93 (17)	0.79 (0.39–1.63)		0.65 (0.30–1.38)	

ARNI indicates angiotensin receptor neprilysin inhibitors; HR, hazard ratio; and SBP, systolic blood pressure.
*Number of events per 100 patient-years of follow-up.

ratio of vericiguat extends to patients potentially predisposed to blood pressure decreases.

These data provide important reassurance to physicians who may be reluctant to prescribe medications likely to cause hypotension, even if they are known to be beneficial. The SBP trajectories in the current report showed that despite an initial small dip in SBP in all subgroups—also seen in the placebo arm—continued treatment with vericiguat was associated with recovery and stabilization of SBP. Such patterns of SBP change have also been previously reported with initiation of renin-angiotensin system inhibitors,[12,13] ARNI,[9] and SGLT2i[10] in HFrEF and have been attributed to a potential improvement in perfusion with beneficial afterload lowering therapies, offsetting any treatment-induced reduction in SBP. Furthermore, the small nonsignificant increase in symptomatic hypotension or syncope during dose titration did not prevent the majority (≥60%) of patients in each subgroup from achieving the 10 mg target dose of vericiguat, and there was reassuringly no further excess safety events with continued treatment.

The relation between baseline SBP, outcomes, and treatment effect in HFrEF is known to be complex. A low SBP is associated with worse outcomes in patients with HFrEF, indicative of more advanced cardiac disease with worse haemodynamic status, or because low SBP reflects underuse of (or intolerance to) effective therapies.[14] Indeed in VICTORIA, the occurrence of syncope or symptomatic hypotension identified patients at higher risk of the primary outcome. It is particularly noteworthy that the efficacy of vericiguat was similar across baseline SBP, even down to a baseline SBP of 100 mm Hg. Vericiguat could be safely initiated and up-titrated, even in patients with baseline SBP <110 mm Hg, following a fixed protocol (based on SBP) that applied to both treatment arms. Among patients with baseline SBP <110 mm Hg, the similar proportion of patients achieving the target 10 mg dose in both vericiguat and placebo sham titration indicates that the dose was limited by the titration protocol rather than by intolerance to vericiguat. The lower baseline SBP in patients receiving ARNI and SGLT2i may similarly explain the lower proportion of patients achieving the target dose of vericiguat in these subgroups. Nonetheless, the consistent beneficial effect on the primary efficacy composite (HF hospitalization or cardiovascular death), coupled with lack of excess safety events (symptomatic hypotension and syncope) in patients with low baseline SBP, suggests that vericiguat is an important therapeutic option in these patients.

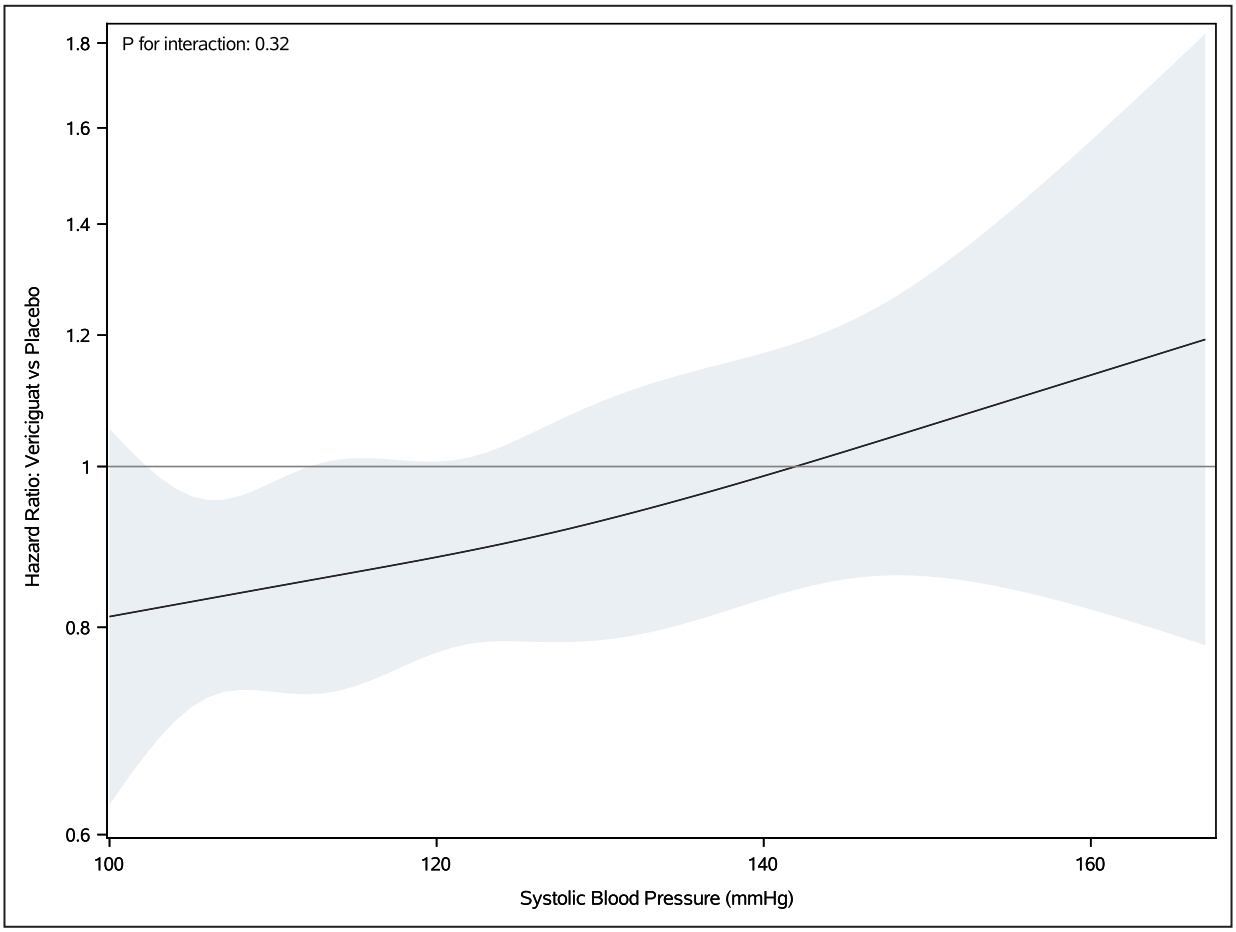

Figure 3. Treatment effect of vericiguat compared with placebo on the primary composite end point (first heart failure hospitalization or cardiovascular death) according to baseline systolic blood pressure.

We acknowledge that these are post hoc analyses, using arbitrary cut-offs for assignment of subgroups, although supplementary analyses were performed to examine other cutoffs for age. VICTORIA excluded patients with SBP <100 mm Hg and included only relatively small subgroups with concurrent ARNI and SGLT2i treatment. The landmark analysis using post-titration data to support tolerability may bias our data by removing patients lost during titration and should therefore be interpreted to refer to patients who tolerated the up-titration. Nonetheless, results were consistent with the overall analysis of all available timepoints and were adjusted for an extensive list of baseline characteristics to minimize bias.

CONCLUSIONS

In conclusion, vericiguat is safe and hemodynamically tolerated in a broad population of patients with worsening HFrEF, even in patients at older age, with lower SBP, and on other HF therapies with the potential to interact in the cyclic guanosine monophosphate pathway or decrease blood pressure (such as ARNI).

ARTICLE INFORMATION

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Affiliations

National Heart Centre Singapore & Duke-National University of Singapore, Singapore (C.S.L.); Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (H.M., K.J.A., A.F.H.); Volgograd State Medical University, Regional Cardiology Centre Volgograd, Volgograd, Russian Federation (Y.L.); Ponce School of Medicine, Ponce, Puerto Rico (J.B.V.); Research & Cardiovascular Center and Cardiometabolic Research Center, Ponce, Puerto Rico (J.B.V.); Li Ka Shing, Faculty of Medicine, The University of Hong Kong, Hong Kong (D.S.); Canadian VIGOUR Centre, University of Alberta, Edmonton, Canada (J.E., P.W.A.); Charité University Medicine, German Heart Center, Berlin, Germany (B.P.); Inova Heart and Vascular Institute, Falls Church, VA (C.M.O.); (L.R.) and Merck & Co. Inc., Kenilworth, NJ (M.J.P.).

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Supplementary Material

Data S1
Tables S1–S3
Figures S1–S5

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SUPPLEMENTAL MATERIAL

VICTORIA Executive Committee

Paul W. Armstrong, Canadian VIGOUR Centre, University of Alberta (Study Chair)

Christopher M. O'Connor, Inova Heart and Vascular Institute, Duke Clinical Research Institute, (Study Co-Principal Investigator)

Burkert Pieske, Charité University Medicine and German Heart Center (Study Co-Principal Investigator)

Kevin J. Anstrom, Duke Clinical Research Institute

Javed Butler, University of Mississippi Medical Center

Justin A. Ezekowitz, Canadian VIGOUR Centre, University of Alberta

Adrian F. Hernandez, Duke Clinical Research Institute

Carolyn S.P. Lam, National Heart Centre Singapore, Duke-NUS Graduate Medical School

Joerg Koglin, Merck & Co.

Piotr Ponikowski, Wroclaw Medical University

Lothar Roessig, Bayer AG

Adriaan A. Voors, Groningen Heart Failure Research Institute, University of Groningen

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Kris Reay, Senior Administrative Assistant

Lisa Soulard, Executive Assistant

Tracy Temple, Associate Director, Clinical Trials

Cynthia Westerhout, Associate Director, Biostatistics/Strategic Planning

Duke Clinical Research Institute (DCRI)

Robert J. Mentz, Associate Professor, Associate Program Director, Duke Cardiovascular Disease Fellowship

VICTORIA Clinical Trial Team

Mahesh J. Patel, Executive Director, Merck Global Clinical Development Cardiovascular

Constance Hamlin, Vericiguat Program Lead, Merck Global Clinical Trial Operations

Rhonda Lovett, Lead Study Manager, Merck Global Clinical Trial Operations

Nicholas Ryan, Lead Clinical Scientist, Merck Global Clinical Trial Operations

Robert Blaustein, Executive Director, Merck Global Clinical Development Cardiovascular

Gregory Golm, Executive Director, Merck Biostatistics and Research Decision Sciences

Gang Jia, Sr Principal Scientist, Merck Biostatistics and Research Decision Sciences

Christi Kent, Vericiguat Program Lead Medical Writer, Merck Global Clinical Trial Operations

Jaco De Klerk, Director, Merck Global Clinical Trial Operations, Therapeutic Area Lead Cardiovascular

Christina Salerno, Executive Director, Merck Global Clinical Trial Operations

Sabine Broeker-Zweering, Clinical Project Manager, Bayer AG

Richard Nkulikiyinka, Vice President, Head of Cardiology & Nephrology, Bayer AG

Elaine Wu, Biostatistics, Bayer AG

Katharina Mueller, Biostatistics, Bayer AG

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German Heart Center Berlin and University Medicine Berlin

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Health Economics

Daniel Mark, Director Outcomes Research, Professor of Medicine, Vice Chief for Academic Affairs, Division of Cardiology, Duke University, DCRI

Linda Davidson-Ray, Project Leader, DCRI

VICTORIA National Leaders

Argentina: M. Cecilia Bahit; **Australia:** David M. Kaye; **Austria:** Diana Bonderman; **Belgium:** Anne-Catherine Pouleur; **Brazil:** Edimar A. Bocchi; **Canada:** Justin A. Ezekowitz; **Chile:** Fernando Lanas; **China:** Jian Zhang; **Colombia:** Clara Saldarriaga; **Czech Republic:** Vojtěch Melenovský; **Denmark:** Jens Refsgaard; **Finland:** Johan Lassus; **France:** Alain Cohen-Solal; **Germany:** Frank Edelmann; **Greece:** Dimitrios N. Tziakas; **Guatemala:** Juan Luis Arango Benecke; **Hong Kong:** David Siu; **Hungary:** Ebrahim Noori; **Ireland:** Kenneth McDonald; **Israel:** Basil S. Lewis; **Italy:** Michele Emdin, Michele Senni; **Japan:** Hiroyuki Tsutsui; **Malaysia:** Imran Zainal Abidin; **Mexico:** Jorge Escobedo; **Netherlands:** Arend Mosterd; **New Zealand:** Richard W. Troughton; **Norway:** Dan Atar; **Peru:** Armando Lionel Godoy Palomino; **Philippines:** Eugenio B. Reyes; **Poland:** Piotr Ponikowski; **Puerto Rico:** Jose B. Vazquez-Tanus; **Republic of Korea:** Myeong-Chan Cho; **Russian Federation:** Yury Lopatin; **Singapore:** David Sim; **South Africa:** Karen Sliwa-Hähnle; **Spain:** José López-Sendón; **Sweden:** Lars H. Lund; **Switzerland:** Diana Bonderman; **Taiwan:** Chern-En Chiang; **Turkey:** M. Ali Oto; **Ukraine:** Vojtěch Melenovský; **United Kingdom:** Martin Cowie; **United States:** Michael M. Givertz, Ileana L. Piña, Nancy K. Sweitzer

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John J.V. McMurray, University of Glasgow (Chair); Christopher B. Granger, Duke Clinical Research Institute, Duke University Medical Center; Thomas D. Cook, Department of Biostatistics & Medical Informatics, University of Wisconsin-Madison; Gary S. Francis, Division of Cardiovascular Disease, University of Minnesota; Karl Swedberg, Department of Molecular

and Clinical Medicine, University of Gothenburg. External independent statistical support, Haley Hedlin, Stanford University.

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VICTORIA Primary Site Investigators / Primary Study Coordinators

Argentina: Eduardo Roque Perna / Maria Galarza Salazan; Ignacio MacKinnon / Florencia Eden; Luis Cartasegna / Viviana Novas; Hugo A. Luquez / Ana Cenci; Miguel Angel Hominal / Maria Veronica Bianchini; Rodolfo Andres Ahuad Guerrero / Andrea Alvarez D Amelio; Carlos Alberto Poy / Maria Poy; Claudio R. Majul / Cecilia Currao; Ezequiel Hector Vottero / Mariana Perrin; Cesar Javier Zaidman / Maria Vanesa Espinosa; Gerardo Zapata / Luciana Arias; Sonia Angelica Sassone / Lucas Tonelli; Daniel Agustin Chirino Navarta /Maria Mangini; Jesus Cuadrado / Paula Bordoni. **Australia:** David Kaye / Kaye Carter; John Amerena / Toni Shanahan; Scott McKenzie / Kathryn Stibijl; Carmine De Pasquale / Fiona Wollaston; David Martin Colquhoun / Antonio Ferreira-Jardim; Alicia Chan / Greer Dymmott; Brendan McQuillan / Katayun Mohammadi; David Cross / Judy Jeffrey; Andrew Sindone / Magdalena Gebran; Amit Shah / Gill Tulloch; Maged William / Bets Conway; James Wong / Donna North. **Austria:** Dirk von Lewinski / Karin Brandner; Uta Hoppe / Kristen Kopp; Regina Steringer Mascherbauer / Claudia Steinkellner; Diana Bonderman / Christina Binder; Christopher Adlbrecht / Maria Leitgeb. **Belgium:** Anne-Catherine Pouleur / Florence Sinnaeve; Matthias Dupont / Carola Claes; Michel De Ceuninck / Els Vancayseele; Philippe Timmermans / Gregory Van Genechten; Pierre Troisfontaines / Mireille Massoz. **Canada:** Thao Thanh Huynh / Caroline Boudreault; Eric

Sabbah / Isabelle Chausse; Ronald Leonard Bourgeois / Karen Boyd; Michael Heffernan / Marie Birch; Marie-Claude Parent / Helene Brown; A. Shekhar Pandey / Tatiana Ballivian; Nadia Giannetti / Reza Sahebjamei; Saul Vizel / Beverley Fox; Dennis Wayne Rupka / Sandi Thiessen; Christian Constance / Marie-France Gauthier; Justin Ezekowitz / Quentin Kushnerik; Allan Schaffer / Wendy Janz; Michael Chan / Jennifer Knight; Serge Lepage / Daniel Soucy; John D. Parker / Elaine Hsu; Lisa Mielniczuk / Ermina Moga; Benoit Coutu / Julie Fleury; Paul MacDonald / Kathleen Hines; Diego Delgado / Natalia Nugaeva; Ying Sia / Isabelle Roy; David Laflamme / Christel Simard; Gilbert Gosselin / Katia Drouin; Brian Clarke / Kimberley Ronak; Denis Saulnier / Melissa Cote; Bruce Alexander Sussex / Bernadette Druken; Miroslaw Rajda / Jayne Falkenham; Ashok Mukherjee / Beverly Bozek; Gordon Willy Pak Ling Moe / Carlos Fernando; Sebastien Bergeron / Hugo Tremblay; Marcelo Coelho Shibata / Bonnie Woloschuk; Dante Manyari / Tracy Cleveland; Frank Nigro / Crystal Forsyth; Annie Roy / Helene Bolduc; Danielle Dion / Nancy Gilbert; James Y Cha / Judy Otis; Melinda Barabas / Marie-Josee Chartrand. **Chile:** Victor Assef / Andrea Eikhof; Manuel Novajas Balboa / Carla Belen Aravena Vasquez; Juan Carlos Prieto Dominguez / Viviana Noriega; Patricio Yovaniniz / Marcela Grandon; Fernando Lanas / Jessica Hidalgo. **China:** Yuhui Zhang / Jing Dong; Haiying Dai / Ying Xiao; Tingbo Jiang / Lin Shi; Jiyan Chen / Peiyu He; Daoquan Peng / Fangmei Qing; Biao Xu / Ruihong Wang; Xiang Gu / Min Wang; Zhuhua Yao / Ying Chen; Peizhi Miao / Zhenfei Chen; Hui Li / Dongyan Huang; Qing Yang / Xuefang Yu; Aidong Shen / Xin Zhang; Xiaohui Liu / Qiang Lv; Yugang Dong / Dan Liu; Jingfeng Wang / Huijun Ouyang; Chengchun Tang / Yong Chen; Hui Gong / Dandan Teng; Jing Yan / Linying Xu; Weihong Jiang / Xiaowei Zhou; Guosheng Fu / Ying Zheng; Shuyang Zhang / Lihong Xu; Zhenyu Yang / Chenying Wu; Xiumin Han / Yuxia Wang; Jing Yu / Qiongying Wang; Lihong Wang / Lili Zheng; Wei Jin / Nan Zhang; Chuanhuan Zhang / Xiaojian Sun; Yali Yao / Peng Lei; Zhaofen Zheng; Junkui Wang / Fengling Ma; Mingzhi Long / Sulan Wang; Hong Zhang / Mingmei Guo; Manhua Chen / Yayun Wang; Zhanquan Li / Ruili Duan; Zuyi Yuan / Tiaotiao Li; Yibin Mei / Linyan Ye; Zhouqing Huang /

Xingyuan Zhang; Wenling Liu / Lei Li; Ruiping Zhao / Jie Gong; Dongqing Zhang / Jiahui Zhu; Chengjian Yang / Chunxia Wang; Zheng Ji / Gao Xinpei; Xia Mei / Mingyun Liu; Xin Zhang. **Colombia:** Clara Saldarriaga / Paula Garcia Amaya; Wilder Castano Osorio / Maria Dussan; Franklin Roberto Quiroz Diaz / Yuleth Prada; Carlos Francisco Jaramillo Munoz / Ana Zapata; Monica Jaramillo / Solmara Bello; Rodrigo Botero / Sandra Salazar; Monica Lopez Pareja / Claudia Mora; Nicolas Ignacio Jaramillo Gomez / Ana Zapata; Juan Camilo Garcia / Fabian Torres; Miguel Alfredo Moncada / Laura Velez Gil; Jaime Andres Torres / Yolanda Lievano. **Czech Republic:** Vojtech Melenovsky / Miroslava Krausova; Jan Malik; Martin Hajsl / Katerina Mala; Jan F Vojacek / Jana Fridrichova; Filip Malek / Dana Rihova; Vladimir Cech / Lenka Masarikova; Vilma Machova; Jindrich Spinar; Jan Macha; Libor Nechvatal. **Denmark:** Kenneth Egstrup / Lene Moltrup; Benedikte Haastrup / Camilla Jespersen; Ole Nyvad / Lene Tanggaard; Lars Fog / Pauline Johansen; Henrik Wiggers / Kristine Serup-Hansen; Jens Due Lomholdt / Kari Niemann; Olav Wendelboe Nielsen / Elisa Stokholm; Mustafa Taskiran / Lotte Ring Pedersen. **Finland:** Kai Nyman / Tiina Sankari; Heikki Ukkonen / Tuija Vasankari; Johan Lassus / Sari Karesvuori. **France:** Alain Cohen-Solal / Miguel Vazquez Ibarra; Karim Gallouj / Angelique Lombart; Thibaud Damy / Mounira Karhoubi; Michel Galinier / Nathalie Rosoli; Guillaume Taldir / Maelle Vomscheid; Jean-Michel Tartiere / Charline Genin; Muriel Salvat / Delphine Pollet; Bernard Citron / Ouarda Lamallem; Nicolas Girerd / Lydie Poinsignon; Francois Jourda / Emmanuelle Mougenot; Hatem Boughanmi / Hanane Fodil; Lionel Benhamou / Ghania Harzi. **Germany:** Stefan Störk / Anja Knoppe; Karl-Friedrich Appel / Petra Becker; Johann Bauersachs / Manuela Geyer; Ekkehard Schmidt / Kristina Schmidt; Frank Edelmann / Sophia Strempel; Daniel Beug / Michael Bruder; Michael Jeserich / Mariana Rupprecht; Hendrik Haake / Bianca Krug-Hoeren; Andreas Hagenow / Anja Kuntzsch; Mirjana Vojvodic-Mayer / Ronny Lux; Thomas Horacek / Manuela Pluemer-Schmidt; Markus Knapp / Edith Suepple-Poch; Veselin Mitrovic / Annerose Peil; Stephan Rosenkranz / Susanne Roelle-Hoehne; Raffi Bekeredjian / Ina Probst; Izabela Tuleta / Marjo Lauterborn; Bernhard Winkelmann / Linda Tenbusch; Wolfgang Zeh /

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Nakamura; Yasuo Okumura / Haruka Sato; Hirotsugu Tabata / Mizuki Saino; Takanori Ikeda / Reiko Kaminishi; Mio Ebato / Akiko Fukatsu; Takahiko Aoyama / Chihiro Kitani; Hiroki Sakamoto / Kaori Amano; Tomoaki Saeki / Kayo Shimano; Kenji Kada / Yoko Tsuzuki; Tetsuo Hashimoto / Madoka Okamoto; Kenshi Fujii / Mari Tsujimoto; Tahei Ichinohe / Saori Okabe; Keiji Hirooka / Yuna Senshu; Tetsuro Ohta / Tomomi Hayashi; Yusuke Kawai / Juri Horio; Atsushi Takaishi / Mikiko Nakamura; Hiroyuki Takatsu / Tomoko Shiota; Koji Maemura / Momoyo Nishida; Yoshisato Shibata / Kaori Nagashima; Taro Shibasaki / Nobue Takahashi; Taro Shibasaki / Nobue Takahashi; Harukazu Iseki / Kenichi Otsuki; Shunzo Matsuoka / Kentaro Motoda; Yoshiharu Higuchi / Hiromi Hayasaki; Mamoru Manita / Riyo Ito; Masahiro Suzuki / Kaori Fumikura; Hiroshi Iwata / Kaori Kinjo; Eiki Takimoto / Yuki Omori; Kazuhiko Yumoto / Jun Yoshizawa; Chisato Izumi / Kanae Hirase; Shinichi Higashiue / Ayaka Ishibaba; Yorihiko Higashino / Takuro Matsumura; Hiroshi Iida / Kaya Kowa; Tokushi Koga / Tomomi Hatakeda; Nobuhiko Atsuchi / Kana Migita; Yukihiko Momiyama / Yusuke Fukuda; Masataka Fukue / Kouji Uchida; Katsumi Saito / Sakiko Iida; Seiji Fukamizu / Junko Harada; Yasuyoshi Takei / Saori Takano; Yoshiki Hata / Arisa Sato; Yumi Shimura / Shinko Hirata; Atsuo Namiki / Noriko Ishida; Ichiro Michishita / Tomomi Ishimoto; Kazuo Usuda / Akiko Oomura; Koichiro Kinugawa / Rumi Sasaki; Takao Matsubara / Hiromi Kidani; Yoshifumi Awaji / Yoko Kaneno; Kentaro Yamashita / Masami Suzuki; Hiroshi Fujita / Aya Mashida; Takahisa Yamada / Shintaro Hirai; Minoru Ichikawa / Takae Muromaki; Tomohito Ohtani / Sachiyo Yamaguchi; Yutaka Furukawa / Mika Takata; Masato Baden / Futoshi Kawasaki; Hideki Tashiro / Yuko Kita; Mizuri Taki / Kuniko Suzuki; Kenji Nakama / Chiaki Oota; Kiyoshi Hibi / Mizuho Shiono; Satoaki Matoba / Natsuki Kimura; Akihiko Takahashi / Megumi Fujino; Tomomi Ide / Chiharu Tanaka; Osamu Ueda / Rieko Shimojima; Takehiko Kuramochi / Michiko Ando; Haruhiko Onaka / Anri Maeda; Tetsuya Higami / Ikumi Nishibe; Mitsunori Abe / Megumi Matsugi; Junya Ako / Kimiko Yamamura; Tomoya Ueda / Yuki Itokazu; Kotaro Sumii / Kano Ichii; Masatoshi Shimizu / Megumi Irikura; Shigeo Shimizu / Misa Ayabe; Taku Matsubara / Satoko Kaneko; Tomomi

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Table S1. Discontinuation Rate by Randomized Treatment and Safety Event Occurrence.

	Vericiguat (N=2519)	**Placebo (N=2515)**	**Overall (N=5034)**
Syncope or Symptomatic Hypotension			
Censor	492/2207 (22.3%)	466/2248 (20.7%)	958/4455 (21.5%)
Event	122/312 (39.1%)	102/267 (38.2%)	224/579 (38.7%)
Symptomatic Hypotension			
Censor	522/2290 (22.8%)	489/2317 (21.1%)	1011/4607 (21.9%)
Event	92/229 (40.2%)	79/198 (39.9%)	171/427 (40.0%)

Numerators are the number of patients who discontinued treatment. Denominators are the number of patients in each treatment arm, who either experienced the specific safety event or were censored. There were 744 participants with discontinuation due to death, who were excluded from these numbers.

Table S2. Treatment effect on time to symptomatic hypotension or syncope by NT-proBNP subgroups.

Safety outcome	Vericiguat Rate (Events)	Placebo Rate (Events)	HR (95% CI)	P-value
Symptomatic hypotension or syncope				
NT-proBNP ≥4000 pg/mL	13.18 (97)	12.28 (90)	1.08 (0.81–1.43)	0.386
NT-proBNP <4000 pg/mL	12.03 (202)	9.61 (161)	1.26 (1.02–1.55)	
NT-proBNP ≥8000 pg/mL	12.92 (33)	15.69 (39)	0.83 (0.52–1.32)	0.102
NT-proBNP <8000 pg/mL	12.32 (266)	9.82 (212)	1.26 (1.05–1.51)	
Symptomatic hypotension				
NT-proBNP ≥4000 pg/mL	9.17 (69)	9.19 (68)	1.00 (0.72–1.40)	0.241
NT-proBNP <4000 pg/mL	8.66 (149)	6.78 (116)	1.29 (1.01–1.64)	
NT-proBNP ≥8000 pg/mL	9.66 (25)	12.37 (31)	0.79 (0.47–1.34)	0.108
NT-proBNP <8000 pg/mL	8.71 (193)	6.95 (153)	1.26 (1.02–1.56)	
Syncope				
NT-proBNP ≥4000 pg/mL	4.39 (34)	3.64 (28)	1.22 (0.74–2.00)	0.884
NT-proBNP <4000 pg/mL	3.60 (64)	3.11 (55)	1.16 (0.81–1.66)	
NT-proBNP ≥8000 pg/mL	3.75 (10)	4.97 (13)	0.76 (0.33–1.73)	0.263
NT-proBNP <8000 pg/mL	3.85 (88)	3.07 (70)	1.26 (0.92–1.72)	

CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide.

Table S3. Treatment effect on time to symptomatic hypotension or syncope by baseline use of SGLT2i.

Symptomatic hypotension or syncope	Vericiguat Rate (Events)	Placebo Rate (Events)	HR (95% CI)	P-value
No use of SGLT-2 inhibitors	12.16 (300)	10.34 (257)	1.18 (1.00–1.39)	0.792
Use of SGLT-2 inhibitors	22.66 (12)	17.94 (10)	1.32 (0.57–3.06)	

CI, confidence interval; HR, hazard ratio; SGLT-2 , sodium-glucose Cotransporter-2.

Figure S1. Distribution of baseline SBP in VICTORIA.

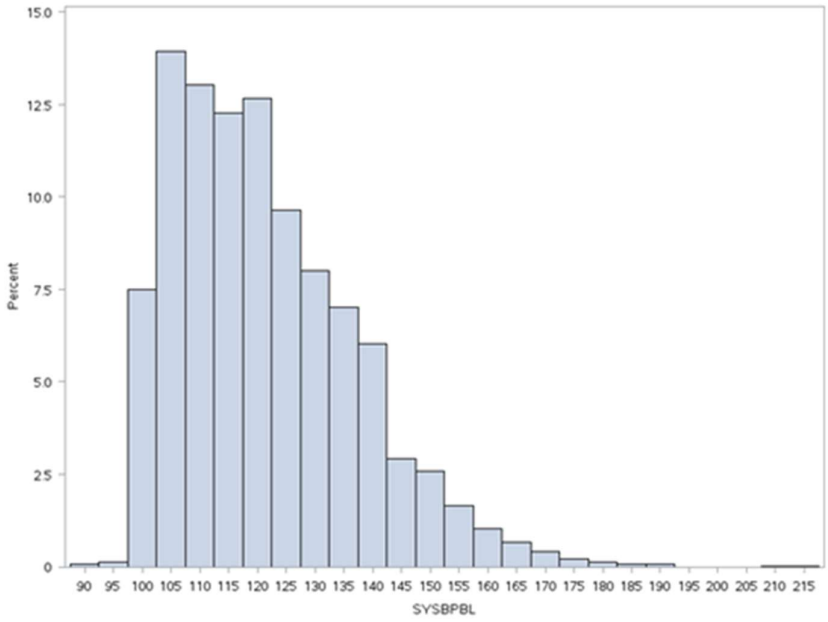

Figure S2. Systolic blood pressure (SBP) trajectory over time by age strata (A) above and below 65 years old, (B) 75 years old, and (C) 85 years old.

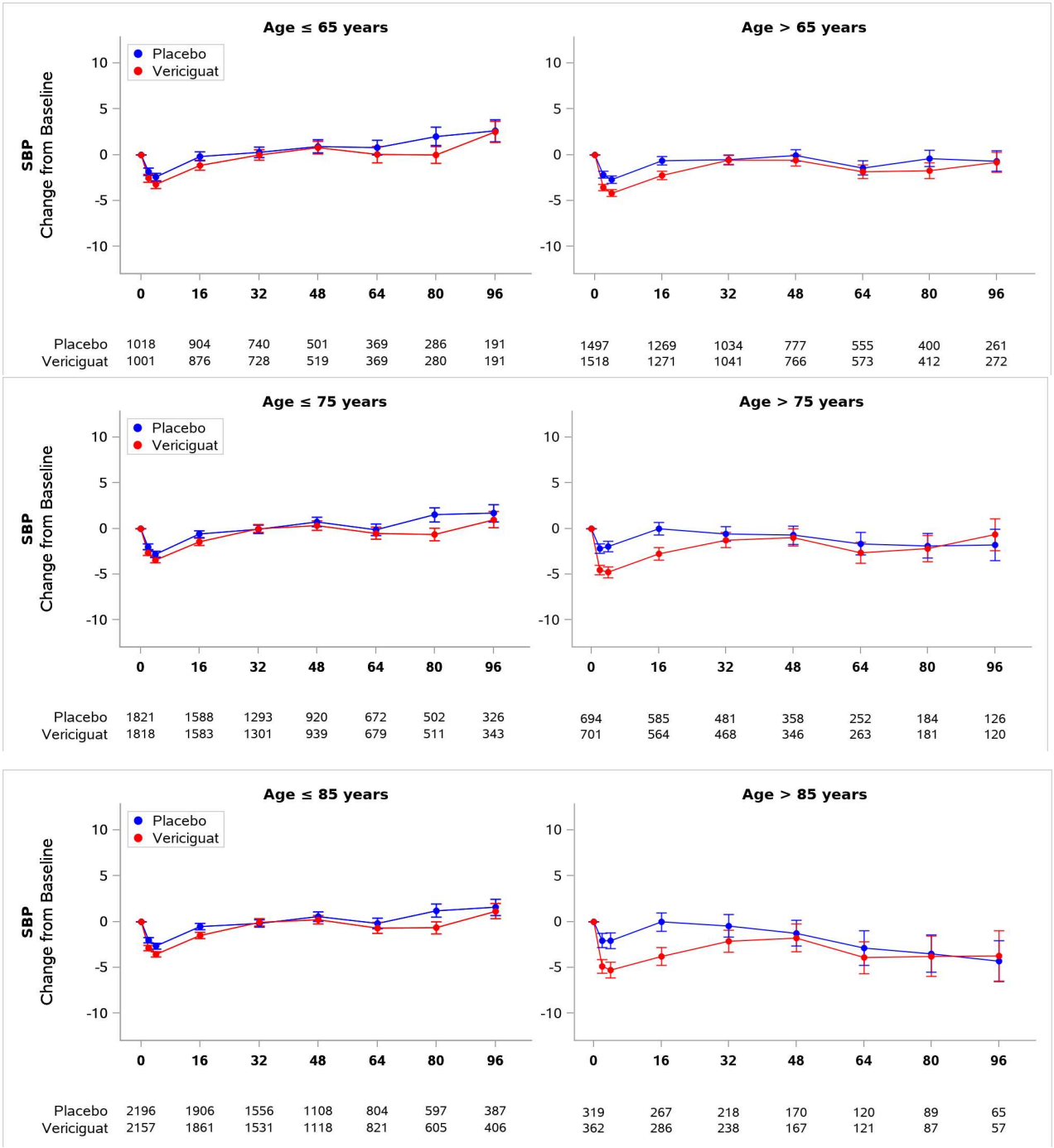

Figure S3. Systolic blood pressure (SBP) trajectory over time in patients receiving (vs not receiving) (A) any renin angiotension system inhibitor (RAS), (B) maximal dose of RAS, and (C) triple therapy (RAS, beta-blocker and mineralocorticoid receptor antagonist) at baseline

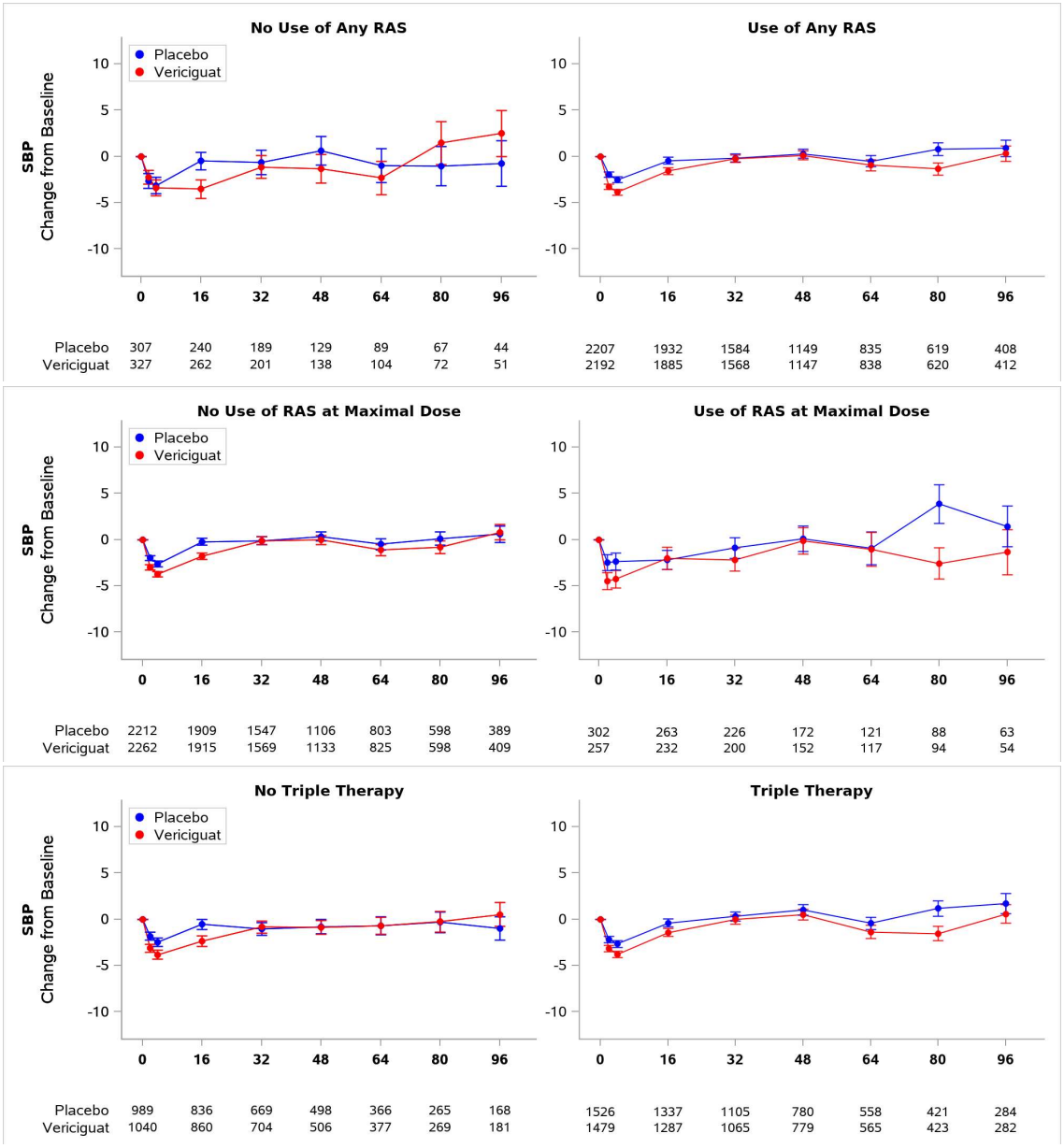

Figure S4. Systolic blood pressure (SBP) trajectory over time in patients with baseline NT-proBNP above and below 4000 pg/mL and 8000 pg/mL

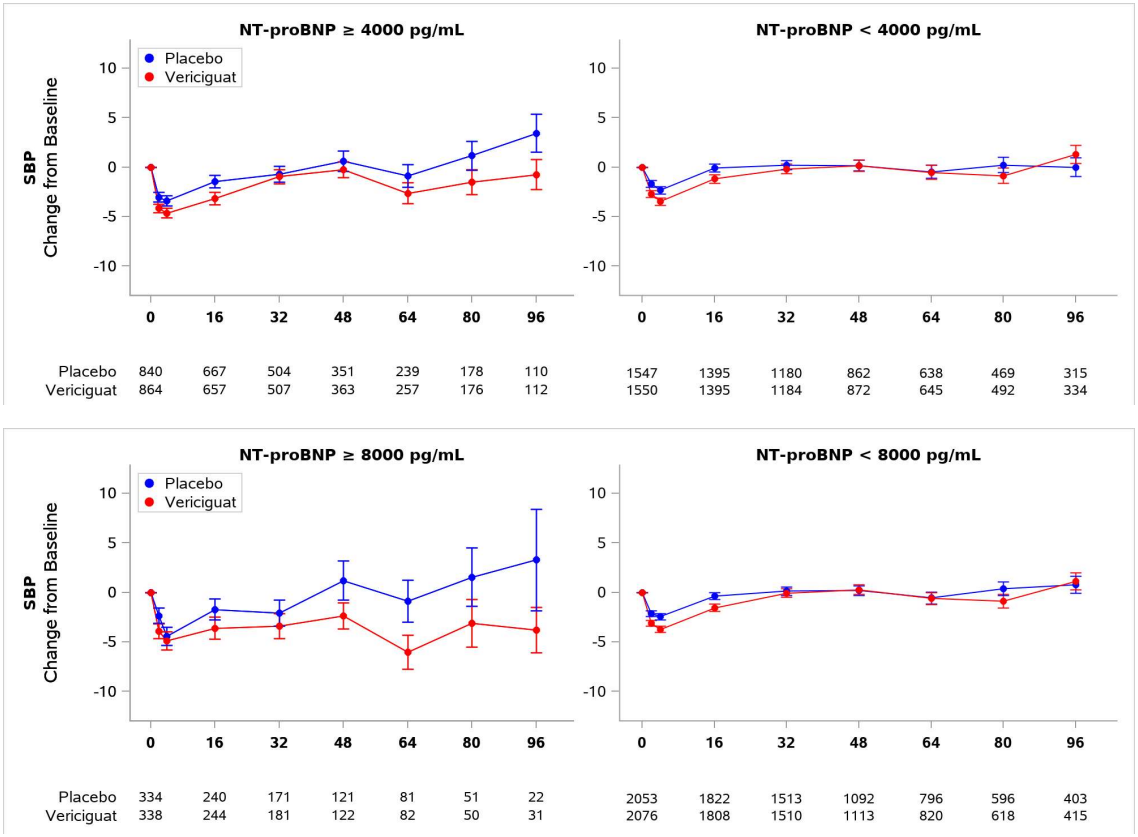

Figure S5. Systolic blood pressure (SBP) trajectory over time in patients time in patients receiving (vs not receiving) SGLT2i