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RESEARCH ARTICLE

Baseline features of the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial

Burkert Pieske[1], Mahesh J. Patel[2], Cynthia M. Westerhout[3], Kevin J. Anstrom[4], Javed Butler[5], Justin Ezekowitz[3], Adrian F. Hernandez[4], Joerg Koglin[2], Carolyn S.P. Lam[6], Piotr Ponikowski[7], Lothar Roessig[8], Adriaan A. Voors[9], Christopher M. O'Connor[4,10], and Paul W. Armstrong[3]*, on behalf of the VICTORIA Study Group†

[1]Charité University Medicine, German Heart Center, Berlin, Germany; [2]Merck & Co. Inc., Kenilworth, NJ, USA; [3]Canadian VIGOUR Centre, University of Alberta, Edmonton, AB, Canada; [4]Duke Clinical Research Institute, Duke University, Durham, NC, USA; [5]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; [6]National Heart Centre Singapore & Duke-National University of Singapore, Singapore; [7]Cardiology Department, Wroclaw Medical University, Wroclaw, Poland; [8]Bayer AG, Wuppertal, Germany; [9]Groningen Heart Failure Research Institute, Groningen, The Netherlands; and [10]Inova Heart and Vascular Institute, Falls Church, VA, USA

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Aim Describe the distinguishing features of heart failure (HF) patients with reduced ejection fraction (HFrEF) in the VICTORIA (Vericiguat Global Study in Patients with Heart Failure with Reduced Ejection Fraction) trial.

Methods and results Key background characteristics were evaluated in 5050 patients randomized in VICTORIA and categorized into three cohorts reflecting their index worsening HF event. Differences within the VICTORIA population were assessed and compared with PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure). VICTORIA patients had increased risk of mortality and rehospitalization: New York Heart Association class (40% class III), atrial fibrillation (45%), diabetes (47%), hypertension (79%) and mean estimated glomerular filtration rate of 61.5 mL/min/1.73 m^2. Baseline standard of HF care was very good: 60% received triple therapy. Their N-terminal pro-B-type natriuretic peptide was 3377 pg/mL [interquartile range (IQR) 1992–6380]. Natriuretic peptides were 30% higher level in the 67% patients with HF hospitalization <3 months, compared to those within 3–6 months of HF hospitalization and those randomized after recent outpatient intravenous diuretic therapy. Overall the median MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score in VICTORIA was 23 (IQR 18–27) as compared to the MAGGIC risk score in PARADIGM-HF of 20 (IQR 16–24).

Conclusions VICTORIA comprises a broadly generalizable high-risk population of three unique clinical strata of worsening chronic HFrEF despite very good HF therapy. VICTORIA will establish the role of vericiguat, a soluble guanylate cyclase stimulator, in HFrEF.

Keywords Soluble guanylate cyclase • Cyclic guanosine monophosphate • Heart failure with reduced ejection fraction • Clinical trial

*Corresponding author. 4-120 Katz Group Centre for Pharmacy and Health Research, 114 Street 87 Ave NW, Edmonton, Alberta T6G 2E1, Canada. Tel: +1 780 492-0591, Fax: +1 780 192-0613, Email: paul.armstrong@ualberta.ca
†Listed in online supplementary *Appendix S1*.

Introduction

Despite recent advances in the management of patients with heart failure (HF) with reduced ejection fraction (HFrEF), this disorder continues to extract considerable penalties as expressed by impaired quality of life coupled with excess morbidity and mortality. This is especially apparent in those HF patients who – even after initial stabilization – experience further worsening of their HF despite receiving best contemporary standard of care.[1] Moreover, the contemporary rise in longevity of the overall population, coupled with continuing advances in the management of coronary artery and other cardiovascular (CV) diseases, prioritizes a search for novel HF therapies.

Based on experimental and initial clinical investigations, one new pathway that appears promising relates to the modulation of nitric oxide (NO)–soluble guanylate cyclase (sGC) pathway that generates cyclic guanosine monophosphate (cGMP), essential for both normal cardiac and vascular function.[2,3] In HF patients, there is reduced NO bioavailability resulting in a relative sGC deficiency and reduced generation of cGMP.[2] Although strategies that include substitution of exogenous NO by nitrates and inhibition of cGMP degradation by phosphodiesterase inhibitors have been undertaken, neither have proven to provide lasting benefit.[2,3] Because sGC plays a key role in generating cGMP, vericiguat was developed as a potential novel addition to the HF treatment armamentarium. Vericiguat has a dual mechanism by which it increases cGMP in that it directly stimulates sGC through a binding site independent of NO and also sensitizes sGC to endogenous NO by stabilizing the NO–sGC binding site.[3,4]

The VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial completed enrolment of 5050 patients in December 2018. VICTORIA was designed to capture a HF population at increased risk for mortality and rehospitalization that represents a major continuing therapeutic challenge.[5] The support for this design was drawn from the phase IIb dose-finding study SOCRATES-REDUCED (Soluble Guanylate Cyclase Stimulator in Heart Failure with Reduced Ejection Fraction Study) of high-risk worsening HF patients in whom vericiguat reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in the highest dose group.[6]

The purpose of this communication is to describe the distinguishing features of this unique population and compare their baseline features with the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) and COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) trials in order to provide a contextual framework with this HFrEF population.[7,8]

Methods

The VICTORIA protocol has been described previously.[5] In brief, this trial assessed whether vericiguat was superior to placebo in increasing the time to the first occurrence of a composite endpoint of CV death or HF hospitalization in patients with HFrEF receiving optimal background standard of HF care. The cardinal entry criteria are summarized in *Table 1* and included an ejection fraction (EF) <45% within 12 months prior to randomization and elevated natriuretic peptide (NP) levels adjusted for the presence of atrial fibrillation. Three distinct cohorts (as reported by sites) were included to represent the evolution of patients with prior stable HF but subsequent symptomatic worsening: <3 months, 3–6 months after hospitalization, as well those receiving intravenous (IV) diuretic therapy, without hospitalization, within the prior 3 months. No more than 20% of subjects were to be randomized with a qualifying HF hospitalization >3 months prior to randomization. The inclusion criteria were intended to be broad. Hence, up to 15% of subjects were intended to have an estimated glomerular filtration rate (eGFR) in the 15 to 30 mL/min/1.73 m^2 range, and all received optimized standard of care: inclusion of patients receiving sacubitril/valsartan background therapy, where available, was encouraged. Enrolment of 5050 patients, across 42 countries, and categorized into five pre-specified geographic regions was completed in 26 months, which was earlier than projected and approximately 3 months ahead of schedule in this endpoint-driven trial (782 clinical events committee (CEC)-confirmed CV deaths required) and it is anticipated that at least 1561 patients will experience a composite primary endpoint. Based on an expected CV death event rate of 11% at 12 months in the placebo group, and an assumed relative risk reduction of 20% in the vericiguat group, a power of 80% will be achieved. The study will continue to accrue endpoints over approximately 35 months with a median follow-up of 12 months. The last patient last visit was achieved on 2 September 2019 and the primary results are anticipated to be available in the first quarter of 2020.

Table 1 VICTORIA trial inclusion criteria

- Ejection fraction <45% assessed within 12 months prior to randomization
- Elevated natriuretic peptide levels within 30 days prior to randomization; for patients in sinus rhythm BNP ≥300 pg/mL and NT-proBNP ≥1000 pg/mL; for those in atrial fibrillation BNP ≥500 pg/mL and NT-proBNP ≥1600 pg/mL[a]
- Prior HF hospitalization within 6 months (those >3 months limited to 20%) or outpatient IV diuretic therapy for HF within 3 months prior to randomization

BNP, B-type natriuretic peptide; HF, heart failure; IV, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
[a]For those subjects receiving sacubitril/valsartan, NT-proBNP criteria will be applied.

Statistical analysis

Patient characteristics available at baseline, including concomitant medications, are presented as counts (percentages) for categorical variables and as medians (25th, 75th percentiles) for continuous variables. The proportion of missing values was reported for the NPs available at screening and the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score.[9] The MAGGIC risk score was adapted according to the method described by the PARADIGM-HF investigators,[10] and was reported in patients with available data in the VICTORIA trial. The following factors comprised the MAGGIC risk score: age, EF, New York Heart Association (NYHA) class, serum

Table 2 VICTORIA patients screening summary

Patients screened	6899
Patients randomized	5050 (73.2%)
Patients not randomized	1849 (26.8%)
Reasons for non-randomization	
Inclusion criteria not met	
Have BNP or NT-proBNP levels within range within 30 days prior to randomization	1080 (58.4%)
Provide written informed consent for the trial	197 (10.7%)
Have a history of chronic HF (NYHA class II–IV)	74 (4.0%)
Have LVEF <45% assessed within 12 months prior to randomization	64 (3.5%)
Have a previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization	63 (3.4%)
Meet one of reproductive criteria	26 (1.4%)
Inability to provide informed consent	23 (1.2%)
Exclusion criteria present	
Clinically unstable at the time of randomization (exclusion)	265 (14.3%)
Medical disorder, condition, or history impairing ability to participate	81 (4.4%)
Concurrent or anticipated use of long-acting nitrates or NO donors	37 (2.0%)
eGFR <15 mL/min/1.73 m^2 or chronic dialysis	19 (1.0%)
Known allergy or sensitivity to any sGC stimulator	14 (0.8%)
Primary valvular heart disease requiring surgery or intervention, or within 3 months after valvular surgery or intervention	13 (0.7%)
ACS (unstable angina, NSTEMI, STEMI, CABG, or PCI)	18 (1.0%)
Miscellaneous	97 (5.2%)

ACS, acute coronary syndrome; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula; HF, heart failure; IV, intravenous; LVEF, left ventricular ejection fraction; NO, nitric oxide; NSTEMI, non-ST-elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; sGC, soluble guanylate cyclase; STEMI, ST-elevation myocardial infarction.

creatinine, diabetes, systolic blood pressure, body mass index, HF duration, chronic obstructive pulmonary disease, male sex, not prescribed a beta-blocker, and not prescribed an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB). Baseline characteristics and treatment of patients in VICTORIA are presented alongside those of the PARADIGM-HF and COMMANDER HF trials as contemporary HFrEF trials. Values for the PARADIGM-HF cohort were sourced from the primary publication,[7] and then the baseline characteristics publication[10] if not available in the former, and values for the COMMANDER HF cohort were sourced from the primary publication.[8]

All analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). The analysis of VICTORIA was based on data available on 10 June 2019. Final database lock is expected in late October 2019.

Results

VICTORIA screening and baseline characteristics

Prior to randomization, a screening period of up to 30 days was performed, during which confirmation that patients fulfilled the entry criteria was established. Among 6899 patients who allowed consent to be screened, 1849 were not randomized; the reasons for which are summarized in *Table 2*.

The baseline characteristics of enrolled patients are shown in *Table 3*. VICTORIA patients were 67.3 years old (mean), about three-quarters were male, two-thirds were white, one-half were Europeans, and one-quarter each from the Asian Pacific region and the Americas. Two-thirds were enrolled within 3 months of their index HF hospitalization and equal numbers of the remainder were either within 3–6 months of hospitalization or within 3 months of outpatient IV diuretics for worsening HF. Other features consistent with worsening HF were the inclusion of 40% of patients in NYHA class III and 45% with a history of atrial fibrillation. Diabetes and hypertension were frequent, major elevations in either NT-proBNP or B-type natriuretic peptide (BNP) were present, and a high MAGGIC risk score of 23.0 was evident at study entry. There was very good application of background standard of care HF therapy as indicated by high usage of either ACE-I, ARBs or angiotensin receptor–neprilysin inhibitors (ARNI), beta-blockers and mineralocorticoid receptor antagonists: 60% of patients received these as triple therapy and 15% were on ARNI. There was also a 28% use of implantable cardioverter-defibrillators (ICDs) and 15% had a biventricular pacemaker.

VICTORIA patient cohorts

The three patient cohorts – distinguished by their differing index clinical presentations – are shown in *Table 3*. Approximately two-thirds had been hospitalized for HF within the 3 months prior to their randomization and the other two cohorts were equally distributed. In general, the baseline characteristics in these three cohorts were similar although those qualifying based on IV diuretic use were somewhat older, more often in Latin

Table 3 VICTORIA baseline characteristics and treatments: overall and by index event

	All (n = 5050)	HF hospitalization within 3 months (n = 3366)	HF hospitalization within 3–6 months (n = 871)	IV diuretics (no hospitalization) (n = 813)
Age (years)				
Mean (SD)	67.3 (12.2)	66.8 (12.4)	68.1 (11.8)	68.8 (11.3)
Median (25th–75th percentile)	69.0 (60.0–76.0)	68.0 (59.0–76.0)	69.0 (60.0–77.0)	70.0 (62.0–78.0)
Sex				
Male	3842 (76.1%)	2562 (76.1%)	667 (76.6%)	613 (75.4%)
Female	1208 (23.9%)	804 (23.9%)	204 (23.4%)	200 (24.6%)
Race				
White	3239 (64.2%)	2103 (62.5%)	567 (65.1%)	569 (70.0%)
Black or African American	249 (4.9%)	169 (5.0%)	65 (7.5%)	15 (1.8%)
Asian	1132 (22.4%)	787 (23.4%)	175 (20.1%)	170 (20.9%)
Native Hawaiian or Pacific Islander	14 (0.3%)	6 (0.2%)	8 (0.9%)	0 (0.0%)
American Indian or Alaskan Native	52 (1.0%)	38 (1.1%)	3 (0.3%)	11 (1.4%)
Multiple	363 (7.2%)	262 (7.8%)	53 (6.1%)	48 (5.9%)
Geographic region				
Eastern Europe	1694 (33.5%)	1155 (34.3%)	263 (30.2%)	276 (33.9%)
Western Europe	889 (17.6%)	592 (17.6%)	161 (18.5%)	136 (16.7%)
Asia Pacific	1183 (23.4%)	824 (24.5%)	204 (23.4%)	155 (19.1%)
Latin and South America	724 (14.3%)	460 (13.7%)	108 (12.4%)	156 (19.2%)
North America	560 (11.1%)	335 (10.0%)	135 (15.5%)	90 (11.1%)
BMI (kg/m^2)				
Median (25th–75th percentile)	26.8 (23.7–30.9)	26.8 (23.7–30.9)	26.6 (23.6–30.5)	27.4 (23.8–30.6)
Ejection fraction recorded at screening (%)				
Mean (SD)	28.9 (8.3)	28.4 (8.4)	28.6 (8.2)	31.4 (7.7)
Median (25th–75th percentile)	30.0 (23.0–35.0)	29.0 (22.0–35.0)	29.0 (22.0–35.0)	32.0 (25.0–38.0)
Ejection fraction ≤40%	4670 (92.7%)	3128 (93.1%)	809 (93.4%)	733 (90.2%)
NYHA class at baseline				
I	2 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.1%)
II	2967 (58.9%)	1931 (57.5%)	541 (62.8%)	495 (60.9%)
III	2000 (39.7%)	1375 (40.9%)	313 (36.3%)	312 (38.4%)
IV	65 (1.3%)	52 (1.5%)	8 (0.9%)	5 (0.6%)
Medical history				
Atrial fibrillation	2269 (45.0%)	1535 (45.6%)	404 (46.5%)	330 (40.6%)
Atrial fibrillation (on the ECG)	1279 (25.3%)	878 (26.1%)	220 (25.3%)	181 (22.3%)
Diabetes mellitus	2377 (47.1%)	1613 (47.9%)	402 (46.3%)	362 (44.5%)
Hypertension	3993 (79.1%)	2664 (79.2%)	700 (80.6%)	629 (77.4%)
Coronary artery disease	2942 (58.3%)	1942 (57.7%)	520 (59.8%)	480 (59.0%)
Stroke	579 (11.5%)	390 (11.6%)	111 (12.8%)	78 (9.6%)
PAD	630 (12.5%)	420 (12.5%)	117 (13.5%)	93 (11.4%)
COPD	863 (17.1%)	574 (17.1%)	147 (16.9%)	142 (17.5%)
Anaemia	1053 (20.9%)	690 (20.5%)	188 (21.6%)	175 (21.5%)
Systolic blood pressure (mmHg)				
Mean (SD)	121.3 (15.7)	120.9 (15.7)	122.5 (16.3)	122.1 (15.3)
Median (25th–75th percentile)	119.0 (109.0–131.0)	118.0 (108.0–130.0)	120.0 (109.0–133.0)	120.0 (110.0–132.0)
Diastolic blood pressure (mmHg)				
Mean (SD)	72.8 (11.1)	73.0 (11.1)	72.3 (11.2)	72.6 (10.9)
Median (25th–75th percentile)	72.0 (65.0–80.0)	72.0 (65.0–80.0)	72.0 (65.0–80.0)	73.0 (65.0–80.0)
Heart rate (bpm)				
Mean (SD)	73.1 (13.1)	73.6 (13.4)	71.9 (12.5)	72.3 (12.2)
Median (25th–75th percentile)	72.0 (64.0–81.0)	72.0 (64.0–82.0)	70.0 (63.0–80.0)	71.0 (64.0–80.0)
Concomitant medications				
ACE-I or ARB	3704 (73.5%)	2465 (73.3%)	628 (72.9%)	611 (75.2%)
Beta-blocker	4691 (93.1%)	3119 (92.7%)	813 (94.3%)	759 (93.5%)
MRA	3548 (70.4%)	2442 (72.6%)	579 (67.2%)	527 (64.9%)

Table 3 (Continued)

	All (n = 5050)	HF hospitalization within 3 months (n = 3366)	HF hospitalization within 3–6 months (n = 871)	IV diuretics (no hospitalization) (n = 813)
ARNI sacubitril/valsartan	731 (14.5%)	484 (14.4%)	137 (15.9%)	110 (13.5%)
Triple therapy (MRA + beta-blocker + ACE-I, ARB or ARNI)	3013 (59.8%)	2075 (61.7%)	493 (57.2%)	445 (54.8%)
ICD	1399 (27.8%)	893 (26.5%)	271 (31.4%)	235 (28.9%)
Biventricular pacemaker	739 (14.7%)	461 (13.7%)	158 (18.3%)	120 (14.8%)
Laboratory results				
Creatinine (mmol/L)[a]				
Median (25th–75th percentile)	106.0 (80.0–141.0)	106.0 (80.0–141.0)	106.0 (80.0–133.0)	106.0 (80.0–133.0)
eGFR (mL/min/1.73 m^2)[a]				
Mean (SD)	61.5 (27.2)	61.1 (27.6)	61.9 (26.5)	62.8 (26.2)
Median (25th–75th percentile)	58.4 (41.2–77.1)	58.0 (39.9–77.0)	58.7 (42.5–76.6)	59.7 (43.8–79.3)
<15 mL/min/1.73m^2	12 (0.2%)	10 (0.3%)	0 (0.0%)	2 (0.2%)
15–30 mL/min/1.73m^2	494 (10.0%)	348 (10.5%)	83 (9.8%)	63 (7.8%)
>30–60 mL/min/1.73m^2	2116 (42.7%)	1408 (42.6%)	363 (42.8%)	345 (42.9%)
>60 mL/min/1.73m^2	2333 (47.1%)	1537 (46.5%)	402 (47.4%)	394 (49.0%)
Sodium (mmol/L)				
Mean (SD)	139.9 (3.4)	139.8 (3.5)	140.3 (3.1)	140.0 (3.1)
Median (25th–75th percentile)	140.0 (138.0–142.0)	140.0 (138.0–142.0)	141.0 (139.0–142.0)	140.0 (138.0–142.0)
Potassium (mmol/L)				
Mean (SD)	4.5 (0.5)	4.5 (0.5)	4.5 (0.5)	4.5 (0.5)
Median (25th–75th percentile)	4.5 (4.2–4.8)	4.5 (4.1–4.8)	4.5 (4.2–4.8)	4.5 (4.2–4.8)
Haemoglobin (g/L)				
Mean (SD)	133.9 (19.1)	134.0 (19.4)	132.4 (18.4)	134.8 (18.7)
Median (25th–75th percentile)	134.0 (121.0–147.0)	134.0 (121.0–147.0)	132.0 (120.0–146.0)	136.0 (122.0–148.0)
NT-proBNP at screening (pg/mL)				
n	4017	2692	689	636
Median (25th–75th percentile)	3377.0 (1992.0–6380.0)	3848.7 (2177.5–7153.0)	2930.0 (1785.0–4700.0)	2731.5 (1750.5–5067.5)
BNP at screening (pg/mL)				
n	1741	1126	329	286
Median (25th–75th percentile)	747.9 (452.4–1340.0)	809.0 (504.4–1465.0)	689.0 (397.0–1172.0)	637.5 (395.0–1018.0)
MAGGIC risk score				
n	4658	3086	796	776
Median (25th–75th percentile)	23.0 (18.0–27.0)	23.0 (19.0–27.0)	23.0 (18.0–27.0)	22.0 (18.0–26.0)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide (these values used only if NT-proBNP unavailable); COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IV, intravenous; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral artery disease; SD, standard deviation.
[a]Acquired at randomization.

America, and had a trend towards less atrial fibrillation and fewer co-morbidities. Of particular interest was the gradation in their entry NP levels across the three cohorts, such that those with a recent HF hospitalization, i.e. <3 months prior to randomization, had an approximate 30% higher level of NPs than those with a longer interval of 3–6 months who were more akin to patients randomized after recent outpatient IV diuretic therapy. In contrast to these differences in the differing baseline NPs, the MAGGIC scores of the patients hospitalized within and beyond 3 months were similar and those receiving IV diuretics only slightly lower.

Comparison with other HFrEF trials

In *Table 4*, a comparison of the VICTORIA and the PARADIGM-HF populations is provided from previously available literature.[7,10] Note that by contrast to the design of VICTORIA, PARADIGM-HF included stable HF patients after a run-in period who were both ACE-I and sacubitril/valsartan tolerant, had a baseline EF of ≤40%, an eGFR of ≥30 mL/min/1.73 m^2 and a minimum BNP of 150 pg/mL or NT-proBNP of ≥600 pg/mL. As will be evident in comparison to PARADIGM-HF, the VICTORIA population is somewhat older, had a higher prevalence of patients with diabetes, hypertension, and a history of stroke, advanced NYHA class, and greater use of both ICDs and biventricular pacemakers. By design, in VICTORIA, the mean eGFR was lower and 10% of subjects had an eGFR between 15 and 30 mL/min/1.73 m^2, 14% had and EF between 40% and 45%, and 14.5% were on ARNI at baseline. Of particular note is the greater than two-fold NT-proBNP entry levels in VICTORIA which likely reflects, at least in part, the differing entry trial criteria.

Table 4 Baseline characteristics and treatment in the VICTORIA, PARADIGM-HF and COMMANDER HF trials

	VICTORIA (*n* = 5050)	PARADIGM-HF (*n* = 8339)	COMMANDER HF[a] (*n* = 5022)
Age (years)			
Mean (SD)	67.3 (12.2)	63.8 (11.4)	66.4
Median (25th–75th percentile)	69.0 (60.0–76.0)	–	–
Sex			
Male	3842 (76.1%)	6565 (78.0%)	3872 (77.1%)
Female	1208 (23.9%)	1832 (22.0%)	1150 (22.9%)
Race			
White	3239 (64.2%)	5544 (65.7%)	4128 (82.2%)
Black or African American	249 (4.9%)	428 (5.1%)	65 (1.3%)
Asian	1132 (22.4%)	1509 (17.9%)	727 (14.5%)
Native Hawaiian or Pacific Islander	14 (0.3%)	–	–
American Indian or Alaskan Native	52 (1.0%)	–	–
Multiple	363 (7.2%)	–	–
Other	–	918 (11.0%)	102 (2.0%)
Geographic region			
Eastern Europe	1694 (33.5%)	2826 (33.5%)	3224 (64.2%)
Western Europe	889 (17.6%)	2051 (24.3%)	458 (9.1%)
Asia Pacific	1183 (23.4%)	1487 (17.6%)	733 (14.6%)
Latin and South America	724 (14.3%)	1433 (17.0%)	458 (9.1%)
North America	560 (11.1%)	602 (7.1%)	149 (3.0%)
Index event			
HF hospitalization within 3 months	3366 (66.7%)	–	–
HF hospitalization 3 to 6 months	871 (17.2%)	–	–
IV diuretic for HF (without hospitalization) within 3 months	813 (16.1%)	–	–
BMI (kg/m^2)			
Mean (SD)	27.8 (5.9)	28.2 (5.5)	27.7 (5.2)
Median (25th–75th percentile)	26.8 (23.7–30.9)	–	–
Ejection fraction recorded at screening (%)			
Mean (SD)	28.9 (8.3)	29.5 (6.2)	–
Median (25th–75th percentile)	30.0 (23.0–35.0)	–	34.5(27.5–38)
Ejection fraction ≤40%	4670 (92.7%)	8339 (100%)	5122 (100%)
NYHA class at baseline			
I	2 (0.0%)	389 (4.7%)	149 (3.0%)
II	2967 (58.9%)	5919 (70.9%)	2218 (44.2%)
III	2000 (39.7%)	2018 (24.1%)	2462 (49.0%)
IV	65 (1.3%)	60 (0.7%)	192 (3.8%)
Medical history			
Atrial fibrillation	2269 (45.0%)	3091 (37.0%)	0%
Diabetes mellitus	2377 (47.1%)	2907 (34.9%)	2052 (40.9%)
Hypertension	3993 (79.1%)	5940 (71.2%)	3783 (75.3%)
Coronary artery disease	2942 (58.3%)	–	5022 (100%)
Stroke	579 (11.5%)	725 (8.7%)	453 (9.0%)
Systolic blood pressure (mmHg)			
Mean (SD)	121.3 (15.7)	121.0 (15.0)	–
Median (25th–75th percentile)	119.0 (109.0–131.0)	–	–
Diastolic blood pressure (mmHg)			
Mean (SD)	72.8 (11.1)	74.0 (NA)[c]	–
Median (25th–75th percentile)	72.0 (65.0–80.0)	–	–
Concomitant medications			
ACE-I or ARB	3704 (73.5%)	8339 (100%)	4660 (92.8%)
Beta-blocker	4691 (93.1%)	7811 (93.6%)	4642 (92.4%)
MRA	3548 (70.4%)	4671 (55.3%)	3840 (76.5%)
ARNI sacubitril/valsartan	731 (14.5%)	–	–
Triple therapy (MRA + beta- blocker + ACE-I or ARB or ARNI)	3013 (59.8%)	–	–

Table 4 (Continued)

	VICTORIA ($n = 5050$)	PARADIGM-HF ($n = 8339$)	COMMANDER HF[a] ($n = 5022$)
ICD	1399 (27.8%)	1243 (14.9%)	438 (8.7%)
Biventricular pacemaker	739 (14.7%)	574 (6.8%)	222 (4.4%)
Laboratory results			
Creatinine (mmol/L)[b]			
Mean (SD)	116.9 (49.8)	99.0 (NA)[c]	–
Median (25th–75th percentile)	106.0 (80.0–141.0)	–	–
eGFR (mL/min/1.73 m^2)[b]			
Mean (SD)	61.5 (27.2)	68.0 (NA)[c]	–
Median (25th–75th percentile)	58.4 (41.2–77.1)	–	–
15–30 mL/min/1.73m^2	494 (10.0%)	–	163 (3.2%)
NT-proBNP at screening (pg/mL)			
n	4017	–	–
Median (25th–75th percentile)	3377.0 (1992.0–6380.0)	1608.0 (886.0–3221.0)	2870.0 (1528.0–6332.0)
BNP at screening (pg/mL)			
n	1741	–	–
Median (25th–75th percentile)	747.9 (452.4–1340.0)	253.0 (154.0–470.0)[d]	698.8 (392.0–1252.0)
MAGGIC risk score[e]			
n	4658	8375[e]	–
Median (25th–75th percentile)	23.0(18.0–27.0)	20.0(16.0–24.0)	–

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide (these values used only if NT-proBNP unavailable); eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IV, intravenous; MRA, mineralocorticoid receptor antagonist; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

[a] Approximated from reference.[8]

[b] Acquired at randomization.

[c] As reported in reference.[9]

[d] Approximated from reference.[7]

[e] Adapted as per PARADIGM-HF score where 1 point ≥1 year for HF duration.

The differences in the background risk of the two populations are especially evident given the substantially greater median MAGGIC risk score (adapted to align with the PARADIGM-HF calculation) in VICTORIA of 23 [interquartile range (IQR) 18–27] as opposed to the score of 20 (IQR 16–24) found in PARADIGM-HF.[11]

Also represented in *Table 4* is COMMANDER HF which, by design, randomized patients with HFrEF and a presumed ischaemic aetiology in whom atrial fibrillation was excluded and who had been treated for an episode of worsening HF (i.e. their index event) within the previous 21 days. VICTORIA patients were slightly older, had less patients in advanced NYHA class III and IV, more with both renal dysfunction and a lower EF and higher NT-proBNP and BNP levels at study entry.

There was considerably greater use of both ICDs and biventricular pacemakers in VICTORIA than in the other two trials.

Discussion

VICTORIA represents a large and well-characterized population of HFrEF patients who at the time of study entry had shown symptomatic deterioration despite optimal background standard of care HF therapy. Overall, the population has high predicted risk on optimal background medical therapy as compared with prior clinical trials and registries.[12,13] Hence, it is not surprising that at least 782 CEC-confirmed CV deaths and more than 1561 patients have experienced a composite primary endpoint: we are thus assured of adequate power to address the primary study hypothesis.

The timely enrolment of these patients suggests that this medically challenging high-risk population continues to exist in substantial numbers worldwide despite good background standard of care therapy, and represents a key underserved cohort that deserves future study as noted previously.[1]

Several unique features set the current study apart from prior work, including the absence of a run-in period, broader inclusion criteria and three differing cohorts based on the symptomatic nature of their index HF worsening events. These subsets describe how previously chronic stable HF patients evolve after a recent exacerbation that requires either hospitalization or acute medical outpatient intervention with IV diuretics. Other novel aspects worthy of note are the 369 patients with an EF between 41% and 45%, the 494 patients with an eGFR between 15 and 30 mL/min/1.73 m^2 and the 14.5% ($n = 731$) who received ARNI: analysis of the outcomes of these 'mid-range' EF, impaired renal function and ARNI-treated patient subsets will be of particular interest.

Examination of *Table 3* highlights the distinctive characteristics of the three pre-defined HFrEF subsets based on their index presentation and underscores that those patients who present within 3 months of a prior hospitalization portend the highest

potential future risk as denoted by their more than 30% increased NT-proBNP than those with worsened symptoms presenting within 3–6 months after hospitalization or those presenting for outpatient administration of IV diuretics. Interestingly however, this finding did not translate into differences in their MAGGIC risk scores. The GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure) investigators have recently reflected on the lack of accuracy of the MAGGIC score in capturing the risk of sudden cardiac death in HFrEF patients and called for new prognostic tools in this population.[14] These new data from VICTORIA should be ultimately helpful in further informing the spectrum of CV risk in HF, as well as the response to therapy and the design of future HFrEF trials.

The PARADIGM-HF trial defined a new standard of care therapy for patients with stable HFrEF who tolerate ACE-I and ARNI therapy. It is noteworthy – but not surprising – given the differing aforementioned differences in entry criteria, that PARADIGM-HF patients have a substantially lower MAGGIC risk score than the current VICTORIA study population.

Conclusion

In conclusion, VICTORIA enrolled a large international high-risk population of worsening chronic HFrEF despite optimal standard of HF therapy. As compared to prior large chronic HFrEF trials, NP levels at entry were higher and reflect not only three common, yet distinctive, clinical presentation streams, but also inclusion of novel subsets with mid-range EF, reduced renal function and baseline ARNI therapy, attesting to the broad contemporary generalizability of the trial. VICTORIA is well positioned to establish the role of vericiguat, a new sGC stimulator in the management of HFrEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
Appendix S1. VICTORIA Study Group.

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