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RESEARCH ARTICLE

Vericiguat in patients with coronary artery disease and heart failure with reduced ejection fraction

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Aims Coronary artery disease (CAD) portends worse outcomes in heart failure (HF). We aimed to characterize patients with CAD and worsening HF with reduced ejection fraction (HFrEF) and evaluate post hoc whether vericiguat treatment effect varied according to CAD.

Methods and results Cox proportional hazards were generated for the primary endpoint of cardiovascular death or HF hospitalization (CVD/HFH). CAD was defined as previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting. Of 5048 patients in VICTORIA with available data on CAD status, 2704 had CAD and were older, were more frequently male, diabetic, and had a lower glomerular filtration rate than those without CAD (all $p < 0.0001$). Use of implantable cardioverter defibrillators and cardiac resynchronization therapy (CRT) was higher in patients with versus without CAD (33.5% vs. 21.1%; $p < 0.0001$ and 16.3% vs. 12.8%; $p = 0.0006$). The primary endpoint of CVD/HFH was higher in those with versus without CAD (40.6 vs. 30.1/100 patient-years; adjusted hazard ratio [HR] 1.23; $p < 0.001$) as was all-cause mortality (17.9% vs. 12.7%; adjusted HR 1.32; $p < 0.001$). The primary outcome of CVD/HFH associated with vericiguat in patients with or without CAD was 38.8 versus 27.6 per 100 patient-years and for placebo was 42.6 versus 32.7 per 100 patient-years (interaction $p = 0.78$).

Conclusion In this post hoc study, CAD was associated with more CVD and HFH in patients with HFrEF and worsening HF. Vericiguat was beneficial and safe regardless of concomitant CAD.

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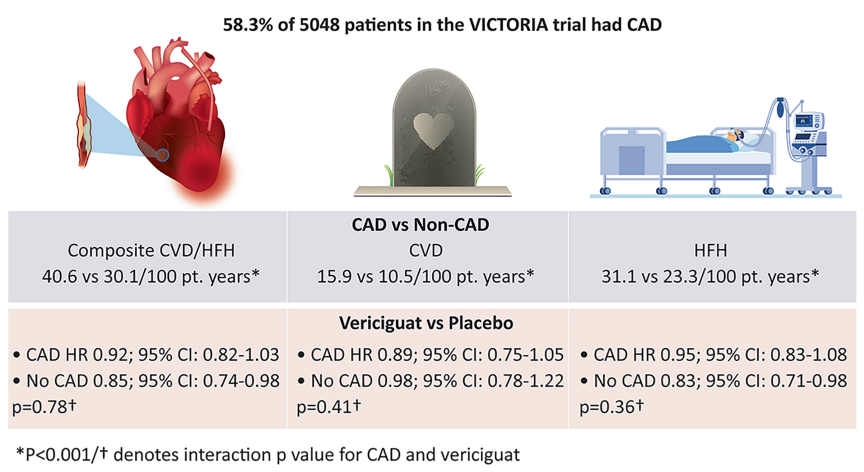
Graphical Abstract



Coronary artery disease (CAD) and cardiovascular outcomes in VICTORIA. CI, confidence interval; CVD, cardiovascular death; HFH, heart failure hospitalization; HR, hazard ratio.

Keywords Heart failure • Coronary artery disease • Comorbidity • Vericiguat • Cardiovascular death • Heart failure hospitalization

Introduction

Chronic heart failure (HF) affects an estimated 6.2 million American adults[1]; nearly 70% of all HF syndromes may be attributed to underlying coronary artery disease (CAD).[2,3] Patients with worsening HF with reduced ejection fraction (HFrEF) and concomitant CAD often have worse long-term outcomes compared with those with HFrEF and no CAD.[2] The reason for this difference is unclear but may be related to endothelial dysfunction and reactive oxygen species known to reduce nitric oxide bioavailability in patients with HF, thereby resulting in a greater deficiency of soluble guanylate cyclase in those with versus without CAD.[4–7] Reduced soluble guanylate cyclase activity is associated with endothelial dysfunction, microvascular disease, and myocardial dysfunction and may be particularly influential in patients with HF and concomitant CAD.[8]

Vericiguat, a novel soluble guanylate cyclase stimulator, reduced the incidence of cardiovascular death or hospitalization for HF in a population of high-risk patients with HFrEF who had recently been hospitalized or received intravenous diuretic therapy.[9–11] Given the poor prognosis for patients with HFrEF and CAD, and taking into account the importance of the nitric oxide pathway in both HF and CAD, we aimed to characterize patients with CAD and worsening HFrEF and evaluate whether differences exist in the efficacy and safety of vericiguat treatment in these patients according to the presence of CAD. Further, we assessed whether the relationship between cardiovascular death and HF hospitalization in this distinct population was related to the presence of CAD.

Methods

The design, baseline characteristics, and results of the VICTORIA trial (NCT02861534) were previously published.[9–11] The trial enrolled 5050 patients with worsening chronic HF (New York Heart Association [NYHA] functional class II to IV), left ventricular ejection fraction <45%, elevated natriuretic peptide levels, and recent HF decompensation. Patients were randomly assigned in a 1:1 ratio to receive vericiguat or placebo. Guideline-based HF therapies were encouraged before inclusion, including the use of sacubitril/valsartan. N-terminal pro-brain natriuretic peptide (NT-proBNP) (Roche Elecsys assay analytical range 10–175 000 pg/ml) and troponin T levels (detection limit: 3 ng/L [Roche]) reported herein were acquired at randomization and measured at a central laboratory.

The investigation conforms with the principles outlined in the Declaration of Helsinki. The trial protocol was approved by regulatory agencies in participating countries, as well as the ethics committees and institutional review boards at participating sites. All patients provided written informed consent.

Coronary artery disease definition

For this analysis, a history of CAD was defined as history of prior myocardial infarction (MI), previous percutaneous coronary intervention, or coronary artery bypass graft surgery acquired by

patient history at enrolling centers. This was unavailable in two patients, resulting in a final sample size of 5048 patients.

Clinical outcomes

The primary outcome of VICTORIA was the composite endpoint of time to cardiovascular death or first HF hospitalization. We describe baseline clinical and demographic characteristics of patients enrolled in VICTORIA by CAD status, and assessed post hoc whether the presence of CAD increased the likelihood of cardiovascular death or HF hospitalization, cardiovascular death, and all-cause death or HF hospitalization in unadjusted and adjusted Cox proportional hazard models. Additional analyses included mode of death according to CAD versus no CAD (sudden vs. non-sudden death) and the occurrence of the pre-specified adverse events of symptomatic hypotension or syncope. An independent clinical events committee, whose members were blinded to treatment assignment, adjudicated all deaths, hospitalizations for cardiovascular causes, and urgent visits for HF (definitions provided in online supplementary *Methods S1*). Finally, an analysis of whether CAD modified the association between treatment effect and the above endpoints was performed.

Statistical analysis

For the clinical characteristics of the population, discrete pre-specified factors are presented as frequencies and percentages. Medians with 25th and 75th percentiles are provided for continuous variables. Statistical comparisons were generated using Chi-square and Fisher's exact tests for discrete factors and Kruskal–Wallis test for continuous measures.

In order to identify the differential effect of treatment in the CAD and no CAD groups, Cox proportional hazard models were generated for the primary endpoint of cardiovascular death or HF hospitalization and the secondary outcomes of cardiovascular death, HF hospitalization, and all-cause death. The primary endpoint of cardiovascular death or HF hospitalization included the following risk factors: randomized treatment, index event, duration of HF, NYHA class, heart rate, history of peripheral artery disease, NT-proBNP, bilirubin, chloride, urate, QT interval, haemoglobin, gamma-glutamyl transferase, and use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB), aspirin, clopidogrel, ticagrelor, warfarin, dabigatran, rivaroxaban, and apixaban.[12] For HF hospitalization, risk factors included randomized treatment, region, index event, NYHA class, duration of HF, history of peripheral artery disease, history of chronic obstructive pulmonary disease, implantable cardioverter defibrillator (ICD), body mass index, heart rate, aspartate aminotransferase, bilirubin, NT-proBNP, chloride, gamma-glutamyl transferase, QT interval, haemoglobin, and use of aspirin, clopidogrel, ticagrelor, warfarin, dabigatran, rivaroxaban, and apixaban. For cardiovascular death, risk factors included randomized treatment, age, region, NYHA class, duration of primary episode, history of peripheral artery disease, history of aanemia, systolic blood pressure, albumin, NT-proBNP, bilirubin, chloride, urate, haemoglobin, and use of beta-blockers, aspirin, clopidogrel, ticagrelor, warfarin, dabigatran, rivaroxaban, and apixaban. Risk factors for all-cause death included randomized treatment, age, region, albumin, bilirubin, chloride, haemoglobin, hospitalization during randomization, NYHA class, duration of primary episode, history of peripheral artery disease, systolic blood pressure, sodium, NT-proBNP, urate, and use of beta-blockers, aspirin, clopidogrel, ticagrelor, warfarin, dabigatran, rivaroxaban, and apixaban.

All modeling assumptions, proportional hazards assumptions, and linearity for continuous measures were verified. Measures that were not linearly related to the outcome of interest were transformed. The competing risk of all-cause mortality was addressed for non-fatal endpoints and the Fine–Gray test statistic is reported. To assess the difference between the hazards of cardiovascular death and HF hospitalization between patients with CAD and those without, the Lunn–McNeil competing risk models were estimated.[13,14] More details on the multivariable model estimates are contained in online supplementary *Tables S1–S4*. The chi-square test was used for the statistical comparisons for the safety outcomes of symptomatic hypotension and syncope. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). A 2-sided p-value <0.05 was considered statistically significant.

Results

A total of 5048 of the 5050 patients in the VICTORIA trial had available data on CAD status and were included in this analysis. Of the 5048 included, 2704 (58.3%) had CAD. Median (25th, 75th) follow-up was 484 (342, 626) days overall; 408 (260, 658) days for those with no CAD and 422 (253, 672) days for those with CAD.

Selected baseline characteristics are described according to the presence or absence of CAD (*Table 1*); a full list, including baseline antithrombotic and antiplatelet medications is provided in online supplementary *Table S5*. Of patients with CAD, 78.4% had a history of MI, 62.0% had undergone prior percutaneous coronary intervention, and 34.5% had prior coronary artery bypass graft surgery. Patients with versus without CAD were significantly older (median 70 vs. 66 years), more often male (81.2% vs. 70.1%), and more frequently white and from Europe or North America. Patients with versus without CAD were more likely to have diabetes (53.7% vs. 39.1%), history of smoking (64.2% vs. 52.5%), and have chronic obstructive pulmonary disease (19.1% vs. 15.0%), but had lower estimated glomerular filtration rates (53.5 vs. 63.3 ml/min/1.73 m^2). Patients with CAD compared with those without CAD less often received ACE inhibitors/ARBs (71.1% vs. 76.0%), mineralocorticoid receptor antagonist (MRA) therapy (66.7% vs. 74.5%), and triple guideline therapy (55.3% vs. 64.8%). The use of sacubitril/valsartan was similar (14.3% vs. 14.7%) between groups; however, the use of ICDs and cardiac resynchronization therapy was higher in those with versus without CAD (33.5% vs. 21.1%; and 16.3% vs. 12.8%). Baseline levels of troponin T (32.4 vs. 26.1 ng/L) and NT-proBNP (2902 vs. 2739 pg/mL) were both significantly higher in patients with versus without CAD. The MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score was also higher in patients with CAD than in those with no CAD (26.0 vs. 23.0; p <0.001).[15]

In *Figure 1A* the primary composite outcome survival curves are shown according to the presence or absence of CAD. Patients with CAD had significantly worse outcomes than those without CAD; this difference was evident early post-randomization and progressively widened thereafter. A similar effect was evident when examining cardiovascular death and HF hospitalization as individual endpoints (*Figure 1B,C*); however, the curves for HF hospitalization, in contrast to cardiovascular death, do not appear to widen further beyond approximately 1 year.

Table 1 Demographic and presenting characteristics, medical history, and medications

Characteristic	All patients (n = 5048)	No CAD (n = 2344)	CAD[a] (n = 2704)	p-value
Age, years, median (25th, 75th)	69.0 (60.0, 76.0)	66.0 (56.0, 75.0)	70.0 (63.0, 77.0)	<0.0001
Male sex, *n* (%)	3840 (76.1)	1644 (70.1)	2196 (81.2)	<0.0001
Race, *n* (%)				<0.0001
Black or African American	249 (4.9)	173 (7.4)	76 (2.8)	
White	3237 (64.1)	1289 (55.0)	1948 (72.0)	
Asian	1132 (22.4)	630 (26.9)	502 (18.6)	
Other	430 (8.5)	252 (10.8)	178 (6.6)	
Region of enrollment, *n* (%)				<0.0001
Asia Pacific	1183 (23.4)	662 (28.2)	521 (19.3)	
Eastern Europe	1694 (33.6)	669 (28.5)	1025 (37.9)	
Latin and South America	724 (14.3)	424 (18.1)	300 (11.1)	
North America	559 (11.1)	213 (9.1)	346 (12.8)	
Western Europe	888 (17.6)	376 (16.0)	512 (18.9)	
HF hospitalization within 3 months, *n* (%)	3377 (66.9)	1627 (69.4)	1750 (64.7)	0.002 (2df)
HF hospitalization 3–6 months, *n* (%)	870 (17.2)	371 (15.8)	499 (18.5)	
IV diuretic for HF (without hospitalization) within 3 months, *n* (%)	801 (15.9)	346 (14.8)	455 (16.8)	
BMI, kg/m^2, median (25th, 75th)	26.9 (23.7, 30.9)	26.7 (23.5, 31.3)	27.0 (23.9, 30.5)	0.14
Medical history				
EF, %, median (25th, 75th)	30.0 (23.0, 35.0)	29.0 (21.0, 35.0)	30.0 (24.0, 35.0)	<0.0001
EF ≤40%, *n* (%)	4667 (92.7)	2164 (92.5)	2503 (92.8)	0.62
NYHA class, *n* (%)				0.17
I	2 (0.0)	2 (0.1)	0 (0.0)	
II	2975 (59.0)	1403 (59.9)	1572 (58.2)	
III	2003 (39.7)	904 (38.6)	1099 (40.7)	
IV	66 (1.3)	34 (1.5)	32 (1.2)	
Systolic BP, mmHg, median (25th, 75th)	119.0 (109.0, 131.0)	118.0 (108.0, 131.0)	119.0 (109.0, 131.0)	0.49
Diastolic BP, mmHg, median (25th, 75th)	72.0 (65.0, 80.0)	74.0 (66.0, 82.0)	71.0 (64.0, 79.0)	<0.0001
Heart rate, bpm, median (25th, 75th)	72.0 (64.0, 81.0)	73.0 (65.0, 83.0)	70.0 (63.0, 79.0)	<0.0001
Atrial fibrillation, *n* (%)	2268 (44.9)	1059 (45.2)	1209 (44.7)	0.74
Diabetes mellitus, *n* (%)	2369 (46.9)	916 (39.1)	1453 (53.7)	<0.0001
COPD, *n* (%)	867 (17.2)	351 (15.0)	516 (19.1)	0.0001
History of smoking, *n* (%)	2972 (58.9)	1230 (52.5)	1742 (64.4)	<0.0001
Time from diagnosis of any HF to randomization, years, median (25th, 75th)	3.3 (1.0, 7.4)	3.0 (0.8, 6.8)	3.6 (1.2, 8.1)	<0.0001
Prior MI, *n* (%)	2121 (42.0)	0	2121 (78.4)	<0.0001
Prior PCI, *n* (%)	1677 (33.2)	0	1677 (62.0)	<0.0001
Prior CABG, *n* (%)	933 (18.5)	0	933 (34.5)	<0.0001
Patient randomized while hospitalized, *n* (%)	574 (11.4)	263 (11.2)	311 (11.5)	0.74
Standard of care therapy, *n* (%)				
ACE inhibitor or ARB	3700 (73.4)	1779 (76.0)	1921 (71.1)	<0.0001
Sacubitril/valsartan	731 (14.5)	345 (14.7)	386 (14.3)	0.65
Beta-blocker	4691 (93.1)	2165 (92.5)	2526 (93.6)	0.15
MRA	3545 (70.3)	1744 (74.5)	1801 (66.7)	<0.0001
Triple therapy[b]	3009 (59.7)	1517 (64.8)	1492 (55.3)	<0.0001
ICD	1399 (27.8)	494 (21.1)	905 (33.5)	<0.0001
Biventricular pacemaker	739 (14.7)	300 (12.8)	439 (16.3)	0.0006
eGFR, ml/min/1.73 m^2, median (25th, 75th)	58.4 (41.2, 77.1)	63.3 (45.5, 83.6)	53.5 (38.2, 72.8)	<0.0001
Core lab NT-proBNP, pg/ml, median (25th, 75th)	2816 (1556, 5314)	2739 (1531, 5218)	2902 (1580, 5437)	0.020
Troponin, ng/L, median (25th, 75th)	29.6 (18.8, 48.7)	26.1 (16.8, 43.8)	32.4 (20.7, 51.7)	0.0004
MAGGIC risk score, median (25th, 75th)	24.0 (20.0, 29.0)	23.0 (18.0, 28.0)	26.0 (21.0, 30.0)	<0.0001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; df, degrees of freedom; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IV, intravenous; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

[a]CAD defined as prior MI, PCI, or CABG.

[b]Triple therapy is angiotensin receptor–neprilysin inhibitor/ACE/ARB, beta-blocker, and MRA therapy.

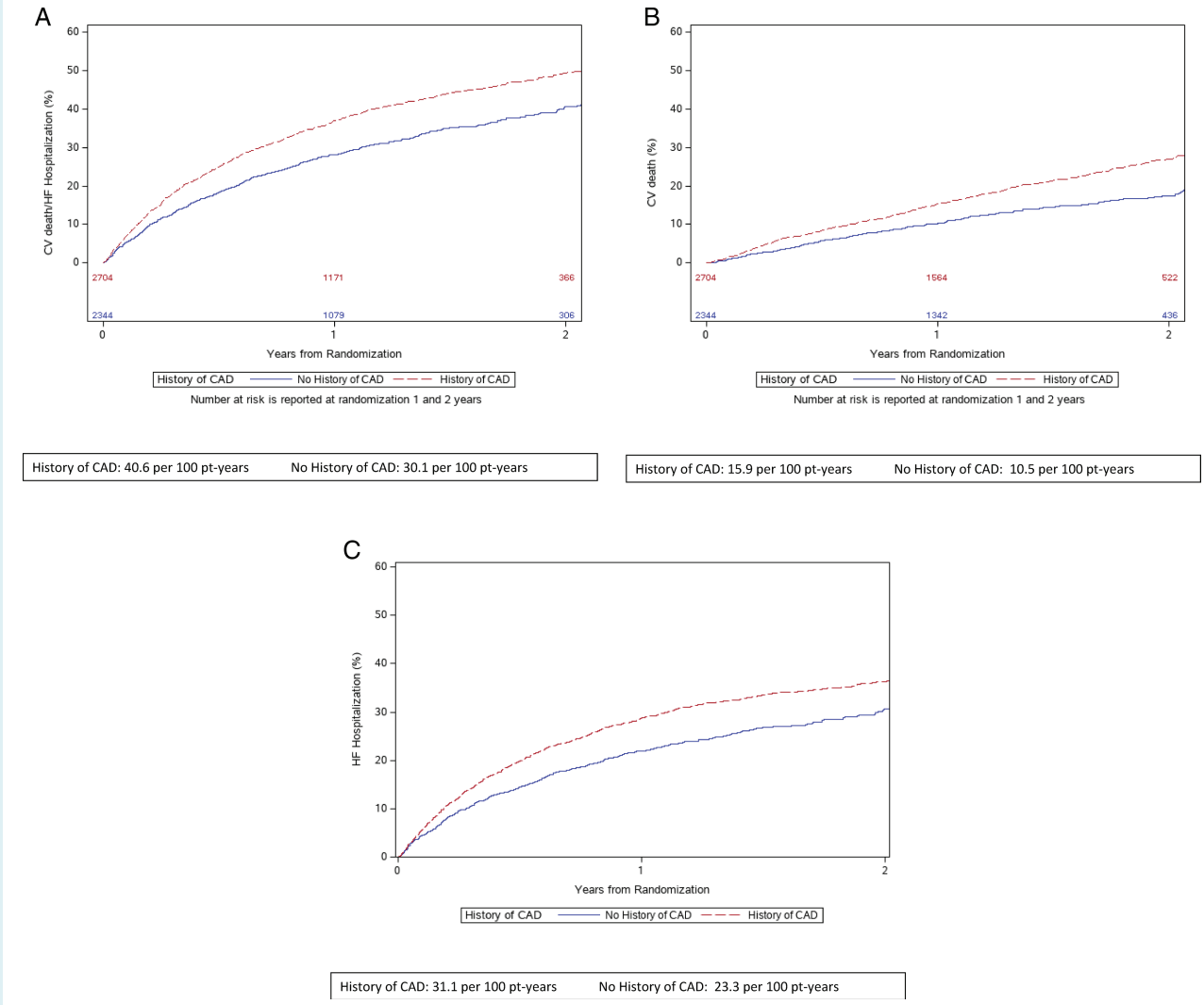


Figure 1 (*A*) Cardiovascular (CV) death or heart failure (HF) hospitalization according to presence of coronary artery disease (CAD). (*B*) CV death according to presence of CAD. (*C*) HF hospitalization according to presence of CAD. Event rates per 100 patient-years are reported in text boxes below each panel.

Table 2 shows the proportion of patients with and without CAD who experienced the key outcomes of the composite endpoint, both its components as individual endpoints, as well as sudden death, all-cause mortality, MI, and stroke. In six of the seven outcome categories, patients with CAD had a higher rate of events than those without CAD. Further examination of cardiovascular death revealed that sudden death was significantly less frequent in patients with CAD who had an ICD compared with those who did not (6.7% vs. 9.6%; $p < 0.001$). Notably, the 3.1% absolute excess incidence of sudden death in patients with versus without CAD (3.95 [CAD] vs. 2.88 per 100 patient-years in [no CAD]) occurred despite much greater use of ICDs (33.5% vs. 21.1%; $p < 0.001$) in patients with versus without CAD (*Table 2*). By contrast, the occurrence of sudden death in patients without CAD was similar in those with and without an ICD (5.7% vs. 4.8%; $p = 0.41$).

The overall incidence of MI in the trial was low but occurred significantly more often in those with versus without CAD (2.0 vs. 0.5 per 100 patient-years; $p < 0.001$), whereas no differences were seen in rates of stroke between the two groups (1.0 vs. 1.3 per 100 patient-years; $p = 0.16$).

Figure 2 displays the hazard ratios (HRs) for the composite outcomes, their components, and all-cause death according to the presence of CAD. After adjustment, the risks of the primary endpoint of cardiovascular death or HF hospitalization and each of its components, along with all-cause death, were all significantly higher in patients with CAD than in those without CAD. The proportion of patients with versus without CAD who experienced cardiovascular death (adjusted HR 1.44) as a fraction of their overall composite endpoint compared with those who had a HF hospitalization (adjusted HR 1.15) tended to be

Table 2 Proportions of patients with outcomes by history of coronary artery disease and no history of coronary artery disease

	No CAD (n = 2344)	CAD (n = 2704)	Log-rank p-value
CV death/HF hospitalization	749 (45.0%)	1118 (52.7%)	<0.001
CV death	310 (21.9%)	543 (30.2%)	<0.001
HF hospitalization[a]	579 (33.9%)	857 (38.6%)	<0.001
Sudden death	85 (5.5%)	135 (8.6%)	0.020
SCD among those with ICD	4.8%	6.7%	0.918
SCD among those with no ICD	5.7%	9.6%	<0.001
All-cause mortality	393 (27.2%)	651 (34.8%)	<0.001
MI[a]	17 (1.0%)	86 (4.0%)	<0.001
Stroke[a]	38 (2.0%)	35 (1.8%)	0.26

CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; SCD, sudden cardiac death.
Note: p-value from log-rank test statistic comparing cumulative incidence for history of CAD and no history of CAD.
Any hypotension includes hypotension and severe hypotension.
Median follow-up of 12 months; maximum follow-up of 982 days. Cumulative incidence estimates are reported at 2.7 years (982 days) from randomization.
[a]Competing risk of death is taken into account.

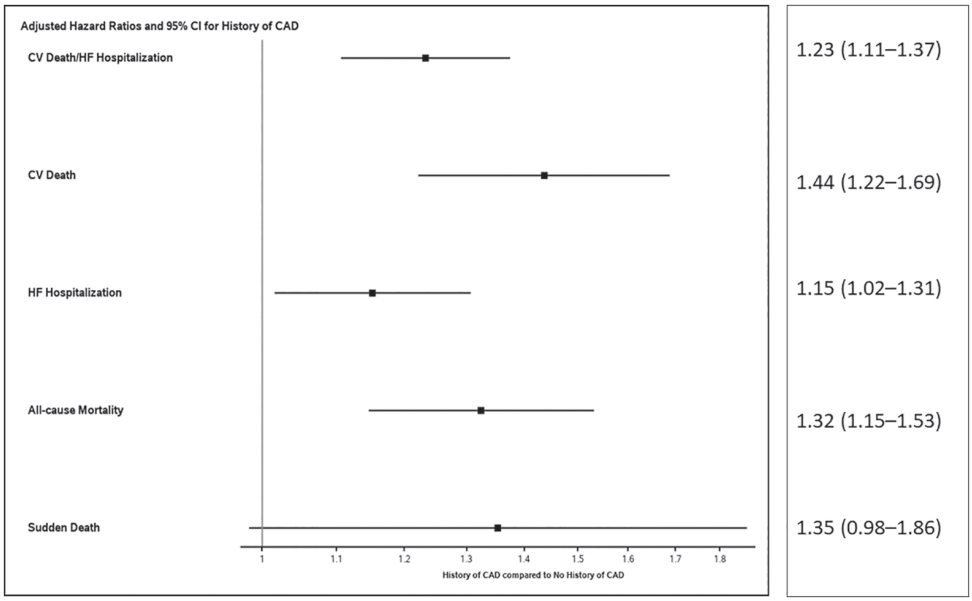


Figure 2 Adjusted hazard ratios and 95% confidence intervals for the composite outcomes, their components, and all-cause mortality according to presence of coronary artery disease (CAD). CV, cardiovascular; HF, heart failure.

greater, but was not statistically different (p = 0.11 [Lunn–McNeil method]).

Review of the two pre-specified safety endpoints of symptomatic hypotension and syncope revealed that patients with CAD had less symptomatic hypotension (7.3% vs. 9.5%; p = 0.006) and similar rates of syncope (3.8% vs. 3.7%; p = 0.85) than those without CAD.

In *Figure 3* and *Table 3* the relationship between treatment with vericiguat and the primary composite endpoint of cardiovascular death or HF hospitalization is shown according to the presence of CAD. In both cases, patients with CAD had significantly worse outcomes than those without CAD. The treatment benefit on the composite endpoint associated with vericiguat, as shown in the *Graphical Abstract*, was similarly evident in both the CAD (HR 0.92; 95% confidence interval [CI] 0.82–1.03) and no CAD groups (HR 0.85; 95% CI 0.74–0.98; interaction p = 0.78). The relationship between treatment with vericiguat and cardiovascular death in CAD (HR 0.89; 95% CI 0.75–1.05) and no CAD (HR 0.98; 95% CI 0.78–1.22; interaction p = 0.41) and on HF hospitalization for CAD (HR 0.94; 95% CI 0.83–1.07) and no CAD (HR 0.83; 95% CI 0.70–0.98: interaction p = 0.36) was also similar between groups. The absolute rates per 100 patient-years for these findings as well as for MI, stroke, symptomatic hypotension,

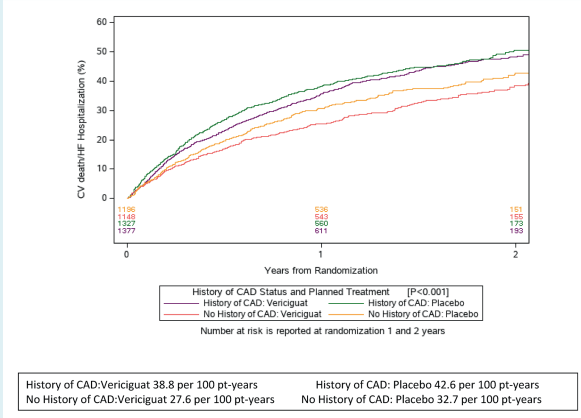


Figure 3 Survival curves of the composite outcome (cardiovascular [CV] death or heart failure [HF] hospitalization) according to presence of coronary artery disease (CAD) and effect of vericiguat treatment. Event rates/100 patient-years are reported in the text box below.

and syncope are shown in *Table 3*. Apart from a marginally significant interaction between hypotension and vericiguat in patients without CAD, there was no evidence of a significant interaction between vericiguat and CAD on these additional outcomes.

Discussion

The principal novel findings of our study are as follows: (i) the presence of CAD had a major impact on increasing the rates of both cardiovascular death and HF hospitalization in high-risk patients with worsening HF in the VICTORIA trial; (ii) the treatment benefit associated with vericiguat was similar in patients with and without CAD; and (iii) vericiguat was equally well tolerated in both cohorts. In particular, the pre-specified endpoints of symptomatic hypotension and syncope were similar in both cohorts. Although the incidence of subsequent MI was low overall, it occurred significantly more often in patients with CAD than in those without CAD; however, the rate of stoke, although also infrequent, was similar in both groups.

The demographic features of the CAD population are reflected in their 3-point higher MAGGIC risk score. Moreover, the inclusion of baseline NT-proBNP and the addition of a troponin T biomarker to this risk score revealed that more prominent elevations of each prognostic marker are seen in the CAD cohort of this high-risk HF population. This pair of biomarkers has been recognized to be of incremental prognostic value in HF,[15–19] but they are generally unavailable in contemporary clinical trials. In the DAPA-HF[20,21] and EMPEROR-Reduced[22] trials, an ischaemic basis for HF was present in approximately half of the patients. Both these trials have established the efficacy of sodium–glucose cotransporter 2 inhibitors by reducing their primary composite outcome of cardiovascular death and HF hospitalizations by ~25% relative to placebo event rates of 21.2% and 24.7%, respectively, over a period of 16–18 months in patients with HFrEF, irrespective of the presence of diabetes.[20,22] However, unlike in VICTORIA,[10] that subgroup contributed a relatively similar proportion to the same primary composite endpoint as compared with patients without ischaemia. This might be related in part to the more stringent definition of CAD used in the current study. An ischaemic cause was present in 51% of patients in PARADIGM-HF[23,24] and this group accounted for 63% of total deaths; however, ICD use (14.8%) was less than half of that in VICTORIA. In addition, digoxin use was substantially higher, ranging between 39% and 45% in PARADIGM-HF[23,24] versus 18% in VICTORIA,[10] thereby making valid cross-trial comparisons difficult. In the GALACTIC-HF trial,[25] troponin I was measured both at baseline and during the course of the trial and revealed a small but significant subsequent increase in those treated with the myosin activator omecamtiv mecarbil compared with placebo.

It is noteworthy that HF hospitalization is the larger component of the composite endpoint in the VICTORIA trial. Importantly, cardiovascular death events also contributed substantially to the composite outcome, but the trajectory of the survival curve for patients with CAD tends to rise more steeply and separate over time from those without CAD. Moreover, non-cardiac deaths accounted for 16.4% of deaths in those with CAD versus the

Table 3 Outcomes by history of coronary artery disease status and randomized treatment

	History of CAD			No history of CAD			
	Vericiguat[a]	Placebo[a]	HR (95% CI)	Vericiguat	Placebo	HR (95% CI)	*p*-value*
HF hospitalization or CV death	38.8	42.6	0.92 (0.82–1.03)	27.6	32.7	0.85 (0.74–0.98)	0.78
CV death	15.0	16.9	0.89 (0.75–1.05)	10.4	10.6	0.98 (0.78–1.22)	0.41
HF hospitalization	30.1	32.3	0.95 (0.83–1.08)	21.0	25.6	0.83 (0.71–0.98)	0.36
MI	2.2	1.9	1.18 (0.73–1.89)	0.6	0.6	0.93 (0.36–2.40)	0.34
Stroke	0.9	1.2	0.72 (0.37–1.40)	1.5	1.1	1.44 (0.76–2.74)	0.13
Symptomatic hypotension	9.4	9.3	1.03 (0.81–1.32)	8.3	5.9	1.38 (1.02–1.87)	0.05
Syncope	4.1	3.1	1.34 (0.90–1.99)	3.5	3.4	1.00 (0.66–1.53)	0.43

CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
[a]Per 100 patient-years.
*p-value for interaction of history of CAD and treatment.

larger proportion of 20.1% of deaths in those without CAD. The trend for cardiovascular death to comprise a higher fraction of the composite endpoint, the apparent widening of the mortality curves over time, as well as the increased propensity for sudden death underscore the continuing unmet therapeutic needs of this CAD population with HFrEF, despite their excellent background of evidence-based medical therapy. Importantly, the absolute increase of 3.1% in sudden cardiac death in patients with CAD occurred despite a much greater overall use of ICDs in patients with CAD, yet their use was associated with significantly less sudden death. By contrast, the incidence of sudden death in patients without CAD was similar irrespective of the presence of an ICD. Hence, our findings also have implications for anticipating mortality outcomes in the planning of future research in patients with HFrEF.

Notwithstanding the higher rates of the primary composite outcome and each of its components of cardiovascular death and HF hospitalization, we did not find evidence of greater efficacy of vericiguat in patients with CAD. Vericiguat proved to be equally safe in this population, as indicated, but with less symptomatic hypotension and a similar incidence of syncope. Given the presumed role of diminished soluble guanylate cyclase activity in endothelial dysfunction and microvascular disease, the reasons for lack of a more pronounced treatment effect of vericiguat in patients with HFrEF and concomitant CAD is unclear. The low incidence of MI and stroke would make it difficult to demonstrate a treatment effect on these tertiary events. It is also possible that the relatively short follow-up of a median of 10.8 months (driven by event accrual) obscured a treatment effect that would be evident after a longer follow-up period.

Our study has both strengths and limitations. This is a post hoc analysis of the VICTORIA trial in which coronary status was defined at study enrolment by site investigators based on a patient-reported history of previous MI or a history of coronary revascularization prior to their index HF hospitalization. Sensitivity analyses (data not shown) examining our findings by defining CAD by prior MI alone did not affect our results. Whereas the presence of CAD defined by the presence of angina may have occurred, it would be unlikely to affect our findings. Although there was somewhat more triple baseline guideline HF therapy in the population without CAD, the converse was true for the use of cardiac devices; these factors may have confounded our assessment. The outcomes reported herein are robust and adjudicated by a clinical events committee. Since the parent trial accumulated the pre-specified number of endpoint events sooner than expected (median follow-up of 10.8 months), a longer follow-up duration may have resulted in greater inter-group differences, particularly in cardiovascular mortality given the pattern of separation in those survival curves. Nonetheless, our findings should be perceived as hypothesis generating and deserving of future investigation.

Conclusion

The presence of prior CAD in high-risk HF patients with a recent worsening HF event is associated with an increase in the composite endpoint of cardiovascular death or HF hospitalization as well as each of its individual components. In this post hoc study, vericiguat was associated with beneficial effects on these outcomes, irrespective of concomitant CAD.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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