Supplemental Online Content

Lam CSP, Giczewska A, Sliwa K, et al; for the VICTORIA Study Group. Clinical outcomes and response to vericiguat according to index heart failure event: insights from the VICTORIA trial. *JAMA Cardiol*. Published online November 13, 2020. doi:10.1001/jamacardio.2020.6455

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Candidate variable list

Category	Variables Included
Trial details	Randomized treatment, subject randomized while hospitalized,
Demographic details	Age, sex, region/race (incorporation of race for NA), ethnicity
HF details	Index event, time from index event to randomization, duration of HF diagnosis, duration of primary diagnosis of HFrEF, ejection fraction, NYHA class
Past medical history	CCSA class, atrial fibrillation, atrial flutter, COPD, angina, diabetes, hypertension, hyperlipidemia, anemia, sleep apnea, peripheral artery disease, prior MI, prior stroke, prior TIA, prior CABG, prior PCI, aortic valve replacement, mitral valve replacement, current tobacco use
Physical exam/vitals	BMI, height, weight, systolic blood pressure, diastolic blood pressure, pulse pressure
Medications and devices	ACE or ARB, beta blocker, MRA, sacubitril-valsartan, ivabradine, ICD, pacemaker
Laboratories	Creatinine, eGFR, NT-proBNP, hemoglobin, potassium, sodium, albumin, ALT, AST, bicarbonate, bilirubin, BUN, calcium, chloride, GGT, glucose, hematocrit, platelets, white blood count, red blood count, urate
ECG	QTcF

ACE indicates angiotensin converting enzyme; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CCSA, Canadian

Cardiovascular Society Angina Score; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; MRA, mineralocorticoid-receptor antagonists; NA, North America; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; QTcF, corrected QT interval by Fredericia; TIA, transient ischemic attack.

eTable 2. Hazard ratios for primary and secondary endpoints by index admission subgroups

Endpoint	Model Type	Index Group*	HR (95% CI)	P-value
Primary Endpoints				
HF hospitalization/CV death	Unadjusted	HF Hospitalization within 3 Months	1.690 (1.464–1.951)	<.0001
	Multivariable-adjusted†	HF Hospitalization within 3 Months	1.482 (1.272–1.728)	<.0001
	Unadjusted	HF Hospitalization 3-6 Months	1.260 (1.057–1.502)	0.0100
	Multivariable-adjusted†	HF Hospitalization 3-6 Months	1.115 (0.925–1.344)	0.2539
Secondary Endpoints				
CV death	Unadjusted	HF Hospitalization within 3 Months	1.394 (1.137–1.710)	0.0014
	Multivariable-adjusted†	HF Hospitalization within 3 Months	1.150 (0.921–1.438)	0.2173
	Unadjusted	HF Hospitalization 3-6 Months	1.199 (0.934–1.538)	0.1541
	Multivariable-adjusted†	HF Hospitalization 3-6 Months	1.168 (0.892–1.530)	0.2577
HF hospitalization	Unadjusted	HF Hospitalization within 3 Months	1.772 (1.501–2.093)	<.0001
	Multivariable-adjusted†	HF Hospitalization within 3 Months	1.573 (1.319–1.876)	<.0001

	Unadjusted	HF Hospitalization 3-6 Months	1.259 (1.027–1.545)	0.0270
	Multivariable-adjusted†	HF Hospitalization 3-6 Months	1.092 (0.878–1.358)	0.4281
All-cause death/HF hospitalization	Unadjusted	HF Hospitalization within 3 Months	1.687 (1.467–1.939)	<.0001
	Multivariable-adjusted†	HF Hospitalization within 3 Months	1.457 (1.256–1.691)	<.0001
	Unadjusted	HF Hospitalization 3-6 Months	1.311 (1.107–1.553)	0.0017
	Multivariable-adjusted†	HF Hospitalization 3-6 Months	1.168 (0.976–1.399)	0.0908
All-cause death	Unadjusted	HF Hospitalization within 3 Months	1.463 (1.212–1.766)	<.0001
	Multivariable-adjusted†	HF Hospitalization within 3 Months	1.234 (1.004–1.516)	0.0456
	Unadjusted	HF Hospitalization 3-6 Months	1.309 (1.044–1.642)	0.0197
	Multivariable-adjusted†	HF Hospitalization 3-6 Months	1.280 (1.004–1.632)	0.0466

*Outpatient worsening group (receiving IV diuretic for HF within 3 months, without hospitalization within 6 months) index group used as reference group.
†Variables included in multivariable adjustment included HF characteristics (longer HF duration, and worse NYHA class); history of peripheral arterial disease (PAD), myocardial infarction (MI); patients baseline characteristics (age, systolic blood pressure, race and region, Anemia and non-use of Beta-Blockers); and laboratory parameters (N-terminal pro-B-type natriuretic peptide [NT-proBNP], hemoglobin, sodium, bilirubin, urate, chloride and albumin).

CI indicates confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio.

eTable 3. Treatment effect by index admission event subgroup

		Vericiguat		Placebo		Unadjusted Model			Multivariable Adjusted Model†		
Event	**Index group**	**No. (%)**	**Event Rates***	**No. (%)**	**Event Rates***	**HR (95% CI)**	**P-value**	**Interaction P-value**	**HR (95% CI)**	**P-value**	**Interaction P-value**
Primary endpoint											
HF hosp/CV death	HF Hospitalization within 3 Months	660 (39.45)	39.29	701 (41.11)	42.46	0.931 (0.837–1.035)	0.1872	0.4333	0.935 (0.836–1.046)	0.2416	0.2066
HF hosp/CV death	HF Hospitalization 3-6 Months	141 (31.06)	27.12	151 (36.21)	32.39	0.848 (0.674–1.066)	0.1578		0.915 (0.716–1.170)	0.4800	
HF hosp/CV death	Outpatient worsening within 3 Months	96 (24.06)	20.46	120 (29.85)	26.39	0.784 (0.599–1.025)	0.0751		0.710 (0.535–0.942)	0.0177	
Secondary endpoints											
CV death	HF Hospitalization within 3 Months	303 (18.11)	14.57	300 (17.60)	14.39	1.013 (0.864–1.189)	0.8717	0.1433	0.981 (0.829–1.160)	0.8213	0.3716
CV death	HF Hospitalization 3-6 Months	65 (14.32)	10.85	78 (18.71)	14.10	0.771 (0.555–1.072)	0.1222		0.822 (0.577–1.171)	0.2768	
CV death	Outpatient worsening within 3 Months	46 (11.53)	8.72	63 (15.67)	11.96	0.731 (0.500–1.069)	0.1064		0.744 (0.495–1.120)	0.1565	

HF hosp	HF Hospitalization within 3 Months	518 (30.96)	30.83	544 (31.91)	32.99	0.941 (0.835–1.062)	0.3249	0.2926	0.950 (0.836–1.079)	0.4297	0.0955
HF hosp	HF Hospitalization 3-6 Months	105 (23.13)	20.25	111 (26.62)	23.81	0.863 (0.661–1.126)	0.2776		0.888 (0.664–1.186)	0.4205	
HF hosp	Outpatient worsening within 3 Months	68 (17.04)	14.49	92 (22.89)	20.24	0.725 (0.530–0.992)	0.0443		0.644 (0.464–0.894)	0.0085	
All-cause death/HF hosp	HF Hospitalization within 3 Months	700 (41.84)	41.67	738 (43.28)	44.70	0.938 (0.846–1.040)	0.2223	0.3712	0.928 (0.831–1.035)	0.1781	0.3040
All-cause death/HF hosp	HF Hospitalization 3-6 Months	155 (34.14)	29.82	167 (40.05)	35.82	0.842 (0.677–1.048)	0.1232		0.913 (0.722–1.154)	0.4454	
All-cause death/HF hosp	Outpatient worsening within 3 Months	102 (25.56)	21.74	127 (31.59)	27.93	0.786 (0.606–1.021)	0.0708		0.736 (0.559–0.968)	0.0283	
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All-cause death	HF Hospitalization within 3 Months	374 (22.36)	17.98	363 (21.29)	17.41	1.034 (0.895–1.194)	0.6543	0.0996	1.007 (0.865–1.173)	0.9249	0.2770
All-cause death	HF Hospitalization 3-6 Months	83 (18.28)	13.85	99 (23.74)	17.89	0.776 (0.580–1.039)	0.0882		0.839 (0.614–1.147)	0.2721	.
All-cause death	Outpatient worsening within 3 Months	55 (13.78)	10.43	72 (17.91)	13.67	0.765 (0.539–1.087)	0.1357		0.758 (0.522–1.101)	0.1451	.

*Event rates/100 patient-yrs.

†Variables included in multivariable adjustment included HF characteristics (longer HF duration, and worse NYHA class); history of peripheral arterial disease (PAD), myocardial infarction (MI); patients baseline characteristics (age, systolic blood

pressure, race and region, Anemia and non-use of Beta-Blockers); and laboratory parameters (N-terminal pro-B-type natriuretic peptide [NT-proBNP], hemoglobin, sodium, bilirubin, urate, chloride and albumin).
CI indicates confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; IV, intravenous.

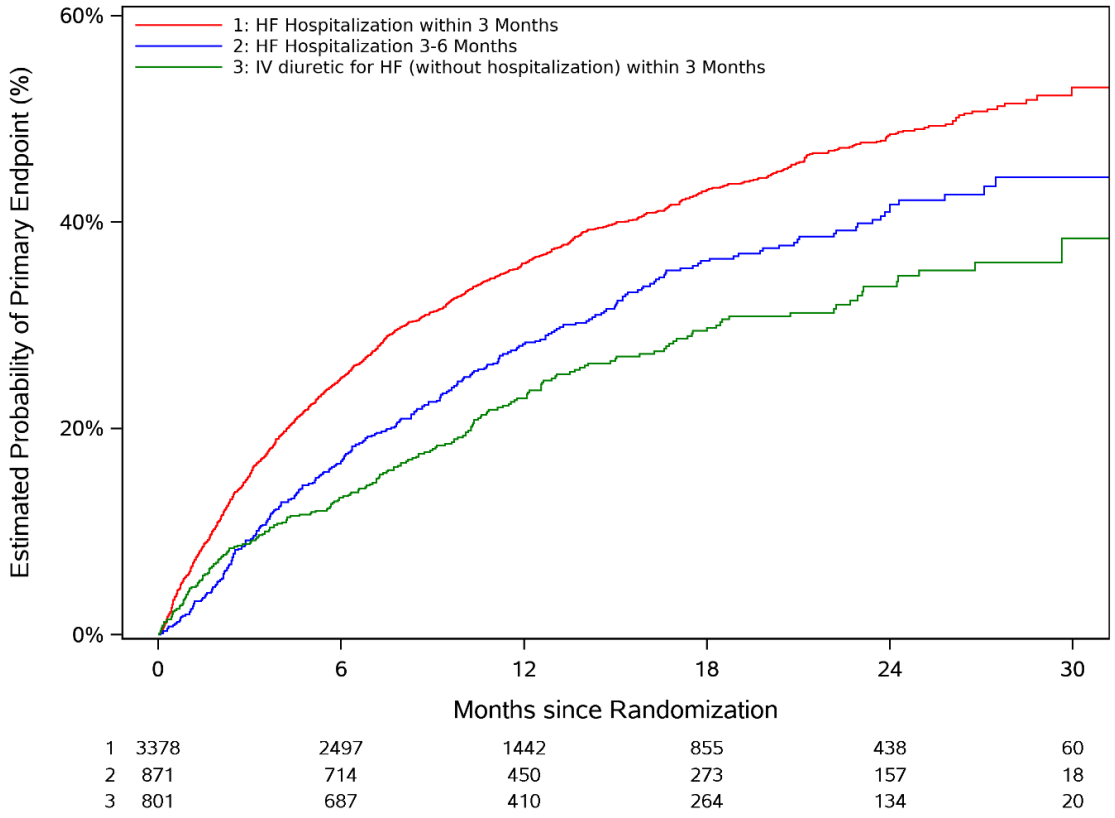
eTable 4. Safety events of interest and serious adverse events by index event group

		Vericiguat		Placebo		Difference in % vs Placebo	
Safety events	**Index group**	**n**	**(%)**	**n**	**(%)**	**Estimate (95% CI)***	**P-value**
Symptomatic Hypotension	Randomized while hospitalized (any hospitalization)	24	(8.136)	17	(6.159)	2.0 (-2.2 to 6.2)	0.361
	≤30 days	72	(10.315)	64	(8.388)	1.9 (-1.1 to 4.9)	0.205
	30-90 days	58	(8.517)	49	(7.402)	1.1 (-1.8 to 4.0)	0.451
	>90 days	38	(8.539)	39	(9.443)	-0.9 (-4.7 to 2.9)	0.644
	Outpatient worsening	34	(8.521)	28	(6.965)	1.6 (-2.1 to 5.3)	0.410
Syncope	Randomized while hospitalized (any hospitalization)	17	(5.763)	11	(3.986)	1.8 (-1.7 to 5.3)	0.326
	≤30 days	20	(2.865)	27	(3.539)	-0.7 (-2.5 to 1.1)	0.466
	30-90 days	27	(3.965)	21	(3.172)	0.8 (-1.2 to 2.8)	0.434
	>90 days	20	(4.494)	15	(3.632)	0.9 (-1.8 to 3.5)	0.523
	Outpatient worsening	17	(4.261)	13	(3.234)	1.0 (-1.6 to 3.7)	0.444
Serious adverse events	Randomized while hospitalized (any hospitalization)	123	(41.695)	114	(41.304)	0.4 (-7.7 to 8.5)	0.925
	≤30 days	228	(32.665)	254	(33.290)	-0.6 (-5.5 to 4.2)	0.800
	30-90 days	204	(29.956)	242	(36.556)	-6.6 (-11.6 to -1.6)	0.010
	>90 days	146	(32.809)	149	(36.077)	-3.3 (-9.6 to 3.1)	0.314
	Outpatient worsening	122	(30.576)	114	(28.358)	2.2 (-4.1 to 8.5)	0.491

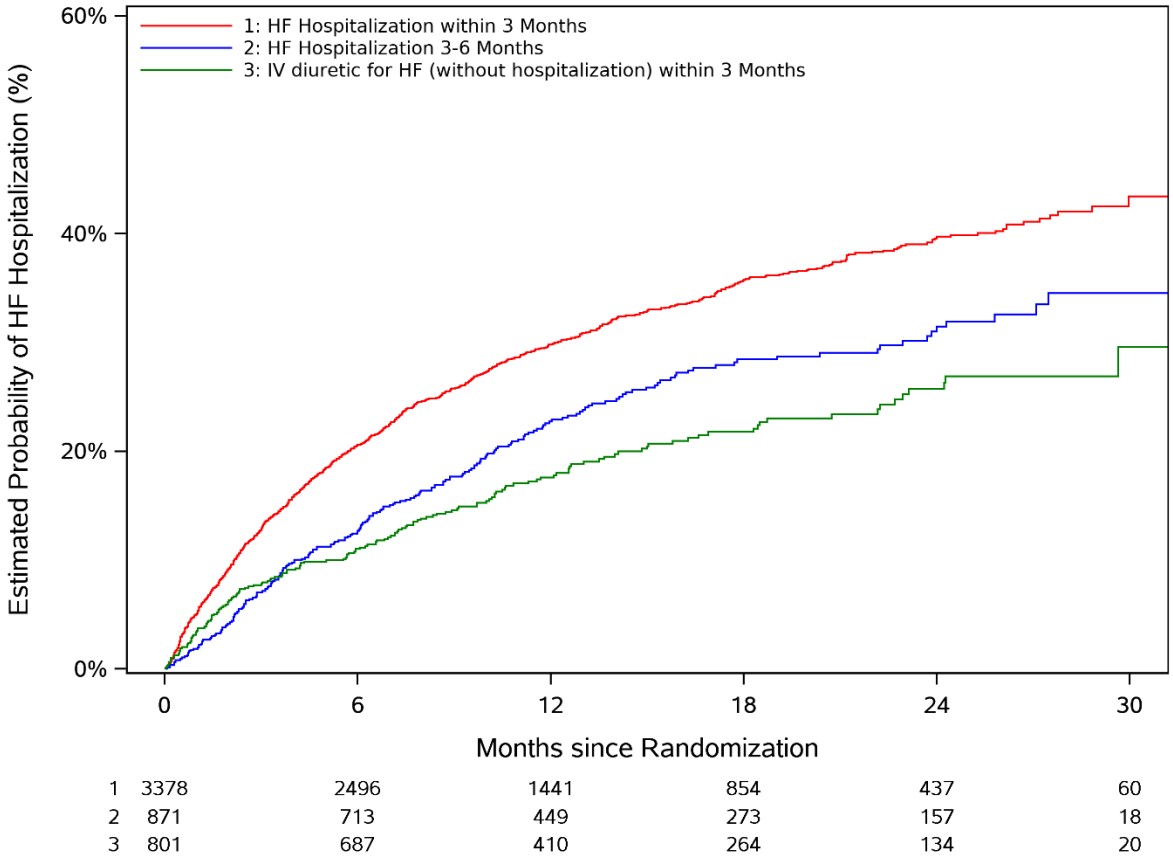
Based on the Miettinen & Nurminen method.
CI indicates confidence interval; IV, intravenous.

eFigure 1. Kaplan-Meier graphs by index event subgroup showing time to first primary composite endpoint (A), time to heart failure (HF) hospitalization (B) and time to cardiovascular death (C). Red lines represent patients randomized within 3 months of HF hospitalization, blue lines those randomized within 3-6 months of HF hospitalization, and green lines those randomized within 3 months of outpatient worsening without HF hospitalization.

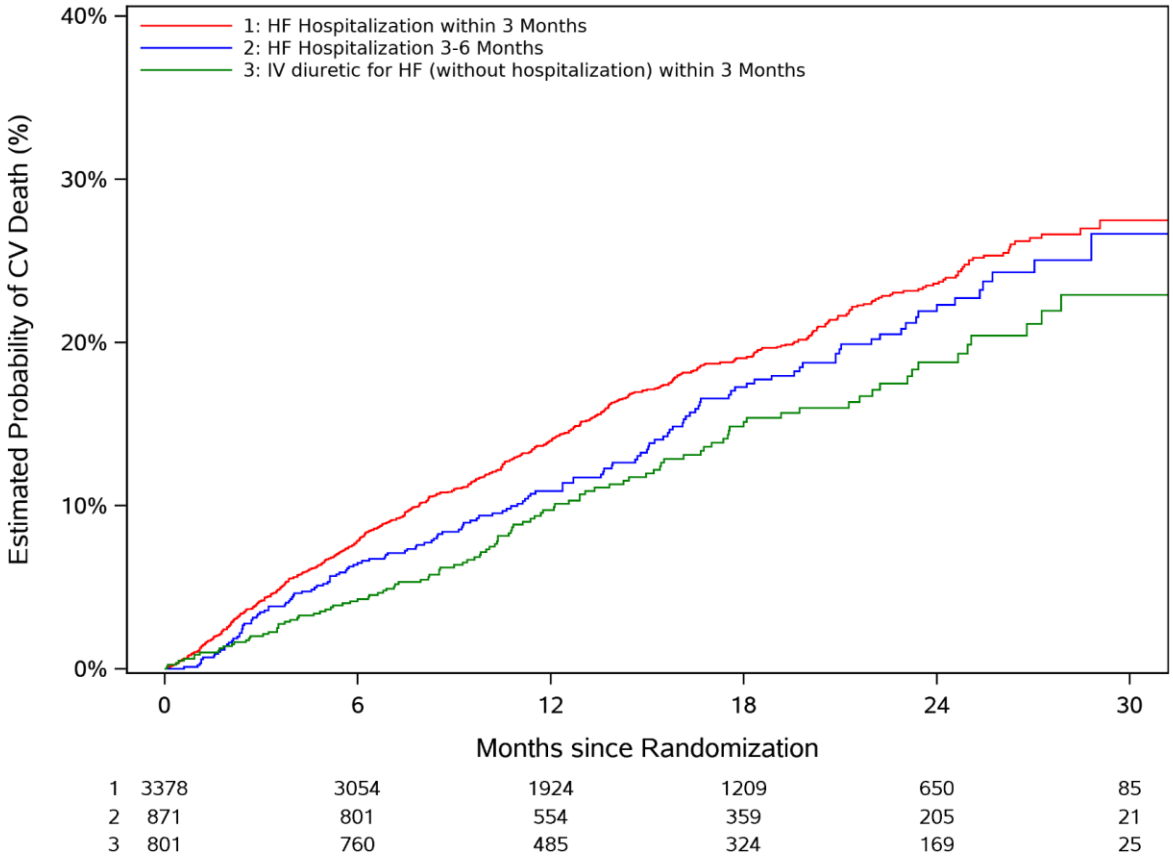
eFigure 1A. Kaplan-Meier analysis for time to first primary composite endpoint by index event subgroup



eFigure 1B. Kaplan-Meier analysis for time to heart failure hospitalization by index event subgroup



eFigure 1C. Kaplan-Meier analysis for time to cardiovascular death by index event subgroup



eFigure 2. Treatment effect of vericiguat compared with placebo analyzed using time from intravenous diuretic administration for outpatient worsening as a continuous variable.

The treatment effect of vericiguat (hazard ratio with 95% confidence interval) is shown as a function of time as a continuous variable from index event to randomization among patients receiving intravenous diuretics for outpatient worsening HF.

Note: Data represents a figure up to 60 days. Model was populated for 769 patients with a follow-up to 180 days (32 patients excluded due to missing data).