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Clinical Outcome Predictions for the VerICiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA) Trial

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ABSTRACT

Background: The prediction of outcomes in patients with heart failure (HF) may inform prognosis, clinical decisions regarding treatment selection, and new trial planning. The VerICiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction included high-risk patients with HF with reduced ejection fraction and a recent worsening HF event. The study participants had a high event rate despite the use of contemporary guideline-based therapies. To provide generalizable predictive data for a broad population with a recent worsening HF event, we focused on risk prognostication in the placebo group.

Methods and Results: Data from 2524 participants randomized to placebo with chronic HF (New York Heart Association functional class II–IV) and an ejection fraction of less than 45% were studied and backward variable selection was used to create Cox proportional hazards models for clinical end points, selecting from 66 candidate predictors. Final model results were produced, accounting for missing data, and nonlinearities. Optimism-corrected c-indices were calculated using 200 bootstrap samples. Over a median follow-up of 10.4 months, the primary outcome of HF hospitalization or cardiovascular death occurred in 972 patients (38.5%). Independent predictors of increased risk for the primary end point included HF characteristics (longer HF duration and worse New York Heart Association functional class), medical history (prior myocardial infarction), and laboratory values (higher N-terminal pro-hormone B-type natriuretic peptide, bilirubin, urate; lower chloride and albumin). Optimism-corrected c-indices were 0.68 for the HF hospitalization/cardiovascular death model, 0.68 for HF hospitalization/all-cause death, 0.72 for cardiovascular death, and 0.73 for all-cause death.

Conclusions: Predictive models developed in a large diverse clinical trial with comprehensive clinical and laboratory baseline data—including novel measures—performed well in high-risk patients with HF who were receiving excellent guideline-based clinical care.

Clinical Trial Registration: Clinicaltrials.gov identifier, NCT02861534.

Lay Summary: Patients with heart failure may benefit from tools that help clinicians to better understand a patient's risk for future events like hospitalization. Relatively few risk models have been created after the worsening of heart failure in a contemporary cohort. We provide insights on the risk factors for clinical events from a recent, large, global trial of patients with worsening heart failure to help clinicians better understand and communicate prognosis and select treatment options. (*J Cardiac Fail* 2021;27:949–956)

Key Words: Heart failure with reduced ejection fraction, predictive models, outcomes, prognosis.

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Despite significant advances in the medical and device-based management of patients with heart failure (HF) with reduced ejection fraction (HFrEF), risk for adverse outcomes remains high in these patients, particularly after a recent decompensation.^{1,2} Risk models may inform the assessment of prognosis, planning of new trials, and clinical management decisions and treatment selection, particularly when there is evidence of a differential benefit of therapies aligned with baseline risk³ or clinical phenotype (ie, baseline characteristics).⁴ Recently, the VerICiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA) trial showed that vericiguat significantly decreased the risk for the primary outcome of HF hospitalization or cardiovascular death in patients with HFrEF.⁵ The VICTORIA trial included 5050 patients with HFrEF with recent clinical worsening despite high utilization of contemporary guideline-directed medical and device therapy. The study included a well-phenotyped patient population in terms of baseline characteristics with few missing data, making this dataset well-suited for risk prediction. Although many risk prediction models have been developed,⁶ the unique nature of the study population and contemporary data acquired in an environment in which there are increasing numbers of available medical therapies for HFrEF underscores the need for further investigation. Accordingly, we developed models to better understand the baseline risk profile of patients in VICTORIA and subsequent clinical outcomes in this understudied, high-risk population with HF.

Methods

Patient Cohort and Trial Overview

The VICTORIA trial design, baseline characteristics, and outcomes have been previously reported elsewhere.^{5,7,8} Briefly, VICTORIA was a multicenter, international, randomized, placebo-controlled trial that investigated the efficacy and safety of the soluble guanylate cyclase stimulator, vericiguat, on a background of evidence-based medical and device therapy in 5050 patients with chronic HFrEF (New York Heart Association [NYHA] functional class II–IV) and a recent worsening HF event. Eligible patients had a left ventricular ejection fraction of less than 45%, an elevated natriuretic peptide level, and a recent deterioration (either HF hospitalization in the prior 6 months or outpatient intravenous diuretics in the prior 3 months). Exclusions included a systolic blood pressure of less than 100 mm Hg and the use of long-acting nitrates, phosphodiesterase type 5 inhibitors, or intravenous inotropes. The trial protocol was approved by institutional review boards or ethics committees at the participating sites and all the patients provided informed consent. Patients were randomized 1:1 to receive vericiguat or matching placebo. A clinical event committee, whose members were blinded to treatment assignment, adjudicated all reported deaths (cardiovascular and noncardiovascular), cardiovascular hospitalizations, and urgent HF visits as previously described.⁷

The trial was event driven with a median follow-up of 10.8 months. Vericiguat decreased the primary end point of HF hospitalization or cardiovascular death (hazard ratio 0.90; 95% confidence interval 0.82–0.98; $P = .02$).

Focus on the Placebo Group

For the present analysis, we focused on the patients randomized to receive placebo to provide generalizable prognostic data for a broad population with a recent worsening HF event.

Data Considerations

Detailed patient characteristics were collected at baseline including demographics, HF characteristics, past medical history, medication and device use, vital signs, and extensive laboratory assessments. Detailed data entry instructions and variable definitions were provided to assist with consistency of form completion.

Statistical Methods

Baseline characteristics were summarized by counts and percentages for categorical variables and by medians with 25th and 75th percentiles for continuous variables. For both the primary end point (HF hospitalization or cardiovascular death) and the secondary end points (all-cause mortality or HF hospitalization, cardiovascular death, and all-cause death), we report the frequency of events as well as the Kaplan–Meier event rate over the median follow-up time. Cox proportional hazards regression models were used to quantify the direction and magnitude of the univariable association between each baseline predictor and each outcome, reported as hazard ratio with 95% confidence intervals.

For both the primary and secondary end points, predictive models were developed using a set of 66 available candidate variables for possible model inclusion (Supplemental Table 1). Using the entire VICTORIA population, we examined missing data patterns among the candidate predictors and conducted multiple imputations via fully conditional specification using the appropriate method for the predictor type (continuous, binary, or nominal) to create 25 analysis datasets with no missing data. We assessed the linearity of continuous predictors using restricted cubic splines, and transformed predictors using an appropriate functional transformation (eg, $\log_2$ transformation) or created linear piece-wise splines, as appropriate. Linearity assessments with the placebo arm resulted in only 2 variables requiring natural cubic splines during the selection process (estimated glomerular filtration rate for all outcomes and platelets for the composite outcomes). Additionally, collinear predictors were identified and 1 predictor for each group of variables was chosen based on the variable with the highest c-statistic from the univariable models.

For each imputed dataset, backward selection with a significance level of 0.01 was used to select the predictors to include in the final model for each outcome. The final

models included any predictor that was selected for inclusion in at least 20 of the 25 imputed datasets.

Final Cox models for each outcome were fit with the chosen predictors. The proportional hazards assumption for the final models was checked using weighted Schoenfeld residuals, and no major violations were found. Model parameter estimates, chi-square statistics, and c-indices were averaged across the 25 imputed datasets to produce final HRs with 95% confidence intervals and *P* values. To assess internal validation, bias-corrected c-indices were calculated using 200 bootstrap samples. Model calibration was graphically assessed for each outcome by plotting 1-year Kaplan–Meier event rates versus predicted rates by decile of predicted risk. All analyses were conducted by the Duke Clinical Research Institute (Durham, NC) using SAS v9.4 (SAS Institute, Inc., Cary NC).

Results

Table 1 presents the baseline characteristics of the study population. The median age of participants was 68 years, 23.9% were female, and 64.1% were White. The majority of patients were in NYHA functional classification II (59.3%) or III (39.4%) at the time of randomization with a median N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) of 2821 pg/mL. Supplemental Table 2 presents the numbers missing for the different variables with most variables having less than 2% missing data. Overall, 84.6% of the population had complete data on candidate predictors.

During a median follow-up of 10.4 months, the primary outcome of HF hospitalization or cardiovascular death occurred in 972 patients (38.5%) in the placebo arm. The event counts for HF hospitalization or all-cause death, cardiovascular death, and all-cause death were 1032 (40.9%), 441 (17.5%) and 534 (21.2%), respectively.

Table 1 presents the univariable associations with the primary end point in the study population of 2524 participants (50%) randomized to placebo. Many of the baseline variables were associated with the primary outcome at a *P* value of less than .05, with notable exceptions of age, sex, race, region, beta-blocker use, anemia, and body mass index. Supplemental Table 3 provides the univariable associations for the secondary end points.

Table 2 presents the predictive model for the primary outcome of HF hospitalization or cardiovascular death. The 9 independent predictors included HF characteristics (longer HF duration, worse NYHA functional class, and index HF event for trial eligibility—HF hospitalization within 3 or 6 months or intravenous diuretics), medical history (prior myocardial infarction), and laboratory values (higher NT-proBNP, bilirubin, urate; lower chloride and albumin) (Visual Take Home). The uncorrected C-index for the HF hospitalization or cardiovascular death model was 0.68 and the optimism-corrected C-index was 0.68. **Fig. 1** presents the calibration of the primary end point model for predicted risk at 1 year. The calibration plot is a measure of how well

the model predicts patient risk compared with the observed risk. Patients are placed into deciles based on their predicted risk, and the observed risk for that decile is calculated. Our calibration plot indicates that the model is good at predicting risk for most of the patients in the cohort. However, the risk prediction is less good for those who are at highest risk of experiencing the primary end point (those in the 9th and 10th deciles of predicted risk).

The predictive models for the secondary outcomes of HF hospitalization or all-cause death, cardiovascular death, and all-cause death are shown in Supplemental Tables 4, 5, and 6, respectively. In general, the variables in the different models were fairly similar, as summarized in **Table 3a** and **b**. Compared with the primary end point model, the all-cause mortality or HF hospitalization model did not include the index HF event or urate, but added the estimated glomerular filtration rate, pulse rate, and implantable cardioverter defibrillator use. The cardiovascular death model also included enrolling region (increased risk in Eastern Europe and Latin/South America), lower systolic blood pressure, and longer QTc, but did not include the index HF event or the laboratory values of bilirubin, urate, or albumin. The all-cause mortality model included enrolling region but did not include HF duration, index HF event, bilirubin, or urate. Optimism-corrected c-indices were 0.68 for HF hospitalization/all-cause death, 0.72 for cardiovascular death, and 0.73 for all-cause death.

Table 3a and **b** also summarizes the consistency of variables across the different end points. Notably, NT-proBNP, NYHA functional class, chloride, and prior myocardial infarction were in all of the end point models. Additional variables that were present in most models included duration of HF and albumin.

Discussion

The VICTORIA model identifies key prognostic variables for the high-risk cohort of patients with HFrEF with recent clinical worsening. These variables include many of those that are routinely known or collected at the time of HF hospitalization or outpatient worsening. Specifically, the clinical characteristics with independent prognostic usefulness for the primary end point of HF hospitalization or cardiovascular death included HF characteristics (longer HF duration and worse NYHA functional class), medical history (prior myocardial infarction), and laboratories (higher NT-proBNP, bilirubin, urate; lower chloride and albumin). The other end point models included similar variables overall but also included other variables such as faster heart rate, lower systolic blood pressure, and lower estimated glomerular filtration rate. These models refining patient prognosis may guide clinical decision-making (particularly in the context of recent HFrEF trials focused on patients with the worsening HF phenotype) as well as future clinical trial design.

The VICTORIA model provides unique insights, given that it focused specifically on patients with HFrEF and a

Table 1. Trial Baseline Characteristics and Univariable Associations Between Clinical Outcomes in the Placebo Cohort

Variable	Placebo Group Trial Characteristics	Univariate Associations with Clinical Outcomes		
		Association Represents	HF Hospitalization or CV Death HR (95% CI)	P Value
Age, years	68.0 (60.0, 76.0)	Per 5-y increase	1.010 (0.984–1.037)	.459
Female	603 (23.9%)	Versus Male	0.875 (0.751–1.019)	.086
Race		Versus Other		.814
White	1618 (64.1%)		0.938 (0.743–1.184)	
Black	126 (5.0%)		1.061 (0.745–1.511)	
Asian	561 (22.2%)		0.965 (0.746–1.249)	
Other	219 (8.7%)			
Region		Versus Western Europe		.309
Eastern Europe	846 (33.5%)		1.071 (0.894–1.284)	
Western Europe	446 (17.7%)			
Asia-Pacific	591 (23.4%)		1.002 (0.821–1.222)	
Latin America	362 (14.3%)		0.866 (0.685–1.095)	
North America	279 (11.1%)		1.106 (0.875–1.396)	
Index event		Versus 3–6 mos		<.001
HF hospitalization prior 3 m	1705 (67.6%)		1.277 (1.071–1.523)	
HF hospitalization prior 3–6 m	417 (16.5%)			
IV diuretics prior 3 m	402 (15.9%)		0.821 (0.646–1.043)	
Randomized in hospital	277 (11.0%)	Versus outside hospital	1.408 (1.171–1.694)	<.001
EF, %	29.0 (23.0, 35.0)	Per 1% increase	0.982 (0.974–0.989)	<.001
NYHA functional class		Versus I/II	III/IV: 1.671 (1.473–1.895)	<.001
I	2 (0.1%)			
II	1497 (59.3%)			
III	993 (39.4%)			
IV	31 (1.2%)			
Duration of HF diagnosis, y	3.3 (1.1, 7.5)	Per doubling	1.080 (1.047–1.115)	<.001
QTc, ms	451.0 (425.0, 480.0)	Per 10 unit increase	1.032 (1.019–1.046)	<.001
Beta-blocker	2342 (93.0%)	Versus No	0.875 (0.690–1.109)	.269
ACE or ARB	1853 (73.6%)	Versus No	0.688 (0.601–0.788)	<.001
ICD	703 (27.9%)	Versus No	1.365 (1.195–1.560)	<.001
Prior MI	1022 (40.5%)	Versus No	1.320 (1.163–1.497)	<.001
Prior PCI	842 (33.4%)	Versus No	1.205 (1.058–1.372)	.005
PAD	309 (12.2%)	Versus No	1.461 (1.228–1.739)	<.001
Anemia	529 (21.0%)	Versus No	1.152 (0.992–1.337)	.063
Heart rate, bpm	72.0 (64.0, 81.0)	Per 5 bpm increase	1.043 (1.018–1.068)	<.001
SBP, mm Hg	119.0 (109.0, 131.0)	Per 5 mmHg increase	0.963 (0.943–0.983)	<.001
BMI, kg/m ²	26.9 (23.8, 31.1)	Per 1 kg/m ² increase	1.003 (0.993–1.014)	.557
Sodium, mEq/L	140.0 (138.0, 142.0)	Per 1 mEq/L increase	0.951 (0.934–0.968)	<.001
eGFR, mL/min/1.73 m ²	58.3 (41.4, 77.4)	Versus >60	≤30: 1.997 (1.633–2.442) >30–60: 1.426 (1.243–1.635)	<.001
NT-proBNP, pg/mL	2821.0 (1548.0, 5206.0)	Per doubling	1.347 (1.285–1.411)	<.001
Chloride, mmol/L	100.0 (97.0, 102.0)	Per 5 mmol/L increase	0.725 (0.675–0.779)	<.001
Albumin, g/dL	4.2 (3.9, 4.5)	Per 1 g/dL increase	0.570 (0.491–0.663)	<.001
Bilirubin, mg/dL	0.6 (0.4, 0.9)	Per 0.5 mg/dL increase	1.203 (1.150–1.258)	<.001
Calcium, mg/dL	9.3 (9.0, 9.6)	Per 1 mg/dL increase	0.812 (0.717–0.920)	.001
Urate, mg/dL	7.7 (6.3, 9.4)	Per 1 mg/dL increase	1.115 (1.087–1.144)	<.001
GGT, IU/L	47.0 (27.0, 97.0)	Per doubling of mg/dL	1.194 (1.138–1.252)	<.001
Platelet count, ×10 ⁹ /L	202.0 (164.0, 244.0)	Per 1 unit increase	<250: 0.999 (0.998–1.001) >250: 1.002 (1.001–1.004)	.004
Hemoglobin, g/dL	13.4 (12.1, 14.7)	Per 1 mg/dL increase	0.917 (0.886–0.949)	<.001

Data presented as median (25th, 75th) or number (%), unless otherwise indicated.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; CI, confidence interval; CV, cardiovascular; EF, ejection fraction; eGFR, estimate glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

recent worsening HF event (either HF hospitalization in the prior 6 months or outpatient intravenous diuretics in the prior 3 months), a phenotype now specifically referenced in the US Food and Drug Administration label indication for vericiguat, with global participant representation and a longer follow-up duration than earlier short-term models (median follow-up of >10 months). Notably, many of the acute HF models included a mixture of both patients with HFrEF and patients with HF with preserved ejection

fraction and/or explored only shorter term clinical outcomes (ie, ≤6 months).

Although multiple prior HF risk models have been developed,⁶ many of these were developed in patients with chronic HF rather than the higher risk group with a recent worsening. For instance, risk models were developed in ambulatory chronic patients with HFrEF for the MAGGIC, HF-ACTION, Seattle HF, and more recently the PARADIGM-HF models.^{9–12} Risk models in the acute HF setting

Table 2. Predictive Model for the Primary Outcome of HF Hospitalization or Cardiovascular Death

Variable	χ^2 Test	P Value	HR (95% CI)
NT-proBNP (per doubling of pg/mL)	73.36	<.001	1.25 (1.18–1.31)
Chloride (per 5 mmol/L increase)	42.40	<.001	0.79 (0.74–0.85)
NYHA functional class III/IV (ref: class I/II)	25.55	<.001	1.39 (1.23–1.59)
Albumin (per 1 g/dL increase)	14.04	<.001	0.74 (0.64–0.87)
History of MI	17.55	<.001	1.31 (1.16–1.49)
Urate (per 1 mg/dL increase)	14.92	<.001	1.05 (1.03–1.08)
Bilirubin (per 0.5 mg/dL increase)	14.41	<.001	1.10 (1.05–1.15)
Time from first HF diagnosis to randomization (per doubling of years)	19.20	<.001	1.08 (1.04–1.12)
Index event (ref: HF hospitalization within 3 months)			
HF hospitalization 3–6 months	4.47	0.035	0.83 (0.69–0.99)
IV diuretic for HF (without hospitalization) within 3 months	9.81	0.002	0.73 (0.60–0.89)

CI, confidence interval; HF, heart failure; HR, hazard ratio; IV, intravenous; MI, myocardial infarction; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; NYHA, New York Heart Association.

include the OPTIMIZE-HF,¹³ OPTIME,¹⁴ ASCEND-HF,¹⁵ PROTECT,¹⁶ ESCAPE,¹⁷ GWTG-HF,¹⁸ and the more recent GUIDE-IT risk model.¹⁹ The BIOSTAT risk model

was developed in patients with worsening symptoms, either in the hospital or in the outpatient setting, and had a high clinical event rate.²⁰ Although the patient populations, study designs (registry vs trial), study end points, and specific variables in these models differ to some extent, there are a number of consistent clinical characteristics with prognostic usefulness in patients with HF. In general, variables that are independently associated with morbidity and mortality outcomes include key demographic features (age, sex, race), measures of HF type or severity (left ventricular ejection fraction, NYHA functional class, ischemic etiology), comorbidity burden (particularly renal and lung disease as well as diabetes), vital sign abnormalities (heart rate, blood pressure, body mass index), HF medication/device therapies, and laboratory values such as those reflecting renal dysfunction (creatinine/GFR) and the renin–angiotensin–aldosterone system activation (hyponatremia). For instance, the GUIDE-IT model for HF hospitalization or cardiovascular death that was developed in patients with HFrEF and recent clinical worsening in the prior 12 months included NYHA functional class, NT-proBNP, heart rate, sodium, serum creatinine, and implantable cardioverter defibrillator use. Many of the variables in the VICTORIA models are consistent with these previously identified predictors. We demonstrate the consistent prognostic usefulness of commonly recognized risk variables such as NT-proBNP, NYHA functional class, and prior myocardial infarction across all of the different morbidity and mortality end points in VICTORIA, and also highlight the

Fig. 1. Calibration plot for the model for the primary end point (cardiovascular death or heart failure [HF] hospitalization).

Table 3a. Summary of the Different End Point Risk Models by Variable Category With Comparison to the Primary End Point Model*

End Point	Trial and Demographic Details	HF Details	PMH	Physical Examination	Medications and Devices	Laboratories	ECG
CV death or HF hospitalization		HF duration Index HF event (hospitalization and IV diuretic) NYHA functional class	MI			NT-proBNP, Bilirubin, Chloride, Urate, Albumin	
All-cause mortality of HF hospitalization		HF duration Index HF event NYHA functional class	MI	+Pulse*	+ICD*	NT-proBNP, Bilirubin, Chloride, Urate, Albumin, +eGFR*	
CV death	+ Enrolling region*	HF duration (No index event) NYHA functional class	MI	+ SBP*		NT-proBNP, Bilirubin, Chloride, Urate, Albumin	+QTc
All-cause mortality	+ Enrolling region*	HF duration (No index event) NYHA functional class	MI	+ SBP*		NT-proBNP, Bilirubin, Chloride, Urate, Albumin	

The optimism-corrected C-index for the HF hospitalization or cardiovascular death model was 0.68. Optimism-corrected c-indices were 0.68 for HF hospitalization/all-cause death, 0.72 for cardiovascular death, and 0.73 for all-cause death.

CV, cardiovascular; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IV, intravenous; MI, myocardial infarction; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

*This variable was added to the model compared with the primary end point (HF hospitalization or cardiovascular death) and text with a mark through (eg, indicates that the variable is not present in the secondary end point model compared with the primary end point.

Table 3b. Variable selection results for each outcome presented by variable.

Variable	Primary (Placebo)	HF Hospitalization/ All-Cause Death (Placebo)	CV Death (Placebo)	All-Cause Death (Placebo)	No. of Models Present In
NT-proBNP	X	X	X	X	4
NYHA	X	X	X	X	4
Chloride	X	X	X	X	4
Prior MI	X	X	X	X	4
Duration of HF	X	X	X		3
Albumin	X	X		X	3
SBP			X	X	2
Region			X	X	2
Bilirubin	X	X			2
Index event	X				1
Urate	X				1
QTc			X		1
eGFR		X			1
ICD		X			1
Pulse		X			1

prognostic usefulness of less commonly emphasized markers such as chloride, bilirubin, and albumin.

In the VICTORIA models, several novel prognostic variables were identified that have not been reported consistently in earlier models. For instance, the independent association of laboratory values such as chloride is notable. The serum chloride level is not a laboratory metric that is emphasized routinely in patients with HF in terms of prognostic value. However, hyponatremia has been associated with worse outcomes in several reports.^{21,22} In fact, some have hypothesized that the poor prognosis that has been previously linked with hyponatremia may actually be related to

hypochloremia.²² Hypochloremia is associated with neuro-hormonal activation and diuretic resistance and a small pilot study suggested that sodium-free chloride supplementation increased serum chloride levels and favorably affected several cardiorenal parameters.²² A further assessment of the prognostic usefulness of hypochloremia in other HF datasets is warranted.

In addition to more novel laboratory values, the prognostic usefulness of the index worsening HF event (either recent hospitalization or outpatient intravenous diuretics) in VICTORIA was also noteworthy. Recent data from PARADIGM-HF have highlighted the prognostic usefulness of

outpatient worsening HF events in the population with chronic HFrEF.²³ Further, recent data from VICTORIA have provided additional insights regarding the hazard associated with proximity to worsening HF events.²⁴

Whereas the VICTORIA models support many of the traditional prognostic variables, they also add incremental insights regarding several novel variables. However, as highlighted in a recent analysis of the prognostic usefulness of several HF risk scores in a European registry, the overall performance of most HF risk scores is modest (eg, c-indices of 0.71–0.74 for mortality) and they are not routinely used in clinical practice.²⁵ The discriminatory capacity of the VICTORIA models (c-indices from 0.68–0.73) is similar to these earlier models, but it is important to note the unique nature of the derivation population of HFrEF with recent clinical worsening and the excellent calibration of the model.

Several limitations of these results are worth noting. Given the lack of a large, comparable dataset inclusive of the comprehensive variable list to externally validate these findings, we were only able to perform internal validation. Although the discriminatory capacity of the VICTORIA models were higher for the fatal end points of cardiovascular and all-cause mortality (c-indices of 0.72–0.73), the discriminatory capacity for the primary end point of HF hospitalization or cardiovascular death was lower (c-index of 0.68). These observations are consistent with prior HF models where the prediction of nonfatal end points such as rehospitalization are more difficult, potentially related in part to the heterogeneity of their determinants.^{14,16} Furthermore, these models were developed in a high-risk group of patients with HFrEF; additional investigation would be warranted to explore their prognostic usefulness in patients at a lower risk of events and those with HF with preserved ejection fraction. The study cohort also was that of a clinical trial, which tend to have comparatively less representation of elderly participants, women, and minorities as well as those with a higher burden of comorbidities than in clinical practice.^{26,27} Moreover, the utilization of newer therapies like sacubitril/valsartan and sodium-glucose transport protein 2 inhibitors was modest given multifactorial delays in the implementation of these evidence-based therapies in HFrEF during the 16-month recruitment period ending December 21, 2018.

Conclusions

Predictive models developed in a large diverse clinical trial with extensive clinical and laboratory data—including novel measures—performed well in high-risk patients with HF who were receiving excellent guideline-based clinical care. These models refining patient prognosis may further guide clinical decision-making and future clinical trial design.

Disclosures

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Supplementary materials

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References

- Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, et al. Clinical course of patients with worsening heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019;73:935–44.
- Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol* 2015;12:220–9.
- Simpson J, Jhund PS, Silva Cardoso J, Martinez F, Mosterd A, Ramires F, et al. Comparing LCZ696 with enalapril according to baseline risk using the MAGGIC and EMPHASIS-HF risk scores: an analysis of mortality and morbidity in PARADIGM-HF. *J Am Coll Cardiol* 2015;66:2059–71.
- Ferreira JP, Duarte K, McMurray JJV, Pitt B, van Veldhuisen DJ, Vincent J, et al. Data-driven approach to identify subgroups of heart failure with reduced ejection fraction patients with different prognoses and aldosterone antagonist response patterns. *Circ Heart Fail* 2018;11:e004926.
- Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020;382:1883–93.
- Ouwkerk W, Voors AA, Zwinderman AH. Factors influencing the predictive power of models for predicting mortality and/or heart failure hospitalization in patients with heart failure. *JACC Heart Fail* 2014;2:429–36.
- Armstrong PW, Roessig L, Patel MJ, Anstrom KJ, Butler J, Voors AA, et al. A multicenter, randomized, double-blind, placebo-controlled trial of the efficacy and safety of the oral soluble guanylate cyclase stimulator: the VICTORIA trial. *JACC Heart Fail* 2018;6:96–104.
- Pieske B, Patel MJ, Westerhout CM, Angstrom KJ, Butler J, Ezekowitz J, et al. Baseline features of the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial. *Eur J Heart Fail* 2019;21:1596–604.
- Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;34:1404–13.
- O'Connor CM, Whellan DJ, Wojdyla D, Leifer E, Clare RM, Ellis SJ, et al. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail* 2012;5:63–71.
- Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006;113:1424–33.
- Simpson J, Jhund PS, Lund LH, Padmanabhan S, Claggett BL, Shen L, et al. Prognostic models derived in PARADIGM-HF and validated in ATMOSPHERE and the Swedish Heart Failure Registry to predict mortality and morbidity in chronic heart failure. *JAMA Cardiol* 2020;5:432–41.
- O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2008;156:662–73.
- Felker GM, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams KF Jr, et al. Risk stratification after hospitalization for decompensated heart failure. *J Card Fail* 2004;10:460–6.
- Khazanie P, Heizer GM, Hasselblad V, Armstrong PW, Califf RM, Ezekowitz J, et al. Predictors of clinical outcomes in acute decompensated heart failure: Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure outcome models. *Am Heart J* 2015;170:290–7.
- O'Connor CM, Mentz RJ, Cotter G, Metra M, Cleland JG, Davison BA, et al. The PROTECT in-hospital risk model: 7-day outcome in patients hospitalized with acute heart failure and renal dysfunction. *Eur J Heart Fail* 2012;14:605–12.
- O'Connor CM, Hasselblad V, Mehta RH, Tassisa G, Califf RM, Fiuzat M, et al. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol* 2010;55:872–8.
- Eapen ZJ, Liang L, Fonarow GC, Heidenreich PA, Curtis LH, Peterson ED, et al. Validated, electronic health record deployable prediction models for assessing patient risk of 30-day rehospitalization and mortality in older heart failure patients. *JACC Heart Fail* 2013;1:245–51.
- O'Connor C, Fiuzat M, Mulder H, Coles A, Ahmad T, Ezekowitz JA, et al. Clinical factors related to morbidity and mortality in high-risk heart failure patients: the GUIDE-IT predictive model and risk score. *Eur J Heart Fail* 2019;21:770–8.
- Voors AA, Ouwkerk W, Zannad F, van Veldhuisen DJ, Samani NJ, Ponikowski P, et al. Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. *Eur J Heart Fail* 2017;19:627–34.
- Cuthbert JJ, Pellicori P, Rigby A, Pan D, Kazmi S, Shah P, et al. Low serum chloride in patients with chronic heart failure: clinical associations and prognostic significance. *Eur J Heart Fail* 2018;20:1426–35.
- Hanberg JS, Rao V, Ter Maaten JM, Laur O, Brisco MA, Perry Wilson F, et al. Hypochloremia and diuretic resistance in heart failure: mechanistic insights. *Circulation Heart Fail* 2016;9:e003180.
- Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, et al. Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF). *Circulation* 2016;133:2254–62.
- Lam CSP, Giczevska A, Sliwa K, Edelmann F, Refsgaard J, Bocchi E, et al. Clinical outcomes and response to vericiguat according to index heart failure event: insights from the VICTORIA trial. *JAMA Cardiol* 2020 Nov 13. <https://doi.org/10.1001/jamacardio.2020.6455>. Online ahead of print.
- Canepa M, Fonseca C, Chioncel O, Laroche C, Crespo-Leiro MG, Coats AJS, et al. Performance of prognostic risk scores in chronic heart failure patients enrolled in the European Society of Cardiology heart failure long-term registry. *JACC Heart Fail* 2018;6:452–62.
- Greene SJ, DeVore AD, Sheng S, Fonarow GC, Butler J, Califf RM, et al. Representativeness of a heart failure trial by race and sex: results from ASCEND-HF and GWTG-HF. *JACC Heart Fail* 2019;7:980–92.
- Tahhan AS, Vaduganathan M, Greene SJ, Fonarow GC, Fiuzat M, Jessup M, et al. Enrollment of older patients, women, and racial and ethnic minorities in contemporary heart failure clinical trials: a systematic review. *JAMA Cardiol* 2018;3:1011–9.