The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 14, 2020 VOL. 382 NO. 20

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

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ABSTRACT

BACKGROUND

The effect of vericiguat, a novel oral soluble guanylate cyclase stimulator, in patients with heart failure and reduced ejection fraction who had recently been hospitalized or had received intravenous diuretic therapy is unclear.

METHODS

In this phase 3, randomized, double-blind, placebo-controlled trial, we assigned 5050 patients with chronic heart failure (New York Heart Association class II, III, or IV) and an ejection fraction of less than 45% to receive vericiguat (target dose, 10 mg once daily) or placebo, in addition to guideline-based medical therapy. The primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure.

RESULTS

Over a median of 10.8 months, a primary-outcome event occurred in 897 of 2526 patients (35.5%) in the vericiguat group and in 972 of 2524 patients (38.5%) in the placebo group (hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; P=0.02). A total of 691 patients (27.4%) in the vericiguat group and 747 patients (29.6%) in the placebo group were hospitalized for heart failure (hazard ratio, 0.90; 95% CI, 0.81 to 1.00). Death from cardiovascular causes occurred in 414 patients (16.4%) in the vericiguat group and in 441 patients (17.5%) in the placebo group (hazard ratio, 0.93; 95% CI, 0.81 to 1.06). The composite of death from any cause or hospitalization for heart failure occurred in 957 patients (37.9%) in the vericiguat group and in 1032 patients (40.9%) in the placebo group (hazard ratio, 0.90; 95% CI, 0.83 to 0.98; P=0.02). Symptomatic hypotension occurred in 9.1% of the patients in the vericiguat group and in 7.9% of the patients in the placebo group (P=0.12), and syncope occurred in 4.0% of the patients in the vericiguat group and in 3.5% of the patients in the placebo group (P=0.30).

CONCLUSIONS

Among patients with high-risk heart failure, the incidence of death from cardiovascular causes or hospitalization for heart failure was lower among those who received vericiguat than among those who received placebo. (Funded by Merck Sharp & Dohme [a subsidiary of Merck] and Bayer; VICTORIA ClinicalTrials.gov number, NCT02861534.)

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This article was published on March 28, 2020, at NEJM.org.

N Engl J Med 2020;382:1883-93.
DOI: 10.1056/NEJMoa1915928

A Quick Take is available at NEJM.org

Heart failure with a reduced ejection fraction imposes a substantial health care burden, particularly among patients for whom rehospitalization or urgent outpatient treatment for heart failure is warranted despite the use of guideline-based medical therapy. New treatment options are desirable in this high-risk group, and the prognosis is poor compared with that of patients for whom hospitalization within 1 year or urgent treatment for heart failure is not warranted.[1]

Vericiguat, a novel oral soluble guanylate cyclase stimulator, enhances the cyclic guanosine monophosphate (GMP) pathway by directly stimulating soluble guanylate cyclase through a binding site independent of nitric oxide, and it sensitizes soluble guanylate cyclase to endogenous nitric oxide by stabilizing nitric oxide binding to the binding site.[2] In a phase 2b dose-finding trial involving patients with worsening high-risk heart failure and a reduced ejection fraction, vericiguat reduced the level of N-terminal pro–B-type natriuretic peptide (NT-proBNP).[3] In the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA), we assessed the efficacy and safety of vericiguat in patients with a reduced ejection fraction and chronic heart failure with recent decompensated heart failure. This population of patients with worsening symptoms for which medical attention is warranted is at risk for death and hospitalization for heart failure.

METHODS

TRIAL DESIGN AND OVERSIGHT

VICTORIA was a multinational, randomized, double-blind, placebo-controlled trial; the trial methods have been described previously.[4] The executive committee designed the trial with national leaders from participating countries and regions and oversaw operations in collaboration with the Canadian VIGOUR Centre and the trial cosponsors, Merck and Bayer.[4] The trial protocol (available with the full text of this article at NEJM.org) was approved by regulatory agencies in the participating countries and institutional review boards or ethics committees at the participating sites. An independent data and safety monitoring committee evaluated patient safety.

The sponsors participated in the trial design, selection of participating centers, site monitoring, and data storage. Analyses were conducted by the sponsors and independently replicated at the Duke Clinical Research Institute (DCRI). The sponsors, the Canadian VIGOUR Centre and the DCRI, and the executive committee participated in the interpretation of the data. The first author had unrestricted access to the data and drafted the initial version of the manuscript, which was reviewed and edited by all the authors. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENT ENROLLMENT

Eligible patients were at least 18 years of age and had chronic heart failure (New York Heart Association [NYHA] functional class II, III, or IV), a reduced left ventricular ejection fraction of less than 45% within 12 months before randomization, and an elevated natriuretic peptide level (determined at the trial sites) within 30 days before randomization. For patients in sinus rhythm, the criteria included a plasma B-type natriuretic peptide (BNP) level of at least 300 pg per milliliter or an NT-proBNP level of at least 1000 pg per milliliter. For patients in atrial fibrillation, the criteria included a BNP level of at least 500 pg per milliliter or an NT-proBNP level of at least 1600 pg per milliliter.

Patients also had to have evidence of worsening heart failure. They were categorized into three cohorts based on the timing of the deterioration: those hospitalized within 3 months before randomization, those hospitalized 3 to 6 months before randomization, and those receiving intravenous diuretic therapy, without hospitalization, within the previous 3 months.[4] The percentage of enrolled patients with an estimated glomerular filtration rate of 15 to 30 ml per minute per 1.73 m^2 of body-surface area was capped at 15%. All the patients received guideline-based medical therapy; the inclusion of patients who were receiving sacubitril–valsartan background therapy (in countries where it was available) was encouraged.

Exclusion criteria included a systolic blood pressure of less than 100 mm Hg; concurrent or anticipated use of long-acting nitrates, soluble guanylate cyclase stimulators, or phosphodiesterase type 5 inhibitors; and use of intravenous inotropes or implantable left ventricular assist devices. A full list of inclusion and exclusion cri-

teria is provided in the Supplementary Appendix, available at NEJM.org.

TRIAL CONDUCT

All the patients provided informed consent and entered a screening period (0 to 30 days), without a run-in period, during which adherence to the entry criteria was confirmed. Patients were then randomly assigned, in a 1:1 ratio, to 2.5 mg of vericiguat or matching placebo, within six strata based on geographic region and, within North America, race. Doses were increased to 5 mg and ultimately to the target dose of 10 mg once daily in a blinded manner, as guided by evaluation of blood pressure and clinical symptoms (see the Supplementary Appendix).[4] Patients were evaluated at weeks 2 and 4, and every 4 months thereafter until the end of the trial. To enhance the likelihood of achieving and maintaining the target dose of 10 mg, investigators were encouraged to address dosing at each visit according to the patient's blood pressure and symptomatic status. The follow-up visit schedule is detailed in the protocol.[4]

TRIAL OUTCOMES

The primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure. The secondary outcomes were the components of the primary outcome, first and subsequent hospitalizations for heart failure, a composite of death from any cause or first hospitalization for heart failure, and death from any cause. Prespecified safety outcomes of clinical interest included symptomatic hypotension and syncope.[4] Members of an independent clinical-events committee who were unaware of the trial-group assignments adjudicated all deaths, hospitalizations for cardiovascular causes, and urgent visits for heart failure (definitions are provided in the Supplementary Appendix).

STATISTICAL ANALYSIS

The sample size was determined to provide adequate power for the assessment of the outcome of death from cardiovascular causes. The expected event rate among patients in the placebo group at 12 months was 11%. Assuming a hazard ratio of 0.80 for the outcome of death from cardiovascular causes, we estimated that a sample of 4872 patients, with an expected 782 events, would provide the trial with 80% power. A total of 1561 primary outcome events were expected. For the primary outcome, this sample size was expected to provide approximately 98% power. These calculations were performed with the use of the log-rank test and a one-sided type I error rate of 0.025. The data and safety monitoring committee reviewed the trial on a regular basis. Interim futility and efficacy analyses were planned but did not occur because of enrollment that was more rapid than expected and a higher than anticipated rate of death from cardiovascular causes.

A hierarchical testing strategy was prespecified for the following secondary outcomes: total hospitalizations for heart failure, the composite of death from any cause or first hospitalization for heart failure, and death from any cause. P values are reported for the primary outcome and for subsequent secondary outcomes until the first outcome with a P value of greater than 0.05. P values are not reported for the components of the primary outcome because these analyses were not controlled for multiple comparisons.

Efficacy outcomes were examined in the intention-to-treat population with the use of time-to-event analyses; data on patients who withdrew from the trial or were lost to follow-up were censored at the last available follow-up time. Analyses used stratified log-rank tests with the same strata considered for randomization. Hazard ratios and associated 95% confidence intervals were obtained with the use of stratified Cox regression models. Subgroup analyses were conducted using a stratified Cox regression model that included trial group and the subgroup variable of interest. The outcome of total hospitalizations for heart failure was analyzed with the use of an Andersen–Gill model with robust standard errors to account for possible correlation among patients who had recurrent events.[5] Safety analyses included all patients who received a trial drug.

Baseline characteristics are summarized as means and standard deviations or medians and interquartile ranges for continuous variables and as counts and percentages for categorical variables. All the analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

Between September 25, 2016, and December 21, 2018, a total of 6857 patients were screened in 42 countries, and 5050 were enrolled at 616 sites

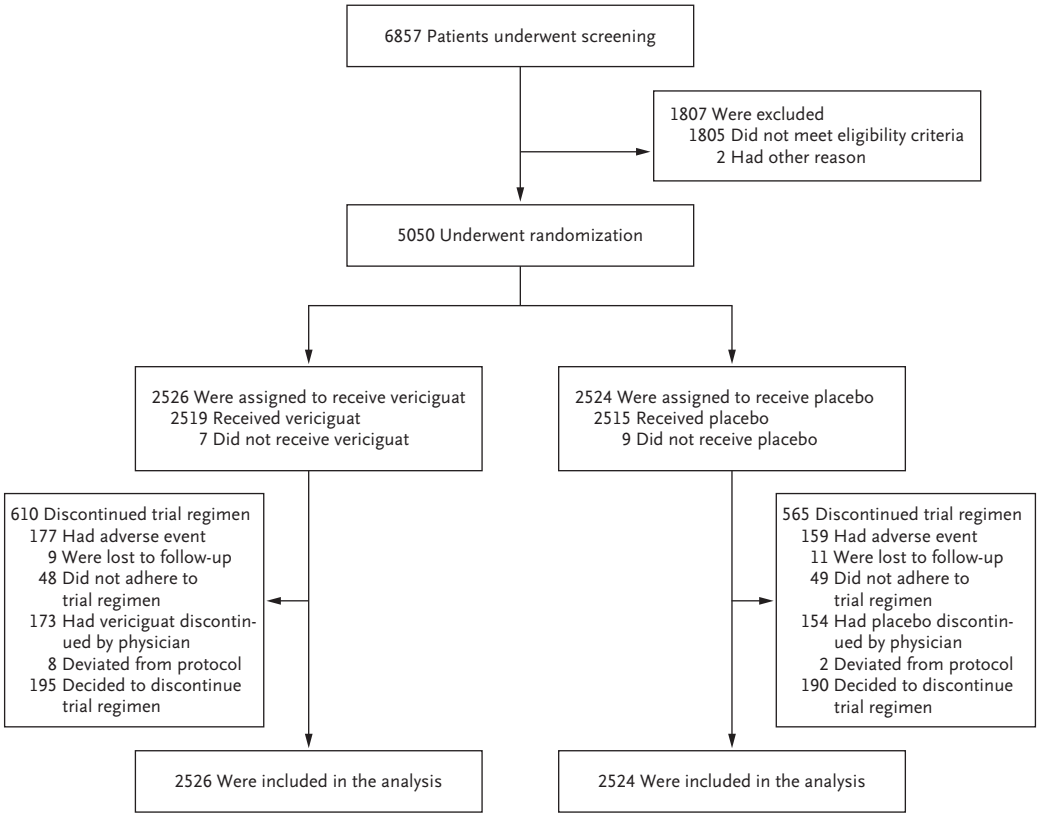


Figure 1. Screening, Randomization, and Follow-up.

Reasons for exclusion are listed in the Supplementary Appendix. Some patients had more than one reason for exclusion.

(Fig. 1).[6] Reasons for exclusion of the other 1807 patients are provided in the Supplementary Appendix. A total of 2526 patients were randomly assigned to receive vericiguat, and 2524 were assigned to receive placebo; 7 patients and 9 patients, respectively, did not receive the assigned vericiguat or placebo.

The baseline characteristics were well matched in the two groups (Table 1 and Table S1 in the Supplementary Appendix). The mean age of the enrolled patients was 67 years, and 24% were women. At randomization, two thirds of the patients had been enrolled within 3 months of their index hospitalization for heart failure, 40% were classified as having NYHA class III heart failure, and the mean ejection fraction was 29%. The median NT-proBNP level was 2816 pg per milliliter, as determined in a central laboratory.

The use of concomitant guideline-based medical therapy was well balanced in the two groups: 60% of the patients received triple therapy (a beta-blocker and a mineralocorticoid antagonist combined with either an angiotensin-converting–enzyme inhibitor, an angiotensin-receptor blocker, or sacubitril–valsartan) and 15% received an angiotensin–neprilysin inhibitor. Notably, 32% of the patients had an implantable cardioverter–defibrillator, a biventricular pacemaker, or both devices. Adherence to the trial drug was greater than 80% in 93.8% of the patients in the vericiguat group and in 93.4% of the patients in the placebo group. The median dose of trial medication was 9.2 mg in the vericiguat group and 9.2 mg in the placebo group. After approximately 12 months, 90.3% of the patients were receiving the 10-mg target dose (89.2% in the vericiguat group and 91.4% in the placebo group).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Vericiguat (N=2526)	Placebo (N=2524)	Total (N=5050)
Mean age — yr	67.5±12.2	67.2±12.2	67.3±12.2
Sex — no. (%)			
Male	1921 (76.0)	1921 (76.1)	3842 (76.1)
Female	605 (24.0)	603 (23.9)	1208 (23.9)
Race — no. (%)†			
White	1621 (64.2)	1618 (64.1)	3239 (64.1)
Black	123 (4.9)	126 (5.0)	249 (4.9)
Asian	571 (22.6)	561 (22.2)	1132 (22.4)
Other	211 (8.4)	219 (8.7)	430 (8.5)
Geographic region — no. (%)			
Eastern Europe	848 (33.6)	846 (33.5)	1694 (33.5)
Western Europe	443 (17.5)	446 (17.7)	889 (17.6)
Asia–Pacific	592 (23.4)	591 (23.4)	1183 (23.4)
Latin America	362 (14.3)	362 (14.3)	724 (14.3)
North America	281 (11.1)	279 (11.1)	560 (11.1)
Index event — no. (%)			
Hospitalization for heart failure in previous 3 mo	1673 (66.2)	1705 (67.6)	3378 (66.9)
Hospitalization for heart failure in previous 3–6 mo	454 (18.0)	417 (16.5)	871 (17.2)
Intravenous diuretic for heart failure (without hospitalization) in previous 3 mo	399 (15.8)	402 (15.9)	801 (15.9)
Mean body-mass index‡	27.7±5.8	27.9±6.1	27.8±5.9
Mean ejection fraction at screening — %	29.0±8.3	28.8±8.3	28.9±8.3
Ejection fraction <40% — no. (%)	2158 (85.8)	2158 (85.6)	4316 (85.7)
NYHA class — no./total no. (%)			
I	0	2/2523 (0.1)	2/5046 (<0.1)
II	1478/2523 (58.6)	1497/2523 (59.3)	2975/5046 (59.0)
III	1010/2523 (40.0)	993/2523 (39.4)	2003/5046 (39.7)
IV	35/2523 (1.4)	31/2523 (1.2)	66/5046 (1.3)
Mean time from initial diagnosis of heart failure with reduced ejection fraction to randomization — yr	4.7±5.5	4.8±5.4	4.8±5.4

* Plus–minus values are means ±SD. Data were missing for the following characteristics: body-mass index (for 17 patients in the vericiguat group and 20 patients in the placebo group), ejection fraction (for 10 patients in the vericiguat group and 4 patients in the placebo group), and time from initial diagnosis of heart failure with reduced ejection fraction to randomization (for 1 patient in the vericiguat group and 3 patients in the placebo group). Percentages may not total 100 because of rounding. NYHA denotes New York Heart Association.
† Race was reported by the patient. In North America, there were 62 black patients in the vericiguat group and 61 in the placebo group.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

FOLLOW-UP AND TRIAL OUTCOMES

During the trial, 610 patients in the vericiguat group and 565 patients in the placebo group discontinued the trial regimen (Fig. 1). Of these patients, 195 in the vericiguat group discontinued vericiguat and 9 were lost to follow-up, and 190 patients in the placebo group discontinued placebo and 11 were lost to follow-up. Ascertainment for the primary outcome was complete for 99.5% and 99.6% of potential patient-years of follow-up in the vericiguat group and the placebo group, respectively. The median follow-up period was 10.8 months.

Death from cardiovascular causes or first hos-

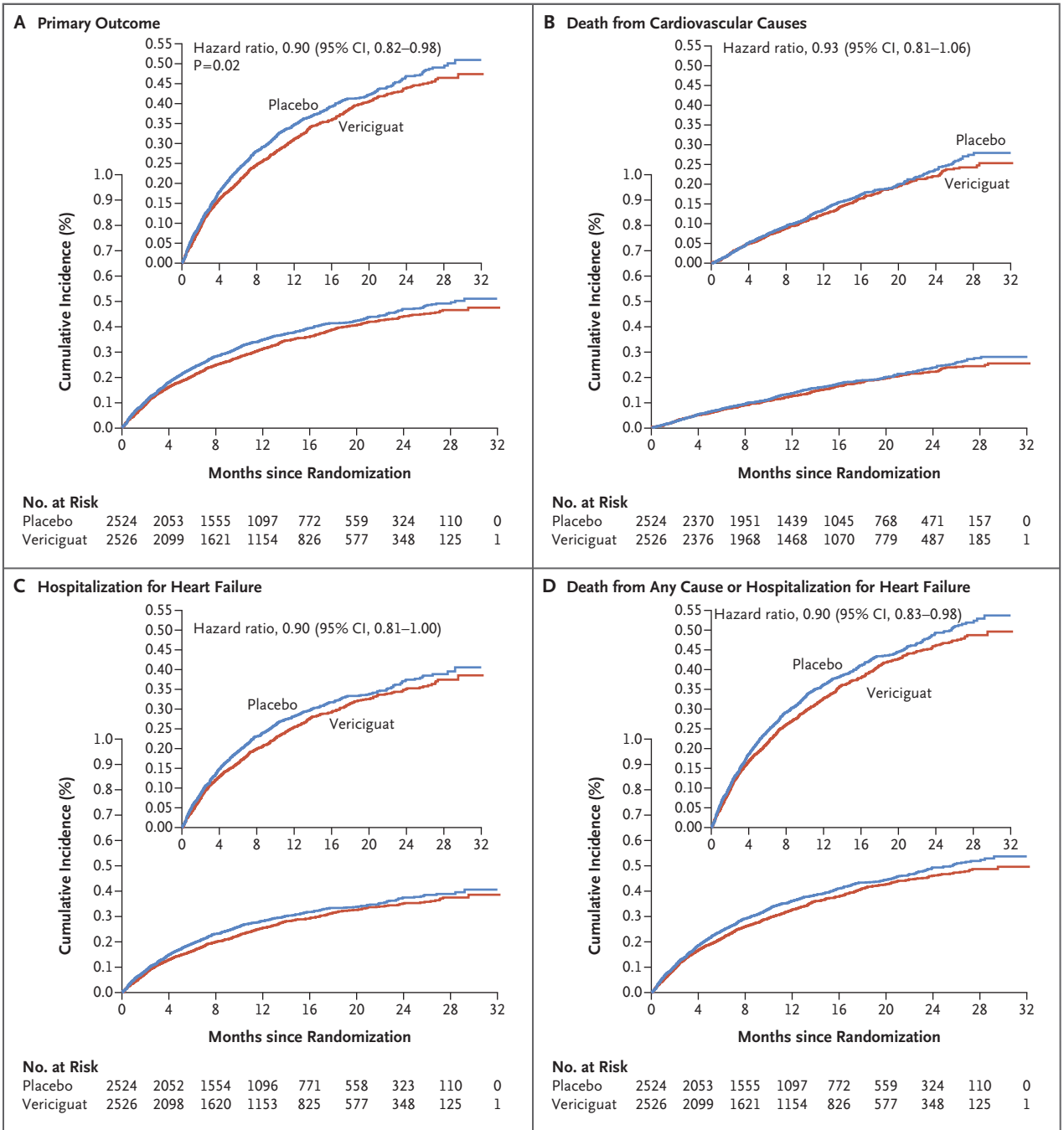


Figure 2. Estimates of the Cumulative Incidence of the Primary Outcome and Secondary Outcomes.

The primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure (Panel A). Shown are the cumulative incidences of death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and the secondary composite outcome (death from any cause or first hospitalization for heart failure) (Panel D). The inset in each panel shows the same data on an enlarged y axis.

pitalization for heart failure (the primary outcome) occurred in 897 patients (35.5%) in the vericiguat group and in 972 patients (38.5%) in the placebo group (hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; P=0.02) (Fig. 2A and Table 2). Death from cardiovascular causes occurred in

Table 2. Primary and Secondary Outcomes.*

Outcome	Vericiguat (N=2526)		Placebo (N=2524)		Hazard Ratio (95% CI)†	P Value‡
	no. (%)	*events/100 patient-yr*	*no. (%)*	*events/100 patient-yr*		
Primary composite outcome and components						
Death from cardiovascular causes or first hospitalization for heart failure	897 (35.5)	33.6	972 (38.5)	37.8	0.90 (0.82–0.98)	0.02
Death from cardiovascular causes§	206 (8.2)		225 (8.9)			
Hospitalization for heart failure	691 (27.4)		747 (29.6)			
Secondary outcomes						
Death from cardiovascular causes	414 (16.4)	12.9	441 (17.5)	13.9	0.93 (0.81–1.06)	
Hospitalization for heart failure	691 (27.4)	25.9	747 (29.6)	29.1	0.90 (0.81–1.00)	
Total hospitalizations for heart failure¶	1223	38.3	1336	42.4	0.91 (0.84–0.99)	0.02
Secondary composite outcome and components						
Death from any cause or first hospitalization for heart failure	957 (37.9)	35.9	1032 (40.9)	40.1	0.90 (0.83–0.98)	0.02
Death from any cause§	266 (10.5)		285 (11.3)			
Hospitalization for heart failure	691 (27.4)		747 (29.6)			
Death from any cause	512 (20.3)	16.0	534 (21.2)	16.9	0.95 (0.84–1.07)	0.38

* Data shown are through the primary analysis cutoff date (June 18, 2019). For patients with multiple events, only the first event that contributed to the composite outcome is counted. CI denotes confidence interval.
† Hazard ratios (vericiguat as compared with placebo) and confidence intervals were calculated with the use of Cox proportional-hazards models controlling for stratification factors (defined according to geographic region and race).
‡ P values were calculated by means of a stratified log-rank test with stratification factors defined according to geographic region and race.
§ Deaths included in the primary and secondary composite outcomes were not preceded by a hospitalization for heart failure.
¶ Patients could have been hospitalized more than once.

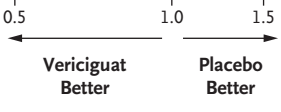
414 patients (16.4%) in the vericiguat group and in 441 patients (17.5%) in the placebo group (hazard ratio, 0.93; 95% CI, 0.81 to 1.06) (Fig. 2B and Table 2). Hospitalization for heart failure occurred in 691 patients (27.4%) in the vericiguat group and in 747 patients (29.6%) in the placebo group (hazard ratio, 0.90; 95% CI, 0.81 to 1.00) (Fig. 2C and Table 2).

There were 1223 total hospitalizations (first and recurrent events) for heart failure (38.3 events per 100 patient-years) in the vericiguat group and 1336 total hospitalizations (42.4 events per 100 patient-years) in the placebo group (hazard ratio, 0.91; 95% CI, 0.84 to 0.99; P=0.02) (Table 2). Death from any cause or first hospitalization for heart failure (a composite secondary outcome) occurred in 957 patients (37.9%) in the vericiguat group and in 1032 patients (40.9%) in the placebo group (hazard ratio, 0.90; 95% CI, 0.83 to 0.98; P=0.02) (Fig. 2D and Table 2). Death from any cause occurred in 512 patients (20.3%) in the vericiguat group and in 534 patients (21.2%) in the placebo group (hazard ratio, 0.95; 95% CI, 0.84 to 1.07; P=0.38) (Fig. S1 and Table 2). The effect of vericiguat on the primary outcome was consistent across most prespecified subgroups (including patients receiving sacubitril–valsartan), except in the subgroups defined according to age and NT-proBNP level (Fig. 3).

SAFETY

Serious adverse events occurred in 32.8% of the patients in the vericiguat group and in 34.8% of the patients in the placebo group (Table S2). Adverse events (serious and nonserious) occurred in 80.5% of the patients receiving vericiguat and in

Subgroup	Vericiguat	Placebo	Hazard Ratio (95% CI)
	no. of events		
All patients	897	972	0.90 (0.82–0.98)
Sex			
Male	704	762	0.90 (0.81–1.00)
Female	193	210	0.88 (0.73–1.08)
Age			
<65 yr	290	348	0.81 (0.70–0.95)
≥65 yr	607	624	0.94 (0.84–1.06)
<75 yr	579	669	0.84 (0.75–0.94)
≥75 yr	318	303	1.04 (0.88–1.21)
Race			
White	593	635	0.91 (0.81–1.02)
Asian	199	207	0.91 (0.75–1.11)
Black	41	50	0.85 (0.56–1.28)
Other	64	80	0.80 (0.57–1.11)
Geographic region			
Eastern Europe	310	345	0.87 (0.75–1.01)
Western Europe	173	178	0.96 (0.78–1.18)
North America	103	117	0.85 (0.65–1.10)
Latin America	100	116	0.83 (0.63–1.08)
Asia–Pacific	211	216	0.96 (0.79–1.16)
Race in North America			
Black	26	29	0.93 (0.55–1.58)
Nonblack	77	88	0.82 (0.60–1.11)
Index event			
Intravenous diuretic in previous 3 mo	96	120	0.78 (0.60–1.02)
Hospitalization in previous 3 mo	660	701	0.93 (0.84–1.04)
Hospitalization in previous 3–6 mo	141	151	0.85 (0.67–1.07)
NYHA class			
I or II	445	484	0.91 (0.80–1.04)
III or IV	451	487	0.87 (0.77–0.99)
Use of sacubitril–valsartan			
Yes	134	153	0.88 (0.70–1.11)
No	760	818	0.90 (0.81–0.99)
Estimated GFR			
≤30 ml/min/1.73 m^2	143	128	1.06 (0.83–1.34)
>30 to ≤60 ml/min/1.73 m^2	392	455	0.84 (0.73–0.96)
>60 ml/min/1.73 m^2	346	372	0.92 (0.80–1.07)
NT-proBNP level			
Quartile 1 (≤1556.0 pg/ml)	128	161	0.78 (0.62–0.99)
Quartile 2 (>1556.0 to ≤2816.0 pg/ml)	165	201	0.73 (0.60–0.90)
Quartile 3 (>2816.0 to ≤5314.0 pg/ml)	213	257	0.82 (0.69–0.99)
Quartile 4 (>5314.0 pg/ml)	355	302	1.16 (0.99–1.35)
Ejection fraction			
<35%	637	703	0.88 (0.79–0.97)
≥35%	255	265	0.96 (0.81–1.14)
<40%	773	851	0.88 (0.80–0.97)
≥40%	119	117	1.05 (0.81–1.36)



81.0% of the patients receiving placebo (Table S3). The prespecified adverse events of clinical interest were symptomatic hypotension and syncope. Symptomatic hypotension occurred in 9.1% of the patients in the vericiguat group and in 7.9% of the patients in the placebo group (P=0.12), and syncope occurred in 4.0% of patients in the vericiguat group and in 3.5% of patients in the

Figure 3 (facing page). Primary Outcome in Prespecified Subgroups.

The primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure. Race was reported by the patient. Data were missing for the following subgroups: New York Heart Association (NYHA) class (for 1 patient in the vericiguat group and 1 patient in the placebo group), use of sacubitril–valsartan (for 3 patients in the vericiguat group and 1 patient in the placebo group), estimated glomerular filtration rate (GFR) (for 16 patients in the vericiguat group and 17 patients in the placebo group), N-terminal pro–B-type natriuretic peptide (NT-proBNP) level (for 36 patients in the vericiguat group and 51 patients in the placebo group), and ejection fraction (for 5 patients in the vericiguat group and 4 patients in the placebo group).

placebo group (P=0.30) (Table S4). Baseline systolic blood pressure was 121.2 mm Hg in the vericiguat group and 121.5 mm Hg in the placebo group. Systolic blood pressure declined slightly in both groups over the first 16 weeks (more so in the vericiguat group than in the placebo group) and returned to baseline thereafter (Fig. S2).

Anemia developed in more patients in the vericiguat group than in the placebo group (in 7.6% and 5.7%); of these cases, 1.6% (in the vericiguat group) and 0.9% (in the placebo group) were considered serious adverse events. The baseline mean (±SD) hemoglobin level was 13.3±1.9 g per deciliter in the vericiguat group and 13.4±1.9 g per deciliter in the placebo group, and the change from baseline in the hemoglobin level at week 16 was −0.38±1.27 g per deciliter and −0.14±1.30, respectively.

DISCUSSION

In this trial involving patients with chronic heart failure and a reduced ejection fraction who had worsening symptoms for which hospitalization or urgent treatment was warranted, the incidence of the composite of death from cardiovascular causes or hospitalization for heart failure was lower with vericiguat than with placebo. The difference favoring vericiguat appeared after approximately 3 months of treatment and persisted throughout the trial. The 10% relative difference between the groups in the primary composite outcome in this high-risk population at a median follow-up of 10.8 months translated into an absolute event-rate reduction of 4.2 events per 100 patient-years. Based on this absolute risk reduction, the number needed to treat with vericiguat for 1 year to prevent a primary-outcome event is approximately 24 patients (or 28 patients according to the difference in 12-month Kaplan–Meier estimates). This outcome occurred in patients who were receiving guideline-based medical therapy.

An analysis of the components of the primary outcome revealed that the incidence of hospitalization for heart failure was lower with vericiguat than with placebo, and the incidence of death from cardiovascular causes was possibly lower. There was no significant between-group difference in the incidence of death from any cause. However, it is noteworthy that the prespecified events were accrued earlier than expected, thereby leaving a relatively short exposure time and potentially limiting our assessment of a later effect.

It is of interest to compare the current trial population with those of two previous trials involving patients with heart failure and a reduced ejection fraction. In the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting-Enzyme Inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure) and the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trials, 25% and 32% of the patients, respectively, had either NYHA class III or IV heart failure, as compared with 41% of the patients in VICTORIA. Similarly, the median NT-proBNP values were 1608 and 1437 pg per milliliter in PARADIGM-HF and DAPA-HF, respectively, as compared with 2816 pg per milliliter in VICTORIA.[7-9] These differences probably account for the 33.6% annualized rate of the primary composite outcome in the vericiguat group in our trial; this is more than two times as high as that seen in the two comparator trials.[9,10] Although both of these trials showed more substantial relative reductions in the primary composite outcome of VICTORIA (a composite of death from cardiovascular causes or first hospitalization for heart failure), the annualized reductions in absolute risk are similar.[11]

A review of the treatment effect across prespecified subgroups indicates a generally consistent treatment effect, even in subgroups defined by the index heart failure event. Whether the patients with very elevated NT-proBNP levels are a subgroup with heart failure that is too advanced

for a favorable effect of vericiguat rather than the play of chance is uncertain. Other high-risk baseline characteristics that affect treatment responses, such as advanced age and diminished renal function, probably coexist within this subgroup and other subgroups. Because of the small number of patients who were already receiving inhibitors of sodium–glucose cotransporter 2, we cannot address the potential incremental role of vericiguat in this population.

As expected, symptomatic hypotension and syncope were more common in the patients receiving vericiguat than in those receiving placebo. At the initial 16-week follow-up visit, the hemoglobin level was slightly lower in the patients receiving vericiguat than in those receiving placebo, as previously reported for this class of agents.[12] The overall frequency of adverse events was similar in the two groups, as were adverse events related to renal function or electrolyte balance.

Modulation of the nitric oxide–soluble guanylate cyclase pathway that generates cyclic GMP is essential for normal cardiovascular function. In heart failure, endothelial dysfunction and reactive oxygen species reduce nitric oxide bioavailability, resulting in relative deficiency of soluble guanylate cyclase and reduced cyclic GMP generation.[13] In contrast to the therapeutic approach of antagonizing counterregulatory neurohormonal pathways characteristic of many other therapies for heart failure, vericiguat enhances the cyclic GMP pathway by directly stimulating soluble guanylate cyclase through a binding site independent of nitric oxide and by sensitizing soluble guanylate cyclase to endogenous nitric oxide.[2] This selectivity in cyclic GMP generation does not occur with nitrates or phosphodiesterase inhibitors.

Heart failure remains a major burden, with many patients facing a considerable risk of death or recurrent hospitalization.[14] Projections suggest that the prevalence will continue to increase, and more than 8 million people in the United States are estimated to have heart failure by 2030, approximately half of whom will have reduced ejection fraction.[15] Adherence to medications is frequently challenging because of side effects, resulting in decreased adherence to guideline-recommended therapies over 2 to 4 months after discharge.[16,17] Given these factors, it is crucial for patients to have treatment options. This is especially true in the emerging era of precision medicine, since patients and providers are searching for personalized treatment based on anticipated benefits, a favorable side-effect profile, value, and ease of use.[18] In this regard, it is noteworthy that there was greater than 89% adherence to the target 10-mg dose of vericiguat after 12 months in our trial.

In conclusion, we conducted a multinational clinical trial involving patients with chronic heart failure who had evidence of clinical worsening. Patients were randomly assigned to receive either the oral soluble guanylate cyclase stimulator vericiguat or placebo. At a median of 10.8 months, the incidence of the primary outcome of death from cardiovascular causes or first hospitalization for heart failure was significantly lower with vericiguat than with placebo.

Supported by Merck Sharp & Dohme, a subsidiary of Merck (Kenilworth, NJ), and Bayer (Wuppertal, Germany).

Dr. Armstrong reports receiving grant support from Sanofi-Aventis Research and Development, Boehringer Ingelheim, and CSL, and consulting fees from AstraZeneca and Novartis; Dr. Pieske, receiving grant support, paid to his institution, advisory board fees, and lecture fees from Servier, lecture fees from Bristol-Myers Squibb, Medscape, and Daiichi Sankyo, and fees for serving on an executive committee, lecture fees, advisory board fees, and travel support from Novartis; Dr. Ezekowitz, receiving grant support and fees for clinical trial site leadership from Servier, Amgen, Sanofi, Novartis, Cytokinetics, American Regent, and Applied Therapeutics; Dr. Hernandez, receiving consulting fees from Amgen, grant support and consulting fees from AstraZeneca and Novartis, and grant support from Verily; Dr. Butler, receiving consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, G3 Pharmaceuticals, Janssen, American Regent, Medtronic, Novartis, Vifor Pharma, and Novo Nordisk; Dr. Lam, receiving grant support and advisory board fees from Boston Scientific and Roche Diagnostics, grant support, advisory board fees, and fees for serving on a steering committee from AstraZeneca, grant support from Medtronic, grant support and fees for serving on a steering committee from Vifor Pharma, advisory board fees and fees for serving on a steering committee from Novartis, advisory board fees from Amgen, Boehringer Ingelheim, Abbott Diagnostics, Novo Nordisk, Biofourmis, and MyoKardia, consulting fees from Stealth BioTherapeutics, Jana Care, Darma, Cytokinetics, WebMD Global, Radcliffe Group, and Corpus, fees for serving on a steering committee from Janssen Research and Development, Corvia Medical, and Applied Therapeutics, and lecture fees and consulting fees from Menarini Group, holding pending patent PCT/SG2016/050217 on a method for the diagnosis and prognosis of chronic heart failure, holding pending patent 16/216,929 on an automatic clinical workflow that recognizes and analyses two-dimensional and Doppler modality endocardiography, and receiving fees for serving as cofounder and nonexecutive director of eko.ai; Dr. Ponikowski, receiving fees for participation in clinical trials, consulting fees, and lecture fees from Novartis, Boehringer Ingelheim, Respicardia, AstraZeneca, and RenalGuard Solutions, grant support, fees for participation in clinical trials, consulting fees, and lecture fees

from Vifor Pharma and Servier, fees for serving in clinical trials and consulting fees from Bristol-Myers Squibb and Cibiem, and lecture fees from Berlin Chemie; Dr. Voors, receiving consulting fees from Amgen, AstraZeneca, Cytokinetics, MyoKardia, Novartis, and Servier, and grant support and consulting fees from Boehringer Ingelheim and Roche Diagnostics; Dr. Roessig, being employed by Bayer; and Dr. O'Connor, receiving consulting fees from Dey and Bristol-Myers Squibb Foundation. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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