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Sacubitril/Valsartan vs Enalapril in Heart Failure Due to Chagas Disease
An Open-Label, Multicenter Randomized Clinical Trial

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IMPORTANCE The efficacy and safety of guideline-recommended treatments for heart failure (HF) are uncertain in patients with Chagas disease.

OBJECTIVE To evaluate the efficacy and safety of the angiotensin receptor-neprilysin inhibitor sacubitril/valsartan in patients with HF with reduced ejection fraction due to Chagas disease.

DESIGN, SETTING, AND PARTICIPANTS From December 10, 2019, through September 13, 2023, patients with HF, confirmed diagnosis of Chagas disease, left ventricular ejection fraction of 40% or less, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 600 pg/mL or greater (or B-type natriuretic peptide [BNP] ≥150 pg/mL) or 400 pg/mL or greater (or BNP ≥100 pg/mL) if hospitalized for HF within the previous 12 months were screened at 83 sites in Argentina, Brazil, Colombia, and Mexico. Statistical analysis was conducted between May and July 2025.

INTERVENTIONS Patients were randomized to receive sacubitril/valsartan (target dose, 200 mg twice daily) or enalapril (target dose, 10 mg twice daily), in addition to standard therapy.

MAIN OUTCOMES AND MEASURES The primary end point was a hierarchical composite outcome tested, in order, of death from cardiovascular causes, hospitalization for HF, or relative change in NT-proBNP from baseline to 12 weeks. The primary analysis was done using a win ratio approach.

RESULTS Overall, 462 participants were randomized to receive sacubitril/valsartan and 460 to receive enalapril (mean [SD] age, 64.2 [10.8] years; 387 [42.0%] were female). Over a median (IQR) follow-up of 25.2 (18.4-33.2) months, cardiovascular death occurred in 110 patients (23.8% [18.3% wins in the hierarchical comparison]) in the sacubitril/valsartan group and 117 patients (25.4% [17.5% wins]) in the enalapril group. A total of 102 patients (22.1% [7.7% wins]) in the sacubitril/valsartan group and 111 (24.1% [6.9% wins]) in the enalapril group experienced a first hospitalization for HF. Patients in the sacubitril/valsartan group had a median (IQR) decrease in NT-proBNP of 30.6% (−54.3% to −0.9%) at 12 weeks, leading to 22.5% wins, while those in the enalapril group had a 5.5% (−31.9% to 37.5%) decrease (7.2% wins). The resulting stratified win ratio was 1.52 (95% CI, 1.28-1.82; $P < .001$) for sacubitril/valsartan compared with enalapril.

CONCLUSIONS AND RELEVANCE In patients with HF with reduced ejection fraction due to Chagas disease, there was no significant difference in clinical outcomes between sacubitril/valsartan and enalapril, but there was a greater reduction in NT-proBNP at 12 weeks in patients in the sacubitril/valsartan group.

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Group Information: The Prevention and Reduction of Adverse Outcomes in Chagasic Heart Failure Trial Evaluation (PARACHUTE-HF) Investigators appear in Supplement 4.

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Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*, affects more than 10 million people worldwide but is still a neglected disease.[1-4] The infection is transmitted directly by the triatomine bug (vector-borne) as well as orally through contaminated food (food-borne), blood transfusion, organ transplant, unintentional laboratory exposure, or congenitally.[5] Also known as *American trypanosomiasis*, Chagas disease is endemic to Latin America and increasingly prevalent in the US, where an estimated 200 000 to 300 000 people are affected.[1,6] Evidence now supports the inclusion of the US as an endemic country for Chagas disease, reflecting ongoing local transmission and the presence of the parasite in vectors, animals, and humans.[7] Persisting social inequities and ecological shifts driven by climate change and deforestation are likely to increase disease transmission.[8] Cases have also been reported in Spain and other European countries due to migration.[9,10]

The most common and severe complication of Chagas disease in its chronic phase is cardiomyopathy, which occurs in 30% to 40% of persons who are infected and can present as chronic myocarditis, conduction system abnormalities, cardioembolic episodes, heart failure (HF), and sudden death.[5,11,12] Chagas cardiomyopathy is distinguished by its unique clinical features, including focal myocardial fibrosis, arrhythmogenicity, and ventricular aneurysm formation as well as a markedly high mortality rate, even in the absence of typical comorbidities.[13] The reasons patients with HF due to Chagas disease have such a poor prognosis are not fully understood but may include persistent immune-mediated myocardial inflammation triggered by chronic parasitic infection, hypercoagulable state, right ventricular dysfunction, microvascular dysfunction, autonomic disturbance, high rates of ventricular arrhythmias, elevated risk of stroke, conduction disturbances, and ventricular aneurysm formation.[5,13,14]

Whether guideline-recommended medical therapies for HF are effective in patients with Chagas cardiomyopathy is unknown. No randomized clinical trial to date has been powered to test the efficacy and safety of any treatment in patients with HF caused by Chagas disease, and these patients were not adequately represented in pivotal HF trials.[14] Although large randomized clinical trials are lacking, enalapril was selected as the comparator as a standard of care for HF management, including in patients with Chagas cardiomyopathy. The study by Szajnbok et al demonstrated that enalapril improved functional class and reduced heart size in patients with chronic Chagas heart disease, suggesting a beneficial hemodynamic effect.[15] More recently, Penitente et al reported that enalapril reduced myocardial fibrosis and improved cardiac function in a murine model of chronic Chagas disease, supporting its role in modulating disease progression.[16] Sacubitril/valsartan may offer incremental benefit over enalapril in patients with Chagas disease not only through neurohormonal and vasodilator effects but also by mitigating myocardial fibrosis and arrhythmias.[14] Additionally, fully understanding the safety of HF treatments in this population is important, as these patients have more dysfunction of the right ventricle and lower blood pressure compared with other HF etiologies.[14]

Key Points

Question Are guideline-recommended treatments for heart failure (HF) effective and safe in patients with Chagas disease?

Findings This trial found that in patients with heart failure with reduced ejection fraction (HFrEF) due to Chagas cardiomyopathy, sacubitril/valsartan was not significantly different from enalapril in the composite outcome of cardiovascular death or hospitalization for HF, but led to a greater reduction in N-terminal pro-B-type natriuretic peptide.

Meaning In patients with HFrEF due to Chagas disease, sacubitril/valsartan did not result in better clinical outcomes.

Therefore, the PARACHUTE-HF (Prevention and Reduction of Adverse Outcomes in Chagasic Heart Failure Trial Evaluation) trial was designed to prospectively evaluate the efficacy and safety of the angiotensin receptor-neprilysin inhibitor sacubitril/valsartan in patients with HF with reduced ejection fraction (HFrEF) caused by Chagas disease.

Methods

Trial Design and Oversight

The study design has been published.[14] In brief, PARACHUTE-HF (NCT04023227) was an international, multicenter, parallel-group, event-driven, randomized, active-controlled, and open-label trial with blinded end point adjudication. Patients with HFrEF caused by Chagas disease received sacubitril/valsartan (at a target dose of 200 mg twice daily [97 mg sacubitril/103 mg valsartan]) or enalapril (at a target dose of 10 mg twice daily), in addition to standard therapy. The steering committee designed and oversaw the conduct of the trial and the analysis of the data in collaboration with the Brazilian Clinical Research Institute (BCRI) and the sponsor (Novartis). The BCRI was responsible for site management, monitoring, clinical events adjudication, safety surveillance, data management, study drug supply, and statistical analyses.

The trial progression and safety and efficacy data were reviewed by an independent data monitoring committee. The trial protocol (Supplement 1) was approved by an institutional review board at each trial center, and all participants in the trial provided written informed consent.

Patients

Eligibility requirements included age 18 years or older and at least 2 positive serological test results for *T cruzi* (each based on different methodological principles or antigenic preparations). The serological assays used could include enzyme-linked immunosorbent assay, indirect immunofluorescence, indirect hemagglutination, Western blot, or chemiluminescent immunoassay. In situations where a prior documented history was unavailable, these tests were performed during the screening phase. Patients were also required to have a left ventricular ejection fraction (LVEF) of 40% or less, New York Heart Association (NYHA) functional class II to IV, and a plasma level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) of

at least 600 pg/mL (or B-type natriuretic peptide [BNP] ≥150 pg/mL) or NT-proBNP of at least 400 pg/mL (or BNP ≥100 pg/mL) if hospitalized for HF within the previous 12 months. NT-proBNP was measured by a central laboratory. Key exclusion criteria were systolic blood pressure lower than 95 mm Hg, serum potassium greater than 5.2 mmol/L, and estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 of body surface area. Detailed eligibility criteria are described in the protocol (Supplement 1).

Randomization

Patients who met the eligibility requirements were randomly assigned in a 1:1 ratio to receive sacubitril/valsartan or enalapril, in addition to their usual therapy, stratified by country, using a central, concealed, web-based, automated randomization system. Both groups entered a titration period of 3 to 6 weeks, aiming to achieve the target dose of sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily.

Outcomes

The primary end point, analyzed as a win ratio, was a hierarchical composite outcome tested in order of (1) time to cardiovascular death, (2) time to first hospitalization for HF, and (3) relative change from baseline to week 12 in NT-proBNP concentration. For the third tier, a win required a greater reduction or smaller increase in NT-proBNP, with a relative change of at least 25%.

The following secondary end points were analyzed without adjustment of *P* values or CIs for multiple comparisons: time to death from any cause, time to sudden death or resuscitated cardiac arrest, number of emergency department visits for HF where intravenous therapy was administered, number of days alive and out of the hospital, and total (first and recurrent) hospitalizations for HF and deaths from cardiovascular causes. Study clinical end points were adjudicated by an independent clinical events committee whose members were blinded to treatment randomization. At every visit, sites were instructed to report all deaths and hospitalizations, irrespective of the cause, as triggers for the clinical events committee review. The reviewers were blinded to treatment randomization during the entire adjudication process.

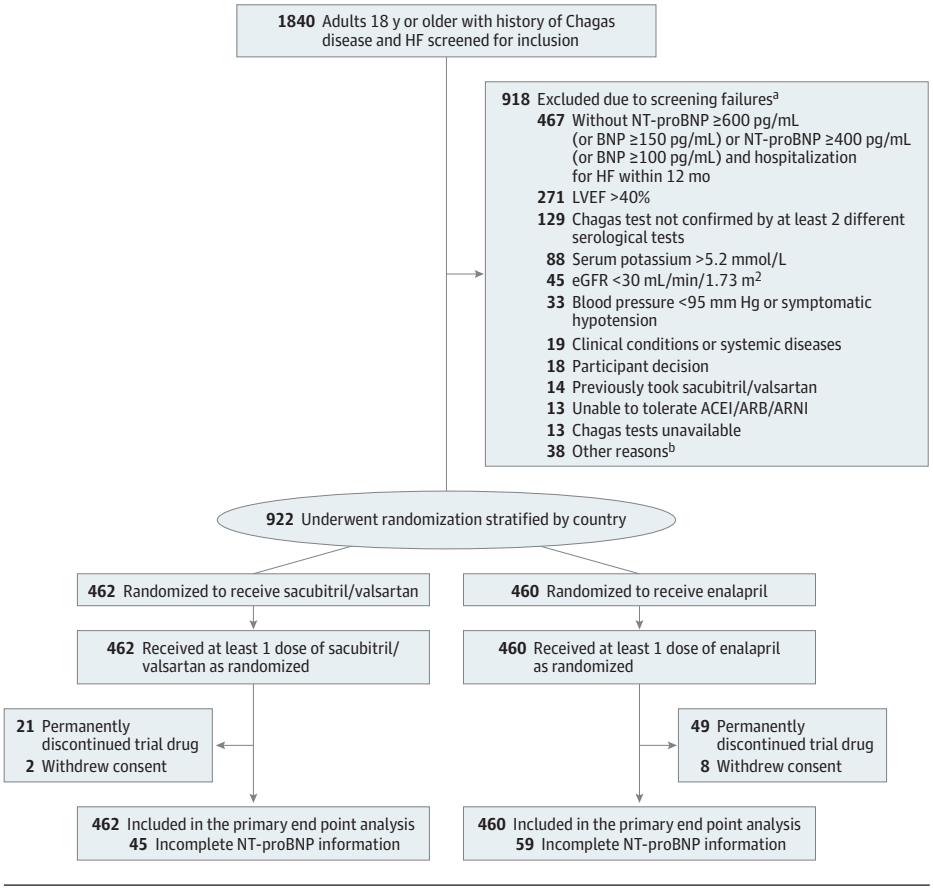
Adverse events were collected throughout the trial in a dedicated form and analyzed in patients who had received at least 1 dose of the study drug. Adverse events of special interest included angioedema, symptomatic hypotension, arrhythmia, hyperkalemia, and kidney dysfunction. All adverse events were classified using MedDRA (Medical Dictionary for Regulatory Activities) version 27.0.

Statistical Analysis

Statistical analysis was conducted between May and July 2025. All patients were included in the analyses according to the intention-to-treat principle. The primary end point was analyzed using an unmatched win ratio, with treatment as a fixed effect and stratified by country.[17,18] With this approach, every participant in the sacubitril/valsartan group was compared with every participant in the enalapril group in each stratum. All pairs were first compared by time to cardiovascular death; participants with a longer time alive were considered the winners. If there was no winner, they were then compared by time to first hospitalization for HF; again, participants with a longer period of follow-up free of hospitalization were declared the winners. In the event of a tie for these first 2 tiers of the hierarchy (ie, within the shorter follow-up time between the participants in the match none had died from cardiovascular causes nor were hospitalized due to HF), the pair was compared according to change in NT-proBNP from baseline to week 12. If the ratio of the NT-proBNP change with sacubitril/valsartan vs enalapril was lower than 0.75, then sacubitril/valsartan was declared the winner, and if the ratio of change with enalapril vs sacubitril/valsartan was lower than 0.75, enalapril was declared the winner. Both participants must have had a valid NT-proBNP value; if either value was missing or invalid, the match was considered a tie. Time-to-event comparisons were performed within the minimum follow-up time of each patient pair. Follow-up was censored at the date of noncardiovascular death, the date of withdrawal of informed consent, or otherwise at the date of the last visit. The overall number of wins was divided by the number of losses for sacubitril/valsartan compared with enalapril and weighted by the inverse of the stratum size to calculate the win ratio. The win ratio was tested with a 2-sided α level of .05. Time-to-event data were evaluated with the use of Kaplan-Meier estimates and Cox proportional hazards models stratified according to country, with treatment group randomization as a fixed effect. We used the Cox models to calculate hazard ratios (HRs) and 95% CIs and a semiparametric proportional rates model to calculate total (including recurrent) events.[19] As an additional analysis, Fine-Gray competing risk models were applied to estimate subdistribution HRs for HF hospitalization, considering death as a competing risk.[20] For NT-proBNP, an analysis of covariance model was used to analyze the ratio of geometric mean of NT-proBNP from baseline to week 12, with treatment and country as fixed effects and baseline log(NT-proBNP) concentration as a covariate. The number of visits to an emergency department for HF (where intravenous therapy was administered) was analyzed using a generalized linear model assuming a negative binomial distribution, using follow-up time as an offset. The mean difference in the number of days alive and out of hospital within 1 year was compared between treatment groups using a linear regression model adjusted by country.

The sample size calculation was based on published event rates in patients with Chagas cardiomyopathy, and we assumed a rate of 20 events per 100 participant-years for the composite of time to first hospitalization for HF or cardiovascular death in the enalapril group, a relative risk reduction of 20% with sacubitril/valsartan, and a relative between-treatment difference in change in NT-proBNP from baseline to week 12 of at least 25%.[6] We prespecified that superiority of sacubitril/valsartan over enalapril would be declared if the win ratio was significantly greater than 1.0, based upon a 2-sided significance level of 5% and 2 further criteria were met: the point estimate of the HR for sacubitril/valsartan compared with enalapril for cardiovascular death was less than 1.0 and the same was true for time to first hospitalization for HF. Based on these assumptions, a trial size of 900 participants, an anticipated 302 patients experiencing the composite of cardiovascular death

Figure 1. Flow of Patients in a Study of Sacubitril/Valsartan vs Enalapril for Patients With Heart Failure (HF) Caused by Chagas Disease



ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

[a]Categories were not mutually exclusive.

[b]Included, in order: total bilirubin greater than 3.0 mg/dL, medical decision, severe gastrointestinal form of chronic Chagas disease, participant on a list for a heart transplant, previous coronary surgery, death, alcohol or drug misuse, history of suspected or proven angioedema, and ineffective contraceptive methods.

or time to first hospitalization for HF, and at least a 25% relative change of NT-proBNP lower in the sacubitril/valsartan group would provide an overall power of 85% with a 2-sided α of 5%. The decision to base the study on 302 events was also expected to provide approximately 50% power to detect the HR of 0.80 assumed in the sample size simulations.

Prespecified subgroup analyses included those based upon age; sex; race and ethnicity; NYHA class; estimated glomerular filtration rate; systolic blood pressure; LVEF; duration of HF; diabetes; history of atrial fibrillation, hypertension, or HF hospitalization; prior use of renin-angiotensin system blockers or sodium-glucose cotransporter 2 (SGLT2) inhibitors; and randomization before January 1, 2022 (end of the COVID-19 pandemic). Details of the subgroup analyses are provided in the statistical analysis plan (Supplement 2).

All analyses were performed using R version 4.4.2 (R Foundation). This study follows the International Council for Harmonisation reporting guidelines.

Results

Enrollment, Randomization, and Follow-Up

From December 10, 2019, through September 13, 2023, a total of 1840 patients from 83 sites in Brazil, Argentina, Colombia, and Mexico were screened, and 922 were randomized to receive sacubitril/valsartan or enalapril (eTable 1 in Supplement 3) and included in the primary efficacy analysis (**Figure 1**). Two patients in the sacubitril/valsartan group and 8 in the enalapril group withdrew consent. No patients were lost to follow-up. A total of 94.5% of the follow-up was done through in-person visits. The median (IQR) duration of follow-up was 25.2 (18.4-33.2) months. Overall, 21 patients (4.5%) in the sacubitril/valsartan group and 49 (10.7%) in the enalapril group permanently discontinued trial medication for reasons other than death before the end of follow-up (eTable 2 in Supplement 3). By the week 12 visit, 270 patients (60.4%) in the sacubitril/valsartan group and 271 (61.5%) in the enalapril group were receiving the target dose of the assigned study drug (eFigure 1 in Supplement 3).

The baseline characteristics of the patients were balanced between the 2 groups (**Table 1**). The mean (SD) age was 64.2 (10.8) years, 387 participants (42.0%) were female, and 502 (54.4%) self-identified as White. The mean (SD) LVEF was 29.8% (7.2%) and the median (IQR) NT-proBNP was 1730 (854-3451) pg/mL. Overall, 352 participants (38.2%) were in NYHA functional class III to IV; 250 (27.1%) had a pacemaker; 155 (16.8%) had an implantable cardioverter-defibrillator; and 727 (78.9%) had been treated with a renin-angiotensin system inhibitor, 839 (91.0%) with a β-blocker, 678 (73.5%) with

Table 1. Baseline Demographics and Disease Characteristics by Treatment Group

Characteristic	No. (%)	
	Sacubitril/valsartan group (n = 462)	Enalapril group (n = 460)
Demographics		
Age, mean (SD), y	64.1 (10.6)	64.2 (11.0)
Sex		
Female	186 (40.3)	201 (43.7)
Male	276 (59.7)	259 (56.3)
Race and ethnicity[a]		
Black	70 (15.2)	70 (15.2)
Native South American	24 (5.2)	18 (3.9)
White	246 (53.2)	256 (55.7)
Mixed ethnicity[b]	122 (26.4)	116 (25.2)
Country		
Brazil	293 (63.4)	298 (64.8)
Argentina	112 (24.2)	108 (23.5)
Colombia	45 (9.7)	43 (9.3)
Mexico	12 (2.6)	11 (2.4)
BMI, mean (SD)	26.2 (5.2)	26.2 (5.2)
Medical history		
Prior hospitalization due to HF	210 (45.5)	199 (43.3)
Hypertension	186 (40.3)	187 (40.7)
Atrial fibrillation	145 (31.4)	136 (29.6)
Ventricular arrhythmia	110 (23.8)	118 (25.7)
Diabetes	70 (15.2)	68 (14.8)
Stroke	55 (11.9)	60 (13.0)
Myocardial infarction	18 (3.9)	22 (4.8)
Previous antiparasitic treatment	19 (4.1)	21 (4.6)
Chronic obstructive pulmonary disease	19 (4.1)	17 (3.7)
Atrial flutter	14 (3.0)	18 (3.9)
Peripheral vascular disease	10 (2.2)	12 (2.6)
Clinical features of HF		
Left ventricular ejection fraction, mean (SD), %	29.8 (7.1)	29.9 (7.3)
NYHA classification[c]		
I	1 (0.2)	0
II	285 (61.7)	284 (61.7)
III	158 (34.2)	161 (35.0)
IV	18 (3.9)	15 (3.3)
Systolic blood pressure, mean (SD), mm Hg	119 (17)	117 (16)
Pulse, mean (SD), beats/min	67 (12)	68 (11)
Treatments at randomization		
β-Blocker	419 (90.7)	420 (91.3)
ACEI or ARB[d]	364 (78.8)	363 (78.9)
ACEI[d]	223 (48.3)	229 (49.8)
ARB[d]	141 (30.5)	134 (29.1)
Mineralocorticoid receptor antagonist	337 (72.9)	341 (74.1)
Loop or thiazide/ thiazide-like diuretic	328 (71.0)	317 (68.9)
Anticoagulant	210 (45.5)	205 (44.6)
Amiodarone	148 (32.0)	141 (30.7)
Aspirin	70 (15.2)	76 (16.5)
SGLT2 inhibitors	21 (4.5)	37 (8.0)
Digoxin/digitalis glycoside	1 (0.2)	2 (0.4)
Pacemaker	136 (29.4)	114 (24.8)
Implantable cardioverter-defibrillator[e]	78 (16.9)	77 (16.7)
Cardiac resynchronization therapy	9 (2.0)	10 (2.2)
Baseline laboratory results		
NT-proBNP, median (IQR), pg/mL[f]	1801 (922-3686)	1679 (812-3220)
Estimated glomerular filtration rate[g]		
Value, mean (SD), mL/min/1.73 m^2	69.9 (22.6)	69.7 (23.6)
<60 mL/min/1.73 m^2	159 (34.4)	173 (37.6)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium glucose cotransporter 2.

[a] Race and ethnicity were defined by the investigator from a predefined list, with an additional "Other" option allowing free-text entry.

[b] Includes Latino, Brown/pardo, mestizo, mixed race, and multiracial identities.

[c] NYHA functional classification: class I (no limitation of ordinary physical activity), class II (slight limitation; comfortable at rest, but ordinary activity causes symptoms), class III (marked limitation; comfortable at rest, but less than ordinary activity causes symptoms), and class IV (severe limitation; symptoms present even at rest). Classification was determined by the investigator based on patient symptoms and clinical evaluation.

[d] At screening.

[e] Implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator.

[f] Normal range is less than 125 pg/mL.

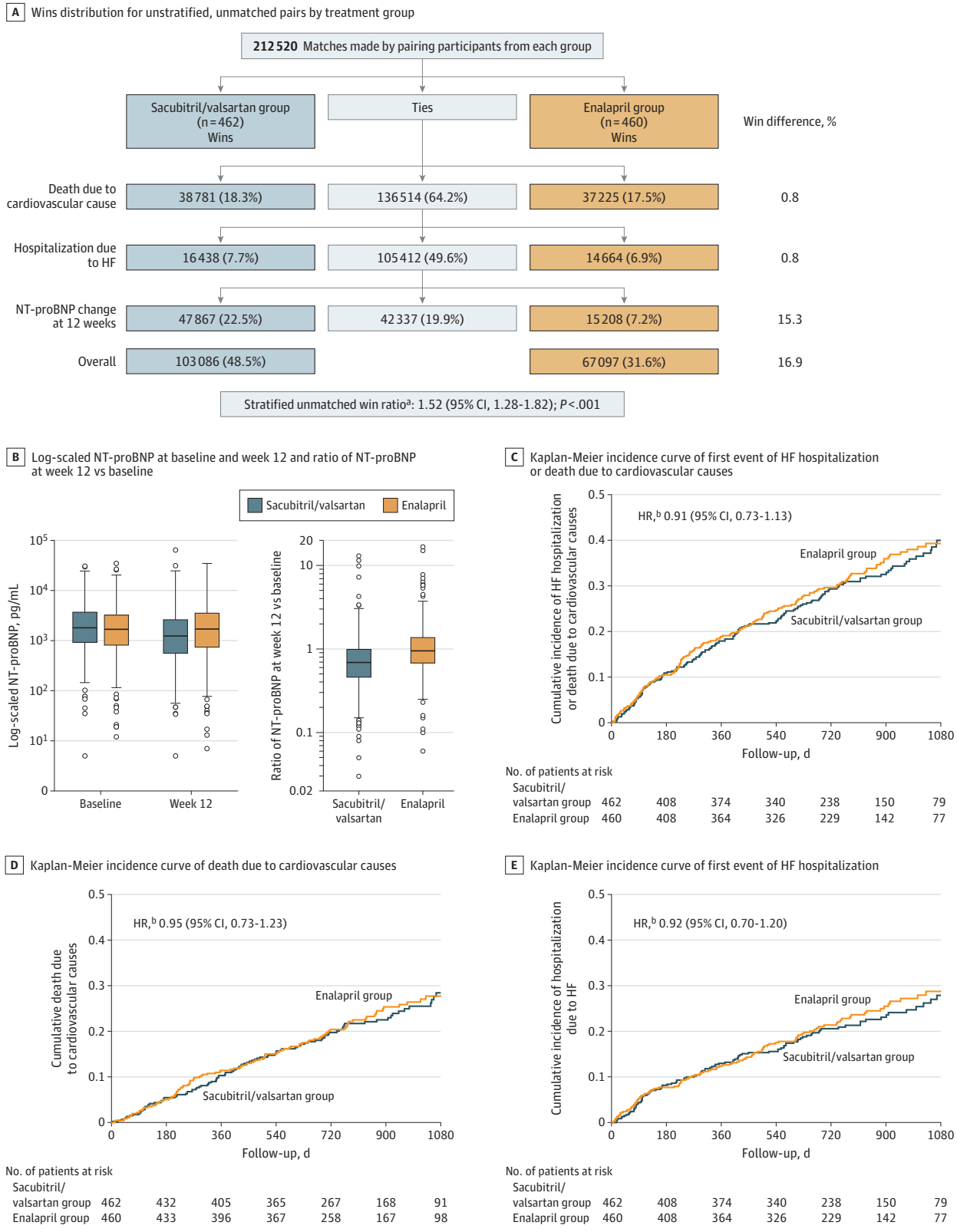
[g] Estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Normal range is greater than 60 mL/min/1.73 m^2.

a mineralocorticoid receptor antagonist, and 58 (6.3%) with an SGLT2 inhibitor (eTable 3 in Supplement 3).

Efficacy

The win ratio for the primary hierarchical composite end point was 1.52 (95% CI, 1.28-1.82; $P < .001$) (**Figure 2**A) (eFigure 2 and eTable 4 in Supplement 3). Death from cardiovascular causes, which was the first hierarchy tier and contributed 46.6% of decisions, occurred in 110 patients (23.8% [18.3% wins in the hierarchical comparison]) in the sacubitril/valsartan group and 117 (25.4% [17.5% wins]) in the enalapril group. The second tier, which accounted for 17.4% of decisions, was first hospitalization for worsening HF, which occurred in 102 patients (22.1% [7.7% wins]) in the sacubitril/valsartan group and 111 (24.1% [6.9% wins]) in the enalapril group. The third tier was a more favorable relative change (larger decrease or smaller increase of at least 25%) in NT-proBNP concentration from baseline to week 12. This final tier accounted for 36.1% of decisions, with

Figure 2. Primary Outcomes by Treatment Group



A, Winners determined hierarchically: time to cardiovascular death; if tied, time to first hospitalization for HF; if tied, ratio of change <0.75 in NT-proBNP from baseline to week 12. Unstratified win ratio, 1.54 (95% CI, 1.34-1.85). Breakdown of matches in eTable 4 and unstratified win ratio in eTable 5 in Supplement 3.

[a]Win ratios derived using Dong method stratified by country.

[b]From Cox proportional hazard models stratified by country.

Table 2. Individual Components of Primary Hierarchical Outcome, Secondary Efficacy, and Safety Outcomes Comparing Sacubitril/Valsartan With Enalapril

End points	Sacubitril/valsartan group (n = 462) No. (%)	Patients with event/100 patient-years	Enalapril group (n = 460) No. (%)	Patients with event/100 patient-years	Adjusted absolute differences, % (95% CI)	Adjusted relative effect measures (95% CI)	*P* value[a]
Primary composite hierarchical outcome							
Overall stratified unmatched win ratio[b]	NA	NA	NA	NA	NA	Win ratio: 1.52 (1.28 to 1.82)	<.001
Components of the hierarchical outcome							
Death from cardiovascular causes	110 (23.8)	11.0	117 (25.4)	11.7	−1.5 (−7.1 to 4.0)[c]	HR: 0.95 (0.73 to 1.23)[d]	.70
First hospitalization due to HF	102 (22.1)	11.0	111 (24.1)	12.4	−2.0 (−7.4 to 3.4)[c]	HR: 0.92 (0.70 to 1.20)[d]	.52
						Subdistribution HR: 0.74 (0.49 to 1.14)[e]	.17
Change in log(NT-proBNP) from baseline to week 12, %[f]	[n = 417]		[n = 401]				
Median (IQR)	−30.6 (−54.3 to −0.9)	NA	−5.5 (−31.9 to 37.5)	NA	−38.1 (−28.6 to −47.6)	Adjusted geometric mean ratio: 0.68 (0.62 to 0.75)	<.001
Mean (SD)	−41.1 (72.8)	NA	−1.5 (66.3)	NA			
Secondary outcomes							
First hospitalization for HF or cardiovascular death	155 (33.5)	16.8	169 (36.7)	18.8	−3.1 (−9.2 to 3.0)[c]	HR: 0.91 (0.73 to 1.13)[d]	.40
Death from any cause	129 (27.9)	12.9	134 (29.1)	13.5	−1.1 (−6.9 to 4.7)[c]	HR: 0.98 (0.77 to 1.25)[d]	.88
Sudden death or resuscitated cardiac arrest[g]	46 (10.0)	4.6	39 (8.5)	3.9	1.7 (−2.0 to 5.4)[c]	HR: 1.17 (0.76 to 1.80)[d]	.48
No. of emergency department visits for HF	23	2.3	21	2.1	0.2 (−1.1 to 1.5)[f]	Rate ratio: 1.12 (0.48 to 2.58)[h]	.80
No. of days alive and out of hospital at 1 y, mean (SD) [total No.][i]	339 (72) [n = 461]	NA	338 (71) [n = 455]	NA	1.1 (−8.2 to 10.4)	NA	.82
Recurrent events of hospitalization due to HF and death from cardiovascular causes (rate per 100 person-years)	289	28.9	316	31.7	−2.8 (−7.7 to 2.0)[f]	Rate ratio: 0.90 (0.63 to 1.28)[j]	.56

Abbreviations: HF, heart failure; HR, hazard ratio; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

[a] All *P* values correspond to relative effect models, except for "mean number of days alive and out of hospital," for which *P* values correspond to absolute differences.

[b] Primary composite outcome: analyzed as time to first occurrence of death from cardiovascular causes, hospitalization for HF, or NT-proBNP change at week 12, defined as at least a 25% greater relative change in 1 group compared with the other. A value greater than 1 indicates superiority. Stratified by country win ratio estimates.

[c] Absolute differences in incidence were estimated using logistic regression models adjusted for country.

[d] HRs were derived from Cox proportional hazards models, with stratification by country.

[e] Subdistribution HR was estimated from Fine-Gray competing risk models, with death treated as a competing event. See eTable 5 in Supplement 3 for additional details regarding NT-proBNP.

[f] Unadjusted absolute rate differences per 100 patient-years.

[g] Only 1 patient with resuscitated cardiac arrest in the enalapril group and no resuscitated cardiac arrest in the sacubitril/valsartan group.

[h] Rate ratios were derived from negative binomial generalized linear models, adjusted for country and accounting for follow-up time as an offset.

[i] Number of days out of hospital considered hospitalizations from any cause; 6 patients who withdrew consent are not included in this outcome.

[j] Total number of (first and recurrent) hospitalizations for HF and cardiovascular death analyzed by the semiparametric proportional rates model (known as the *LWYY method*); treatment effect is a rate ratio.

a logarithmic median (IQR) change from baseline of −30.6% (−54.3% to −0.9%) among those in the sacubitril/valsartan group (22.5% wins) (Figure 2B and **Table 2**) and −5.5% (−31.9% to 37.5%) among those in the enalapril group (7.2% wins) (adjusted geometric mean ratio, 0.68 [95% CI, 0.62-0.75]). The reduction in NT-proBNP was generally sustained at month 8 (eTable 5 in Supplement 3). Sensitivity analyses using the per-protocol population, another using total death instead of cardiovascular death, and computing an unstratified win ratio gave similar results (eTables 6 and 7 in Supplement 3) (Figure 2A).

To declare superiority of sacubitril/valsartan over enalapril, it was also prespecified that the point estimate of the HR for cardiovascular death and time to first HF hospitalization must be less than 1.0. These criteria were met, as the HR calculated for time to cardiovascular death was 0.95 (95% CI,

Table 3. Adverse Events Comparing Sacubitril/Valsartan With Enalapril[a]

Adverse event	No. of patients (%)	
	Sacubitril/valsartan group (n = 462)	Enalapril group (n = 460)
Follow-up time, median (IQR), y	2.10 (1.52-2.76)	2.10 (1.55-2.77)
Participants with ≥1 adverse event	331 (71.6)	348 (75.7)
Participants with ≥1 serious adverse event[b]	211 (45.7)	234 (50.9)
Discontinuation (temporary or permanent) of study drug due to adverse event	28 (6.1)	45 (9.8)
Adverse events of special interest		
Symptomatic hypotension	146 (31.6)	126 (27.4)
Led to temporary interruption of trial drug	19 (4.1)	27 (5.9)
Led to hospitalization	3 (0.6)	9 (2.0)
Kidney dysfunction[c]	101 (21.9)	92 (20.0)
Hyperkalemia	91 (19.7)	101 (22.0)
Led to hospitalization	2 (0.4)	5 (1.1)
Led to death	0	1 (0.2)
Arrhythmia	77 (16.7)	73 (15.9)
Led to hospitalization	41 (8.9)	41 (8.9)
Led to death	10 (2.2)	8 (1.7)
Angioedema[d]	2 (0.4)	4 (0.9)
No treatment or use of antihistamines only	2 (0.4)	3 (0.7)
Use of catecholamines or glucocorticoids without hospitalization	0	1 (0.2)

[a] All patients received at least 1 dose of the allocated study drug.

[b] Serious adverse events are those adverse events that meet any 1 of the following criteria: death, life-threatening (resulted in persistent or significant disability/incapacity), constituted a congenital anomaly or birth defect), required inpatient hospitalization or prolongation of existing hospitalization, or was medically significant (eg, defined as an event that jeopardized the participant or may have required medical or surgical intervention to prevent 1 of the outcomes listed above).

[c] Defined by the investigator.

[d] No cases of angioedema resulted in hospitalization, required mechanical airway protection, or led to death.

0.73-1.23) and time to HF hospitalization was 0.92 (95% CI, 0.70-1.20).

The results for the primary outcome were consistent across all prespecified subgroups (eTable 8 in Supplement 3).

The secondary efficacy end points are shown in Table 2. The first secondary end point was the composite of time to first HF hospitalization or death from cardiovascular causes (Figure 2, C, D, and E), which occurred in 155 patients (33.5%) in the sacubitril/valsartan group and 169 (36.7%) in the enalapril group (HR, 0.91 [95% CI, 0.73-1.13]).

A total of 129 patients (27.9%) in the sacubitril/valsartan group and 134 (29.1%) in the enalapril group died from any cause (HR, 0.98 [95% CI, 0.77-1.25]).

Adverse Events

Serious adverse events, including death, were reported in 211 patients (45.7%) in the sacubitril/valsartan group and 234 (50.9%) in the enalapril group (**Table 3**). Adverse events that led to either temporary or permanent discontinuation of the study drug were reported in 28 patients (6.1%) in the sacubitril/valsartan group and 45 (9.8%) in the enalapril group (Table 3) (eTable 9 in Supplement 3).

Symptomatic hypotension was the most common adverse event of special interest, reported in 146 patients (31.6%) in the sacubitril/valsartan group and 126 (27.4%) in the enalapril group (rate ratio, 1.28 [95% CI, 0.96-1.70]), with few resulting in treatment discontinuations in either group. The rates of symptomatic hypotension, arrhythmia, angioedema, kidney dysfunction, and hyperkalemia did not differ significantly between the sacubitril/valsartan group and the enalapril group (Table 3).

Discussion

In patients with HFrEF due to Chagas disease, the rates of the composite of death from cardiovascular causes or hospitalization for worsening HF with sacubitril/valsartan vs enalapril were not significantly different. However, in patients in the sacubitril/valsartan group, there was a greater relative change in NT-proBNP from baseline to week 12 compared with enalapril. In the win ratio approach, the primary results were driven by a reduction in NT-proBNP, which accounted for 36% of decisions, without any significant impact on clinical outcomes.

HF due to Chagas disease is a neglected and distinct problem, reflected by the participants in the present trial.[13,21,22] Notable features include the high proportion of female individuals, Black patients, and participants with more advanced symptoms of HF, more frequent prior pacemaker implantation, and use of amiodarone compared with prior trials in patients with HFrEF.[22] Despite the low prevalence of diabetes and coronary artery disease in PARACHUTE-HF, rates of death were high compared with other global and contemporary trials in HFrEF.[23,24] PARACHUTE-HF demonstrates the feasibility of conducting randomized clinical trials to better understand the nature of this condition and to identify treatments for it.

This trial was neither designed nor powered to assess a conventional morbidity-mortality outcome, with only one-sixth as many participants experiencing the composite of death from cardiovascular causes or hospitalization for HF (the first secondary end point in PARACHUTE-HF) as in the PARADIGM-HF (Prospective Comparison of ARNI With ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial (324 patients experienced this composite outcome in PARACHUTE-HF vs 2031 in PARADIGM-HF).[25] For the PARACHUTE-HF trial to be declared positive, not only did the win ratio need to be significantly greater than 1.0 but, for the composite end point, the HR for the sacubitril/valsartan group compared with the enalapril group had to be less than 1.0. The 95% CI around the HR observed in PARACHUTE-HF (HR, 0.91 [95% CI, 0.73-1.13]) incorporated the treatment effect shown in PARADIGM-HF (HR, 0.80 [95% CI, 0.73-0.87]), which also compared sacubitril/valsartan with enalapril.

The main beneficial effect of sacubitril/valsartan in PARACHUTE-HF was on the concentration of NT-proBNP. NT-proBNP is a biomarker that reflects cardiac wall stress and predicts future risk of hospitalization for HF and mortality.[26-28] Effective pharmacologic therapies for HFrEF decrease the concentration of natriuretic peptides.[23,24,28,29] Prior studies have

shown that elevated NT-proBNP is an important predictor of worse survival in patients with HF due to Chagas disease. The prespecified requirement in PARACHUTE-HF to demonstrate a favorable change in NT-proBNP from baseline of at least 25% was based on data from the PARADIGM-HF trial, showing that this change was associated with an approximately 15% relative reduction in the risk of cardiovascular death or hospitalization for HF.[30] The overall 38% reduction in NT-proBNP concentration observed in PARACHUTE-HF with sacubitril/valsartan, compared with enalapril, was consistent with the difference in the PARADIGM-HF (34%) and PIONEER-HF (Comparison of Sacubitril-Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode; 29%) trials and was observed despite high rates of background treatment with recommended therapies for HFrEF.[28,31] This reduction in NT-proBNP with sacubitril/valsartan, compared with enalapril, reflects inhibition of neprilysin, the enzyme that breaks down several vasoactive peptides, including the A- and B-type natriuretic peptide and, potentially, bradykinin, adrenomedullin, substance P, and vasoactive intestinal peptide, leading to venous and arterial vasodilation and natriuresis, resulting in reductions in pre- and afterload and left ventricular filling pressure and wall stress.

Sacubitril/valsartan was well tolerated in PARACHUTE-HF, and no new adverse event findings were identified. As expected, hypotension was the most commonly reported adverse event of interest, but this rarely led to discontinuation of randomized treatment. This is clinically relevant, as patients with HF caused by Chagas disease are more likely than patients with other causes of HF to experience hypotension, possibly reflecting autonomic nervous system involvement.[21,32,33]

Limitations

This trial has limitations. First, the open-label design could have introduced bias in the ascertainment or reporting of potential end points and adverse events because site investigators, with knowledge of treatment assignment, could potentially report more events in 1 group compared with the other. However, the use of objective triggers (any death or hospitalization, irrespective of potential cause) to prompt a systematic, central, and blinded adjudication should have mitigated, at least in part, the risk of bias. Second, the use of SGLT2 inhibitors was relatively low, but these drugs were not approved when enrollment in PARACHUTE-HF began. Third, the follow-up NT-proBNP measurement used as the third component of the hierarchical composite outcome was measured relatively early during follow-up (at 3 months) because of concerns about missing measurements, including due to death, if done later in the trial. Fourth, the findings cannot be extrapolated to patients with Chagas cardiomyopathy more widely, including those with a mildly reduced or preserved ejection fraction or without symptomatic HF.

Conclusions

In patients with HFrEF due to Chagas disease, sacubitril/valsartan was not significantly different from enalapril with respect to the composite outcome of cardiovascular death or hospitalization for HF. The significant win ratio for the primary outcome was primarily driven by a greater reduction in NT-proBNP at week 12 in the sacubitril/valsartan group, without any significant difference in clinical outcomes.

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