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ORIGINAL RESEARCH ARTICLE

Sacubitril-Valsartan for the Prevention of Anthracycline Cardiotoxicity in Patients With Elevated Cardiac Troponin I Concentration During Chemotherapy: A Double-Blind Randomized Placebo-Controlled Clinical Trial: The SARAH Trial

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BACKGROUND: The clinical effects of sacubitril-valsartan, an angiotensin receptor-neprilysin inhibitor, on anthracycline-induced cardiotoxicity remain unknown. Experimental evidence suggests cardioprotective properties. This study evaluated the efficacy of sacubitril-valsartan in reducing cardiotoxicity in patients with increased cardiac troponin I concentrations during anthracycline chemotherapy.

METHODS: This randomized, double-blind, placebo-controlled trial enrolled 114 patients with elevated cardiac troponin I levels during anthracycline treatment. Participants were randomized 1:1 to receive either sacubitril-valsartan or placebo for 6 months, with a target dose of 97/103 mg twice daily. The primary end point was the occurrence of a >15% reduction in the global longitudinal strain from baseline to 6 months. Secondary end points included changes in biomarkers, echocardiographic and cardiac magnetic resonance parameters, and adverse events. This trial was initially conceptualized as a pilot investigation because of its exploratory nature. Data were analyzed according to the intention-to-treat principle.

RESULTS: Among the randomized patients, 90% were women, and 80.7% had breast cancer. The primary end point occurred in 4 patients (7%) in the sacubitril-valsartan group and 14 patients (25%) in the placebo group (odds ratio, 0.23 [95% CI, 0.07–0.75]; P=0.015). The sacubitril-valsartan group showed a 2.5% improvement in global longitudinal strain, whereas the placebo group experienced a 7.6% decline (P<0.001). No significant differences in changes in cardiac troponin I or NT-proBNP (N-terminal pro-B-type natriuretic peptide) were observed. Hypotension (systolic blood pressure <100 mm Hg) occurred more frequently in the sacubitril-valsartan group than in the placebo group (8 cases versus 1 case; P=0.032).

CONCLUSIONS: The SARAH trial (Sacubitril-Valsartan for the Prevention of Anthracycline Cardiotoxicity in Patients With Elevated hs-cTnI Concentrations During Chemotherapy) demonstrated the potential of sacubitril-valsartan therapy to reduce the incidence of left ventricular dysfunction, as assessed by global longitudinal strain, in patients with elevated high-sensitivity cardiac troponin I after anthracycline treatment.

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Key Words: anthracyclines ■ cardiotoxicity ■ global longitudinal strain ■ prevention and control ■ sacubitril and valsartan sodium hydrate drug combination ■ ventricular dysfunction

Editorial, see p XXX

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Clinical Perspective

What Is New?

- Various neurohormonal agents have been evaluated for their potential to prevent cardiotoxicity from anthracycline-based chemotherapy, but sacubitril-valsartan has not been previously studied in this context.
- This trial is the first randomized, double-blind, placebo-controlled study assessing sacubitril-valsartan as a preventive strategy against cardiotoxicity in patients with cancer undergoing chemotherapy with increased cardiac troponin I levels attributable to anthracycline treatment.
- In patients with elevated cardiac troponin I during anthracycline treatment, sacubitril-valsartan may prevent left ventricular dysfunction as assessed by global longitudinal strain.

What Are the Clinical Implications?

- If confirmed by larger trials, these findings suggest that sacubitril-valsartan may provide protection against anthracycline-induced cardiotoxicity and subsequent cardiac dysfunction.

Nonstandard Abbreviations and Acronyms

CMR	cardiac magnetic resonance
GLS	global longitudinal strain
HER2	human epidermal growth factor receptor 2
HF	heart failure
HFA-ICOS	Heart Failure Association–International Cardio-Oncology Society
hs-cTnI	high-sensitivity cardiac troponin I
LV	left ventricular
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SAFE	Cardiotoxicity Prevention in Breast Cancer Patients Treated With Anthracyclines and/or Trastuzumab
SARAH	Sacubitril-Valsartan for the Prevention of Anthracycline Cardiotoxicity in Patients With Elevated hs-cTnI Concentrations During Chemotherapy
PRADA	Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy

Anthracyclines are widely used chemotherapeutic agents for malignancies such as breast cancer, leukemia, lymphoma, and sarcoma owing to their potent antineoplastic effects.[1] However, these drugs carry a significant risk of cardiotoxicity that can lead to increased morbidity and mortality, and they may require discontinuation of therapy.[2]

Anthracycline cardiotoxicity is initiated by a cellular injury that leads to abnormalities in myocardial deformation that can progress to left ventricular (LV) dysfunction and overt heart failure (HF).[3] Early studies have suggested that elevated cardiac troponin levels during anthracycline treatment are associated with an increased risk of LV dysfunction and adverse clinical outcomes, effectively identifying high-risk individuals who may benefit from cardioprotective interventions.[4,5]

In high-risk cohorts, enalapril has demonstrated efficacy in reducing cardiotoxicity from high-dose anthracycline exposure, although other recent studies have not replicated these results.[6,7] Indeed, recent studies show that carvedilol and candesartan do not significantly reduce cardiotoxicity or affect cardiac function in patients with elevated cardiac troponin levels undergoing contemporary anthracycline regimens.[8] These findings emphasize the need for new tailored cardioprotective strategies for current reduced-dose anthracycline regimens.

Newer medications approved for the treatment of HF may have potentially protective effects against cardiotoxicity. Sacubitril-valsartan combines inhibition of neprilysin with blockade of the angiotensin II receptor and has shown promise in preventing LV dysfunction in animal models of anthracycline-induced cardiotoxicity.[9] Until very recently, however, data on the cardioprotective effects of sacubitril-valsartan in preventing anthracycline-induced cardiotoxicity in humans have been missing.[9–11]

Accordingly, we conducted a randomized controlled trial to evaluate the efficacy of sacubitril-valsartan in preventing cardiotoxicity in patients with increased high-sensitivity cardiac troponin I (hs-cTnI) levels after anthracycline administration.

METHODS

Trial Design

The SARAH trial (Sacubitril-Valsartan for the Prevention of Anthracycline Cardiotoxicity in Patients With Elevated hs-cTnI Concentrations During Chemotherapy) was a single-center, randomized, double-blind, placebo-controlled clinical trial. This study was investigator initiated and funded by local charitable donations. The trial was planned and developed as a postgraduate program under the supervision of the Heart Institute at the University of São Paulo Medical School, with a thorough evaluation by the postgraduate committee, statisticians, and supervisors. The trial was conducted at the Erasto Gaertner Hospital, Curitiba, Brazil, and the trial protocol (Supplemental Appendix) was approved by the institutional review board of the study center. Written informed consent was obtained from all patients. The trial was approved by a safety monitoring committee and conducted in accordance with the principles of the

Declaration of Helsinki. The authors assume responsibility for the accuracy and completeness of the data and analyses and for the adherence of the trial and this report to the protocol. The trial was registered in the Brazilian Registry of Clinical Trials (https://ensaiosclinicos.gov.br/rg/RBR-5q4gm5b) before study initiation.

Patients

The study included patients >18 years of age with neoplasms undergoing anthracycline chemotherapy who showed an increase in hs-cTnI above the sex-specific 99th percentile after any anthracycline chemotherapy session. The chemotherapy regimens are listed in Table S1. The exclusion criteria included inability to assess LV function, previous chemotherapy or radiotherapy, pre-existing heart disease, use of neurohormonal antagonist therapies or sodium-glucose cotransporter 2 inhibitors, and contraindications to sacubitril-valsartan. A complete list of inclusion and exclusion criteria is provided in the Supplemental Appendix.

Trial Procedures

Eligible patients underwent screening for hs-cTnI, which was measured immediately after each anthracycline chemotherapy session and 30 days after the last dose. Hs-cTnI was quantified with the VITROS XT 7600 Integrated System from Ortho Clinical Diagnostics using a chemiluminescent immunoassay. The detection limit was 1.5 ng/L, and the 99th percentile was 9 ng/L for women and 12 ng/L for men. Patients with hs-cTnI levels above the sex-specific 99th percentile were randomized in a 1:1 ratio to receive sacubitril-valsartan or placebo. Randomization was stratified by the planned cumulative anthracycline dose of ≥300 mg/m^2 or <300 mg/m^2 using a computer-based list in blocks of 4, with 2 patients assigned to sacubitril-valsartan and 2 to placebo. Patients in the sacubitril-valsartan group received an initial dose of 24/26 mg twice daily. Doses were escalated progressively every 2 weeks to reach a maximum dose of 97/103 mg twice daily or until the occurrence of adverse effects such as symptomatic hypotension, creatinine clearance <30 mL·min^{-1}·m^{-2}, or serum potassium >5.5 mmol/L. In the presence of any of these effects, the dose was reduced to the previous dose. In cases of persistent adverse events, the dose could be reduced further or discontinued. Patients in the placebo group received medication in a staggered and progressive manner similarly to the intervention group. Treatment was maintained for 24 weeks in both groups. Compliance was evaluated from pill counts at follow-up visits and monthly phone calls to reinforce adherence and to identify potential issues with intake. During the study follow-up, the patients underwent clinical evaluations and measurements of hs-cTnI, NT-proBNP (N-terminal pro-B-type natriuretic peptide), creatinine, and potassium levels, as well as echocardiography and cardiac magnetic resonance (CMR) imaging at 4 time points: T1 (baseline; baseline before starting anthracycline), T2 (baseline prerandomization; increase in hs-cTnI above the 99th percentile and before the start of trial intervention), T3 (end of chemotherapy), and T4 (end of trial intervention at 24 weeks). The end of the complete chemotherapy regimen (T3) could occur during or after the point of randomization (T2), depending on when hs-cTnI levels were elevated during chemotherapy (Figure 1 and Figure S1). Evaluations with echocardiography and CMR, along with the quantification of hs-cTnI and NT-proBNP levels, were performed in accordance with institutional protocols and are comprehensively detailed in the Supplemental Appendix.

If a patient's LV ejection fraction (LVEF) dropped below 50 percentage points, blinded therapy was discontinued, and the patient was referred for further evaluation. Subsequent treatments were performed at the discretion of the attending cardiologist. These patients were included in the analysis in accordance with the intention-to-treat principle.

Study Outcomes

The primary outcome was the incidence of a >15% reduction in the global longitudinal strain (GLS) of the LV from randomization to 24 weeks of treatment with sacubitril-valsartan or placebo. Secondary outcomes were analyzed independently without a hierarchical structure. Increases in biomarkers and variations in echocardiographic and CMR parameters were assessed as continuous variables. Changes in the echocardiographic and CMR indices included ventricular dimensions and function, diastolic parameters, ventricular mass, GLS variation, and T1 and T2 mapping. Biomarker increases were defined as changes in hs-cTnI and NT-proBNP levels. A decline in LVEF, defined as a reduction of >10 percentage points, resulting in a final value of <53 percentage points, was assessed as a categorical outcome. Composite clinical events (symptomatic HF, hospitalization for HF, death, or heart transplantation) and adverse events occurring after 24 weeks were analyzed as categorical variables. Primary and secondary outcomes were

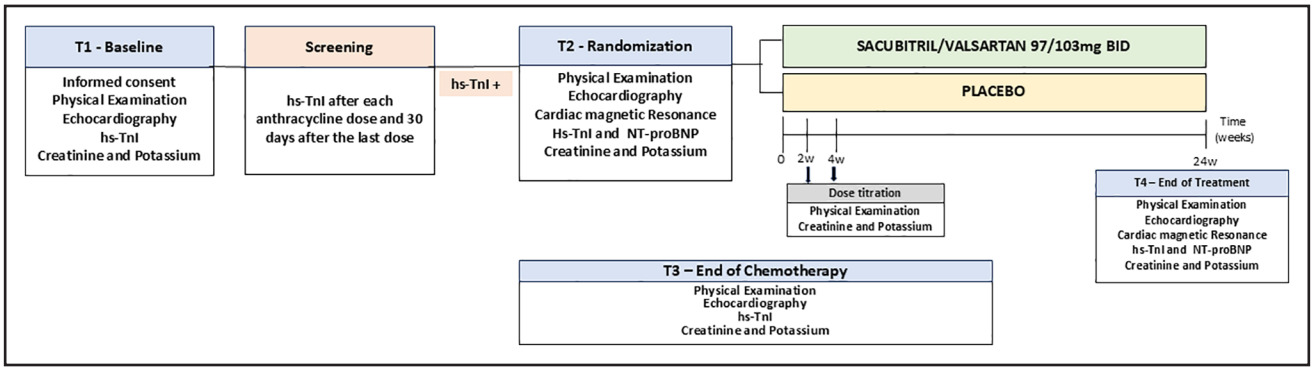

Figure 1. Trial design.
BID indicates twice a day; hs-cTnI, high-sensitivity cardiac troponin I; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

evaluated from T2 (baseline prerandomization) and T4 (end of intervention). Outcome adjudication was blinded and conducted according to prespecified criteria.

Study Hypotheses

The primary objective of this study was to evaluate whether sacubitril-valsartan differs from placebo in the occurrence of the primary outcome, defined as the incidence of a >15% reduction in the GLS of the LV from randomization to 24 weeks of treatment.

Statistical Analysis

Data concerning primary and secondary outcomes from all randomized patients were analyzed according to the intention-to-treat principle, with all possible directions of effect considered in relation to the placebo.

Categorical variables were described as absolute frequencies and percentages. Continuous variables were presented as mean±SD or medians and ranges, depending on their distribution. Treatment group comparisons were made with the Student *t* test for independent groups, the nonparametric Mann-Whitney *U* test for continuous variables, and the Fisher exact test for categorical variables. Logistic regression models were adjusted to evaluate the probability of the primary outcome and to assess the independent effect of the treatment group based on clinical variables. Likelihood ratio tests were performed to compare nested logistic regression models. For the longitudinal analysis of repeated measures over time, multilevel linear mixed-effects models with random intercepts and slopes were used, including the treatment group, time of assessment (T1, T2, T3, and T4), and interaction between the treatment group and time, to assess differences between groups. Difference-in-difference analyses were performed to compare changes over time between the groups. Maximum likelihood estimation and unstructured variance-covariance structures were considered. Secondary end points were analyzed individually without hierarchy, and *P* values were adjusted for multiple testing with the Benjamini-Hochberg procedure. As an exploratory analysis, we generated additional multivariable models to evaluate the potential confounding effects of trastuzumab use, the presence of hypertension or diabetes at baseline, cumulative anthracycline dose, patient age, and change in systolic blood pressure during the study. Because of the limited power of the study, these subanalyses were performed after adjustment only for confounding predictors. Statistical significance was set at $P<0.05$. The *P* value threshold for significance was based on a 2-sided test.

Statistical Power and Sample Size Considerations

The estimated sample size related to the power of the statistical tests was initially based on the experience and judgment of experts in the field because of the absence of available information about the intervention being tested and the difficulty in making a priori assumptions. We carefully considered the ethical and practical implications of enrolling a large or small number of participants, particularly in terms of safety, and ensured that the sample size was sufficient to detect meaningful differences in the outcomes of interest. Recognizing the exploratory nature of this study, we initially designed it as a pilot study. After initial protocol approval, we became aware of a relevant new study that reported such outcomes.[12] Estimating an event rate of 35% in the placebo group and 12% in the sacubitril-valsartan group, we anticipated that the reduction would be greater than that with ramipril, given that sacubitril-valsartan demonstrated superiority over other renin-angiotensin-aldosterone system inhibitors in animal models. Consequently, we estimated the required sample size to be ≈50 patients per group to achieve 80% power and a type I error rate of 0.05. In addition, the sample size was increased by 10% to account for potential losses during follow-up. Statistical analyses were performed with Stata/SE version 17 (StataCorp LP). The data will be available for future analysis on request.

RESULTS

We randomized 114 patients between July 2022 and February 2024 for the intention-to-treat analysis. The mean age was 51.7±11.7 years; 90% were women, and 92.1% had breast cancer. The mean indexed dose of anthracycline was 244.28±40.5 mg/m^2. The average daily dose was 345 mg of sacubitril-valsartan and 344 mg of placebo. The baseline characteristics of the patients were statistically balanced across all groups and are presented in Table 1. Most patients (81%) were randomized after receiving the final anthracycline dose. Among the remaining 19%, 1%, 6%, and 12% were randomized after receiving 25%, 50%, and 75% of the total anthracycline dose, respectively (Figure S2). After completion of anthracycline sessions, the chemotherapy regimen could be either concluded or continued with other non-anthracycline drugs, depending on the neoplasm and the proposed regimen. The end of chemotherapy (T3) was defined as the point at which all chemotherapeutic agents were administered. In 5.3% (6 patients), T2 (randomization) was the same time point as T3 (end of chemotherapy) because randomization occurred after the last session of chemotherapy. In the remaining 75.7% (n=108), T2 preceded T3. In these patients, randomization occurred either during anthracycline chemotherapy (22 patients) or after the completion of anthracycline but before the end of chemotherapy with other agents (86 patients).

The baseline characteristics of nonrandomized patients and the Heart Failure Association–International Cardio-Oncology Society (HFA-ICOS) risk score classification of all patients are available in Tables S2 and S3.

Primary Outcome

The primary outcome was analyzed in 112 patients who completed the follow-up because 2 patients, one from each group, died of oncological causes during the study. A flowchart of this process is shown in Figure 2. The primary outcome occurred in 25% of patients in the placebo group and 7.1% in the sacubitril-valsartan group

Table 1. Baseline Characteristics Between Patient Groups

Variable	Sacubitril-valsartan (n=57)	Placebo (n=57)	Total (N=114)
Age, y	51.6±11.6	51.7±11.6	51.7±11.6
Women, n (%)	53 (93.0)	50 (87.7)	103 (90.4)
Oncological disease, n (%)			
Breast cancer	47 (82.5)	45 (79)	92 (80.7)
Leukemia	0 (0)	1 (1.8)	1 (0.9)
Lymphoma	9 (15.7)	10 (17.4)	19 (16.7)
Sarcoma	1 (1.8)	1 (1.8)	2 (1.7)
Comorbidities, n (%)			
Any	37 (64.9)	36 (63.2)	73 (64.0)
Hypertension	18 (31.6)	18 (31.6)	36 (31.6)
Diabetes,	6 (10.5)	5 (8.8)	11 (9.6)
Hypercholesterolemia	10 (17.5)	3 (5.3)	13 (11.4)
Smokers, n (%)	1 (1.8)	2 (3.5)	3 (2.6)
Body mass index, kg/m^2	27.4±5.3	29.0±5.0	28.2±5.2
Systolic blood pressure, mm Hg	120 (110, 140)	130 (110, 140)	120 (110, 140)
Diastolic blood pressure, mm Hg	78.5 (70, 80)	80 (70, 82)	80 (70, 80)
Heart rate, bpm	82.8±12.6	78.0±11.5	80.4±12.2
Serum creatinine, mg/dL	0.8 (0.7, 0.9)	0.7 (0.7, 0.9)	0.7 (0.7, 0.9)
Serum potassium, mmol/L	4.5±0.4	4.4±0.4	4.5±0.4
Tolerated dose sacubitril-valsartan/placebo, mg/d	345 (0–400)	344 (0–400)	345.5 (0–400)
Cumulative anthracycline dose (doxorubicin equivalent), mg/m^2	240 (236, 242)	239 (231, 240)	239 (233, 241)
Trastuzumab, n (%)	9 (19.1)	18 (40.0)	27 (29.3)
Radiotherapy, n (%)	41 (71.9)	41 (71.9)	82 (71.9)
Serum hs-cTnI baseline, ng/L	1.5 (1.5, 1.5)	1.5 (1.5, 1.5)	1.5 (1.5, 1.5)
Serum hs-cTnI randomization, ng/L	24.9 (16.9, 37.9)	19.1 (13, 35.3)	22.4 (14.9, 37.4)
Serum NT-proBNP randomization, pg/mL	10 (4, 27)	12 (5, 25)	10.5 (5, 25)
GLS baseline, %	−20.2 (−22.4, −18)	−20.1 (−21.9, −18.7)	−20.1 (−221, −18.4)
GLS randomization, %	−18.8 ±2.8	−19.1±3.2	−19.0±3.0
Echo LVEF baseline, %	64.4±4.9	63.7±3.9	64.0±4.4
Echo LVEF randomization, %	63.3±3.9	62.3±4.3	62.8±4.1
CMR LVEF randomization, %	58.8±8.7	60.3±5.8	60.3±5.8

Values are mean±SD, median (25th percentile, 75th percentile) or number (percentage). There were no significant differences between the 2 groups (P>0.05).

CMR indicates cardiac magnetic resonance; Echo, echocardiogram; GLS, global longitudinal strain; hs-cTnI, high-sensitivity cardiac troponin I; LVEF, left ventricular ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

(odds ratio, 0.23 [95% CI, 0.07–0.75]; P=0.015) from baseline prerandomization (T2) to after 24 weeks of treatment (T4; Tables 2 and 3).

In multivariable logistic regression adjusted for human epidermal growth factor receptor 2 (HER2) status, hypertension, diabetes, indexed cumulative anthracycline dose, and age, the treatment effect remained significant (Table S4). For trastuzumab use, we also conducted an analysis stratifying patients according to their HER2 status. Sacubitril-valsartan reduced the incidence of the primary end point in the overall cohort and in HER2-negative patients but not in HER2-positive patients (Table S5). A regression model was fitted that included treatment group, HER2 status (positive or negative), and interaction terms. Neither HER2 status nor the treatment×HER2 status interaction was statistically significant (Table S6). In subgroup analyses comparing sacubitril-valsartan with placebo, the odds ratio for the primary end point was 0.19 (95% CI, 0.05–0.76; P=0.018) in HER2-negative patients and 0.44 (95% CI, 0.04–4.62; P=0.492) in HER2-positive patients (Figure 3; Tables S7 and S8). Given the potential of GLS to be sensitive to changes in preload and afterload, we conducted additional statistical analyses to assess whether the hemodynamic effects of sacubitril-valsartan contributed to the observed results. The findings revealed that the treatment group was

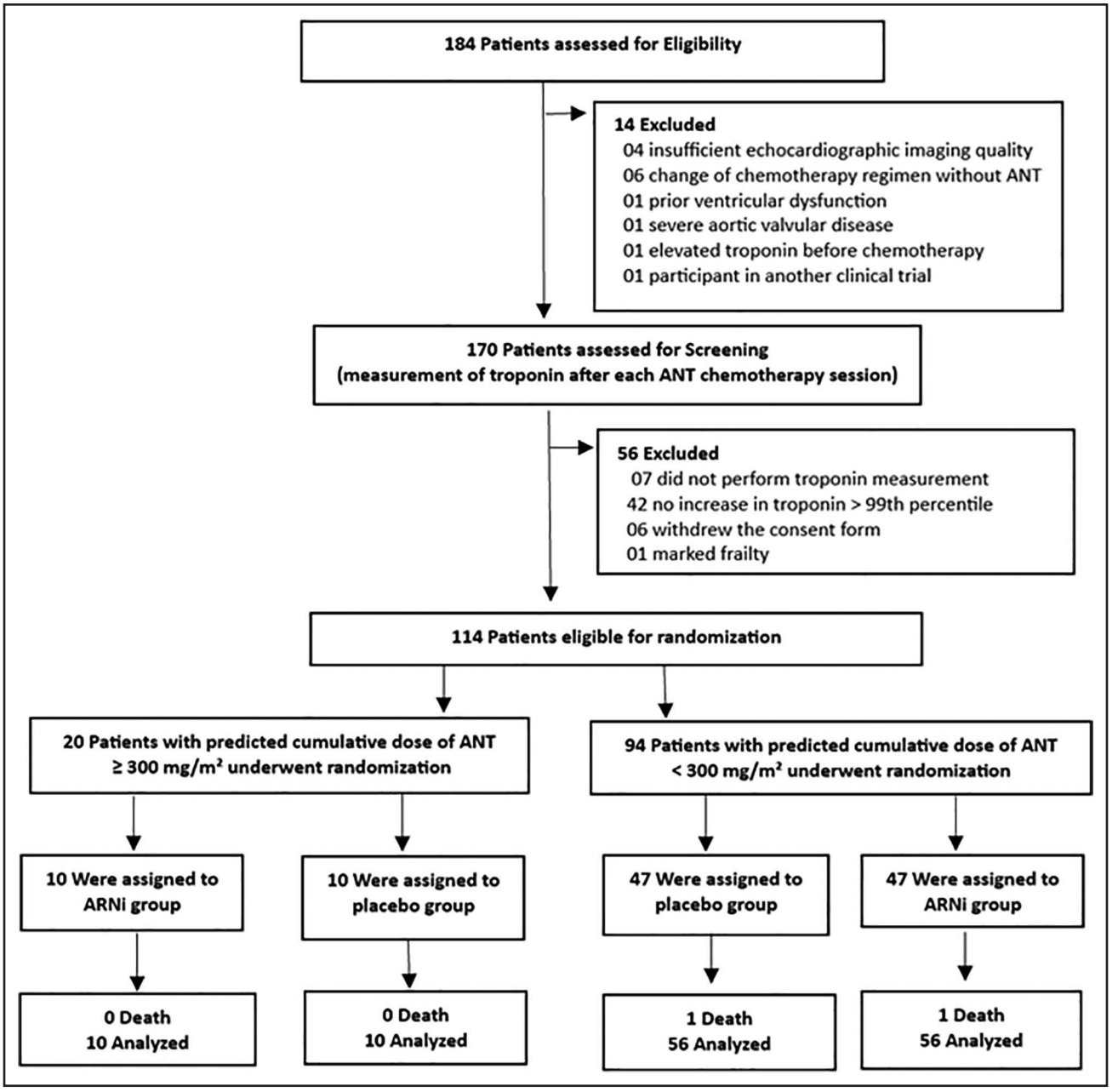

Figure 2. Patient enrollment and randomization.

significantly associated with the primary end point, independently of the change in systolic blood pressure from prerandomization (T2) to the end of the intervention (T4; *P*=0.419; Table S9). None of the patients in this study used diuretics. The average weight from T2 to T4 remained unchanged in the placebo group and increased by ≈0.8 kg in the sacubitril-valsartan group (*P*=0.322).

Secondary Outcomes

The sacubitril-valsartan group showed an improvement in GLS, whereas the placebo group experienced a decline, and the between-group difference in the absolute change of GLS was −1.9 percentage points (95% CI, −2.9 to −0.85; *P*<0.001; Figure 4A; Figure S3). Cardiotoxicity, defined as a reduction in LVEF of >10 percentage points resulting in a final LVEF <53 percentage points,[13] occurred in 8 patients (7.1%) by echocardiography, distributed equally between the groups, and was detected in 8 patients (7.8%) by CMR. Among these, 2 patients (3.7%) were in the sacubitril-valsartan group, and 6 (11.3%) were in the placebo group (odds ratio, 0.30 [95% CI, 0.05–1.72]; *P*=0.161; Tables 2 and 3).

By echocardiography, the change in LV end-diastolic volume did not differ significantly between the sacubitril-valsartan group and the placebo group (Tables 2 and 3). Moreover, change in LVEF did not differ between the sacubitril-valsartan and the placebo group, with a

Table 2. Primary End Points: Change From Prerandomization (T2) to End of Trial Intervention (T4)

Primary end point	Sacubitril-valsartan (n=56)	Placebo (n=56)	Total (N=112)	OR (95% CI)	*P* value
GLS decrease >15%	4 (7.1)	14 (25)	18 (16.1)	0.23 (0.07–0.75)	0.015
GLS decrease >15% adjusted to HER2				0.23 (0.07–0.76)	0.016

Values are median (95% CI) or number (percentage), and the *P* values in this table are from comparisons of the 2 groups using the Student *t* test for independent samples or the nonparametric Mann-Whitney test.

GLS indicates global longitudinal strain; HER2, human epidermal growth factor receptor 2; and OR, odds ratio.

between-group difference in absolute change of 1.2% (95% CI, −0.7 to 3.2; *P*=0.304; Tables 2 and 3; Figure 4B and 4C; Table S3).

By CMR, the reduction in LVEF was less in the sacubitril-valsartan group compared with the placebo group, with a between-group difference in absolute change of 2 percentage points (95% CI, 0–6; *P*=0.011; Figure 4D; Figure S3; Tables S10 through S12). The change in LV end-systolic volume did not differ significantly between the sacubitril-valsartan and placebo groups (Table 2). Secondary end points were also analyzed according to HER2 status (Tables S7 and S8).

The change in hs-cTnI and NT-proBNP levels did not differ between groups (Tables 2 and 3; Figure S4).

Exploratory End Points

A greater proportion of participants in the placebo group completed the study with LV dysfunction, defined by an LVEF <50 percentage points on CMR (*P*=0.029) or GLS less negative than −18% (*P*=0.018; Table S13).

No significant differences were observed between the groups in other echocardiographic or CMR parameters such as change in ventricular mass, diastolic dysfunction indices, extracellular volume, and T1 and T2 mapping values (Tables S14 and S15).

Clinical Events

Symptomatic HF occurred in 2 patients in the placebo group (1.7%), and one patient was hospitalized for HF. One patient in the sacubitril-valsartan group experienced an acute myocardial infarction. One death occurred in each group. Overall, 15.8% of the patients in the placebo group and 19.3% of the patients in the sacubitril-valsartan group experienced adverse effects (*P*=0.806). Hypotension was more frequent in the sacubitril-valsartan group (8 cases,14%) compared with the placebo group (one case, 1.8%; *P*=0.032). Dose reduction occurred in 14% of the sacubitril-valsartan group compared with 7% of the placebo group; however, a higher percentage of patients in the placebo group discontinued the medication. Notably, most episodes of hypotension resolved with dose reduction, allowing patients to continue sacubitril-valsartan treatment without the need for discontinuation or impact on oncological care (Table S16). In addition, at the time of study completion, when the final GLS was calculated, no significant difference was observed in the mean systolic or diastolic blood pressure between groups (Table S17). No significant differences were observed in final serum creatinine levels between groups. The final serum potassium level was higher in the sacubitril-valsartan group (*P*=0.047; Figure S4; Table S17).

DISCUSSION

This is the first prospective, randomized, placebo-controlled, double-blind clinical trial to report the effect of sacubitril-valsartan on cardiotoxicity in patients with cancer undergoing anthracycline chemotherapy who had increased cardiac troponin I levels. The results demonstrated a significant reduction in the incidence of the primary outcome, subclinical LV systolic dysfunction, defined as a ≥15% reduction in GLS, in the sacubitril-valsartan group compared with the placebo group. Sacubitril-valsartan was also associated with less deterioration in some secondary outcomes, including change in CMR-LVEF; however, these findings should be considered hypothesis generating.

Compared with previous studies, the importance of our findings can be contextualized by 2 key aspects: the selection of patients at higher risk for cardiotoxicity based on increased hs-cTnI concentrations after anthracycline treatment and the assessment of sacubitril-valsartan efficacy on subclinical cardiotoxicity through changes in GLS and LVEF measured by CMR.

The inclusion of patients at higher risk of cardiotoxicity to identify those who could benefit most from cardioprotective strategies has been a major focus of research. Risk stratification through scoring systems such as the HFA-ICOS risk score[14,15] has been proposed as a valuable approach. However, the increase in cardiac troponin levels within the HFA-ICOS risk score was evaluated with baseline cardiac troponin levels measured before the initiation of chemotherapy,[14,15] whereas in the SARAH study, the selection of individuals at increased risk of cardiotoxicity was based on evidence of acute myocardial injury, characterized by elevated hs-cTnI levels after anthracycline administration. This scenario was not addressed by the HFA-ICOS score or any other similar scoring systems.

Table 3. Secondary End Points: Change From Prerandomization (T2) to End of Trial Intervention (T4)

Secondary end points	Sacubitril-valsartan (n=56)*	Placebo (n=56)*	Total (N=112)*	*P* value	Adjusted *P* value†
LVEF decrease >10 points with final value <53% (Echo), n (%)	4 (7.1)	4 (7.1)	8 (7.1)	1	1
LVEF decrease >10 points with final value <53% (CMR), n (%)	2 (3.7)	6 (11.3)	8 (7.8)	0.161	0.322
GLS, %					
Prerandomization (T2)	−18.9 (−19.9, −18.6)	−19.3 (−20.3, −18.3)	−19.1 (−19.6, −18.7)	0.623	0.623
End of treatment (T4)	−19.7 (−20.2, −18.4)	−18.3 (−19.6, −17.3)	−19.3 (−19.7, −18.4)	0.008	0.011
Absolute change	−0.5 (−1.4, 0.5)	1.4 (0.7, 1.9)	0.6 (−0.2, 1.0)	<0.001	0.002
Percentage change	−2.5 (−9.1, 2.3)	7.6 (3.4, 10.2)	2.9 (−1.2, 6.0)	<0.001	0.002
DiD (absolute change)‡	−1.9 (−2.9, −0.85)				
LVEF (Echo), %					
Prerandomization (T2)	63.2 (62.4, 64.6)	63 (62.9, 65)	63 (62.9, 64.3)	0.498	0.498
End of treatment (T4)	64 (63, 65.1)	62 (61.3, 63.5)	63.2 (62.2, 64)	0.052	0.208
Absolute change	0.5 (−1.2, 2.5)	−0.7 (−1.8, 0.4)	−0.4 (−0.9, 0.7)	0.304	0.405
Percentage change	0.8 (−1.8, 3.9)	−1.1 (−2.7, 0.6)	−0.5 (−1.4, 1.1)	0.294	0.405
DiD (absolute change)‡	1.2 (−0.7, 3.2)				
LVEF (CMR), %					
Prerandomization (T2)	59 (58, 62)	60 (59, 63)	59 (58, 61)	0.756	0.756
End of treatment (T4)	61 (61, 62)	58 (57, 61)	60 (59, 61)	0.027	0.036
Absolute change	0 (−1, 3)	−2 (−3, 0)	0 (0, 2)	0.011	0.024
Percentage change	0 (−1.5, 4.3)	−3.4 (−6.2, 0)	0 (0, 3.4)	0.012	0.024
DiD (absolute change)‡	2 (0, 6)				
LVEDV (Echo), mL					
Prerandomization (T2)	88.1 (78.6, 92.4)	88.5 (82.4, 93)	88.2 (82.6, 92.4)	0.554	0.554
End of treatment (T4)	83.1 (78.6, 92.4)	92.4 (87.7, 102)	87.9 (83.1, 92.4)	0.026	0.104
Absolute change	−4.2 (−7.5, 5.7)	4.3 (−1, 9.1)	1 (−4, 5.8)	0.115	0.187
Percentage change	−5.3 (−7.8, 7.4)	5.1 (−1.1, 10.9)	1 (−4.6, 6.6)	0.140	0.187
DiD (absolute change)‡	−8.5 (−13.7, 2)				
LVESV (CMR), mL					
Prerandomization (T2)	43 (37, 49)	45 (42, 49)	45 (43, 49)	0.130	0.260
End of treatment (T4)	43 (39, 49)	48 (44, 53)	45 (43, 49)	0.036	0.144
Absolute change	1.5 (−1, 5)	4 (0, 8)	3 (1, 8)	0.274	0.274
Percentage change	5 (−2.9, 13.9)	10.5 (0, 21.1)	6.7 (2, 16)	0.262	0.274
DiD (absolute change)‡	−2.5 (−7.5, 2.5)				
High-sensitivity cardiac troponin I, ng/L					
Prerandomization (T2)	25.2 (18.2, 31.1)	19.1 (13.8, 27.9)	22.4 (18.6, 27.9)	0.192	0.384
End of treatment (T4)	2.9 (2.2, 3.5)	2.5 (2.1, 3.5)	2.7 (2.3, 3.2)	0.924	0.924
Absolute change	−22.5 (−26.9, −15.1)	−17.2 (−21.2, −11.2)	−19.1 (−23.5, −15.1)	0.254	0.339
Percentage change	−89.3 (−91.2, −82.3)	−85.9 (−87.9, −79.2)	−86.9 (−89.1, −82.1)	0.230	0.339
DiD (absolute change)‡	−5.3 (−13.2, 4.2)				
NT-proBNP, pg/mL					
Prerandomization (T2)	10 (7, 19)	12 (8, 17)	10.5 (8, 14)	0.742	0.872
End of treatment (T4)	17 (11, 28)	17 (13, 24)	17 (13, 24)	0.872	0.872
Absolute change	6 (1, 12)	2 (0, 11)	4 (1, 8.5)	0.439	0.872
Percentage change	50 (33.3, 138.5)	41.9 (0, 100)	49.1 (15.8, 81.5)	0.526	0.872
DiD (absolute change)‡	4 (−5, 10)				

Values are median (95% CI) or number (percentage), and the *P* values in this table are from comparisons of the 2 groups using the Student *t* test for independent samples or the nonparametric Mann-Whitney test.

CMR indicates cardiac magnetic resonance; DiD, difference in differences; Echo, echocardiogram; GLS, global longitudinal strain; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; OR, odds ratio; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Missing values of CMR variables: 2 for sacubitril-valsartan group and 3 for placebo group because the examination was not performed, as some patients underwent temporary breast implantation procedures with metallic materials.

†Adjusted *P* value by Benjamini-Hochberg.

‡DiD estimated as the difference in median changes between groups (sacubitril-valsartan−placebo). CIs were derived from bootstrap resampling.

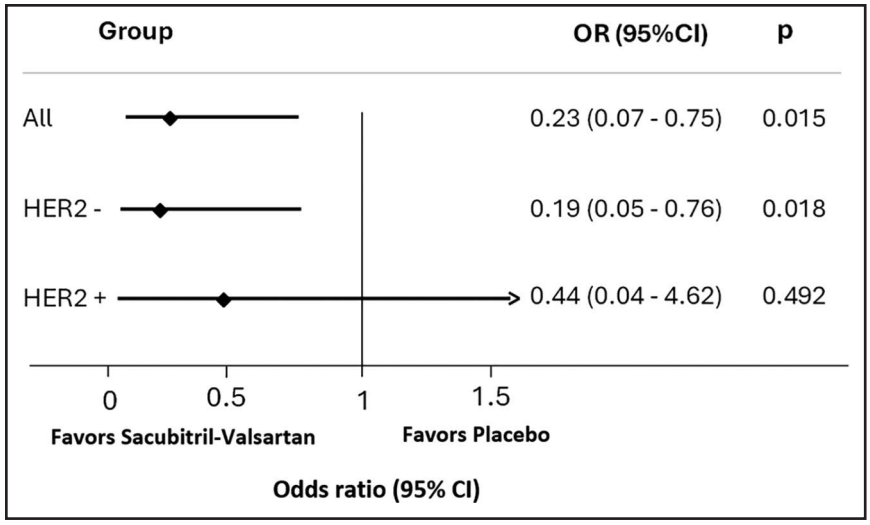

Figure 3. Primary end point associated with sacubitril-valsartan vs placebo for the overall population and HER2-negative and HER2-positive subgroups from baseline prerandomization (T2) to the end of the intervention (T4).
HER2 indicates human epidermal growth factor receptor 2; and OR, odds ratio.

Furthermore, the HFA-ICOS score incorporates variables for risk assessment, including previous heart disease, elevated cardiac troponin or NT-proBNP levels at baseline (before initiation of chemotherapy), and previous treatment with cardiotoxic agents (chemotherapy or thoracic radiotherapy),[14] all of which were exclusion criteria for the SARAH study. Consequently, this may have resulted in the exclusion of some high-risk patients in SARAH.

Our study identified patients at increased risk of cardiotoxicity by monitoring hs-cTnI levels exceeding the 99th percentile after each anthracycline session. Evidence indicates that cardiac troponin levels commonly rise immediately after anthracycline exposure,[4,5] and consistent with our protocol, the 99th percentile is used as the threshold for defining myocardial injury in current practice.[15] Cardinale and Cipolla[4] and Cardinale et al[5,6] demonstrated that an increase in cardiac troponin after high-dose anthracycline exposure is a strong predictor of decline in LVEF and adverse events in the subsequent months. In addition, patients who do not exhibit increased cardiac troponin I levels have a high negative predictive value for cardiotoxicity.[4–6] A cardiac troponin–guided prevention strategy has previously been proposed,[5,16] and this design was used in 2 previous studies.[6,8] The first study demonstrated a significant benefit of enalapril in reducing cardiotoxicity in patients receiving high-dose anthracyclines. That study did not consider baseline hs-cTnI but rather the peak value among several measurements taken within the first 72 hours after the cycle.[6] The second study found no significant effect of combined carvedilol and candesartan therapy in attenuating declines in LVEF, GLS, or cardiotoxicity incidence. In that study, patients were randomized on the basis of hs-cTnI measurements taken before each chemotherapy cycle according to predefined thresholds, which could fall below the 99th percentile.[8]

Over time, anthracycline chemotherapy protocols have evolved, with the use of lower doses. A lower anthracycline dose was used in our study than in the other 2 studies.[6,8] Our findings demonstrate that the prevention of subclinical cardiotoxicity, as evaluated by GLS, is possible even at reduced anthracycline doses. It is notable that our strategy seems to have successfully identified increased-risk individuals, as evidenced by the higher incidence of subclinical cardiotoxicity by GLS in our placebo group compared with that typically reported.[8,17,18] This approach excluded individuals without anthracycline-induced myocardial injury, thereby avoiding unnecessary treatment for low-risk patients unlikely to benefit and reducing both costs and the risk of side effects.[5] It is important to note that early detection of subclinical cardiotoxicity allows prompt intervention, potentially preventing structural changes that could result in HF.[19]

The SARAH trial is one of the first randomized trials to evaluate sacubitril-valsartan as a treatment strategy for preventing cardiotoxicity.[10,11] Our results align with an open-label, randomized study with a small intervention group in which low doses of sacubitril-valsartan reduced cardiotoxicity, mitigated GLS impairment, and demonstrated good tolerability without affecting biomarkers.[10] Both the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) II and SARAH studies showed some benefits in attenuating GLS reduction. However, the PRADA II trial found no significant overall reduction in LVEF decline measured by CMR or in subgroups (HER2 positive or elevated troponin), although sacubitril-valsartan attenuated the increase in biomarkers.[11] Conversely, the SARAH study demonstrated a reduction in LVEF decline measured by CMR in patients with elevated hs-cTnI, but no significant effects were observed on biomarkers. One hypothesis to explain this difference is that in the SARAH study, patients were already stratified with elevated hs-cTnI, indicating higher risk of cardiotoxicity, which may have enhanced the observed benefits on GLS and LVEF. Previously, some studies have documented its use in HF or established HF attributable to cardiotoxicity.[20,21] In animal models of

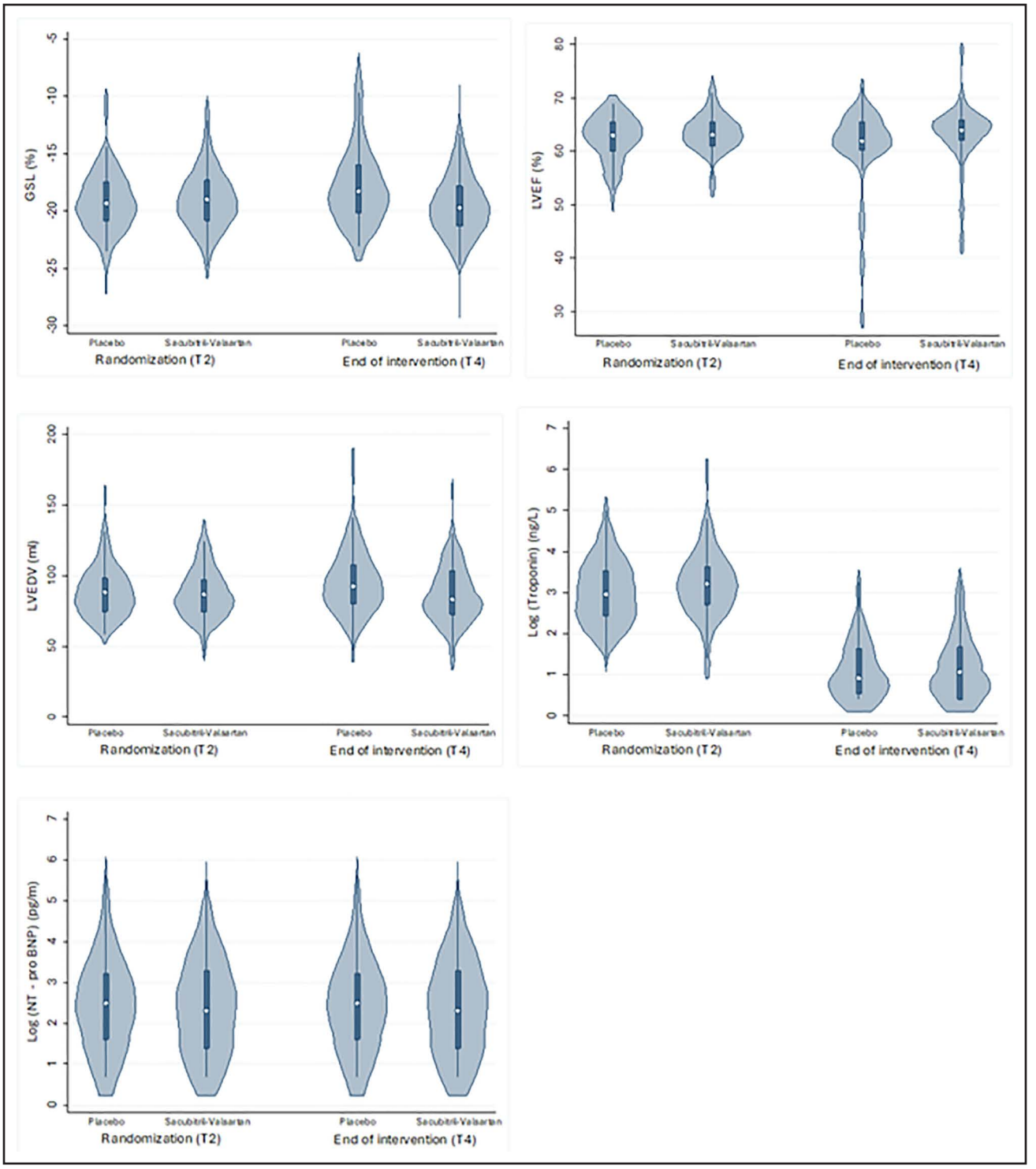

Figure 4. Violin plot of GLS, LVEF, LVEDV, hs-cTnI, and NT-proBNP from baseline prerandomization (T2) to the end of the intervention (T4).

GLS indicates global longitudinal strain; hs-cTnI, high-sensitivity cardiac troponin I; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

anthracycline-induced cardiotoxicity, sacubitril-valsartan reduced oxidative stress, protected against mitochondrial and endothelial dysfunction, inhibited myocardial inflammation, decreased hypertrophy and fibrosis, and improved renin-angiotensin-aldosterone system balance. These findings suggest that sacubitril-valsartan may offer potential advantages over monotherapy with other renin-angiotensin-aldosterone system blockers.[9] Although previous studies with other renin-angiotensin-aldosterone system inhibitors have reported benefits,

these findings derive predominantly from legacy chemotherapy protocols that used higher anthracycline doses. In contrast, recent investigations with lower anthracycline doses have produced less conclusive results for the prevention of cardiotoxicity.[22] Multiple trials, including OVERCOME (Prevention of Left Ventricular Dysfunction With Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for the Treatment of Malignant Hemopathies), PRADA, CECCY (Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity, and CARE, have evaluated the efficacy of various cardioprotective agents, demonstrating only modest or no benefits in preserving LVEF and preventing cardiotoxicity.[23–26] Collectively, these inconsistent results led to limited use in routine clinical practice in patients receiving low-dose anthracycline.

An important aspect of our study was the use of GLS as a criterion for defining cardiotoxicity. GLS may be a sensitive early measure of LV subclinical dysfunction, and its value in predicting outcomes has been reported.[15,25–28] A reduction of >15% has been described as a predictor of a future decline in LVEF with high specificity, making it the threshold recommended by guidelines when GLS is monitored during cancer therapy.[15] Sacubitril-valsartan significantly reduced the incidence of cardiotoxicity as evaluated by GLS, demonstrating a more substantial effect on GLS than previously studied drugs.[22,24,25,29] Interim analysis results of the SAFE study (Cardiotoxicity Prevention in Breast Cancer Patients Treated With Anthracyclines and/or Trastuzumab), which evaluated the preventive effect of ramipril or bisoprolol on anthracycline-induced cardiotoxicity, is one of the few trials to report positive findings. SAFE used a cardiotoxicity definition that included a decrease in GLS; however, this study used a change in GLS threshold of 10%, lower than the currently recommended threshold of 15% used in the SARAH trial. Furthermore, the SAFE study noted only a modest attenuation in the GLS decline with either carvedilol or combination therapy, with no additional benefit observed with ramipril alone.[12]

The incidence of clinical events was low in our study, which is consistent with contemporary studies[8,10,11,24] demonstrating that lower doses of anthracyclines are associated with low rates of cardiovascular events.

The intervention used in this study was generally safe and well tolerated. Despite the higher rate of hypotension and need for dose reduction in the sacubitril-valsartan group, few patients required therapy discontinuation. It is notable that 81% of the participants were randomized after the final session of anthracycline treatment, highlighting the cumulative nature of the toxicity associated with these agents. It is possible that initiating a cardioprotective strategy after the completion of chemotherapy could enhance tolerability.

Strengths of this study include its randomized double-blind design in a contemporary cohort of patients receiving low doses of anthracycline, the inclusion of patients with biochemical evidence of acute myocardial injury, and the use of a structured, prospective protocol with advanced monitoring techniques.

Limitations

The study should be interpreted within the context of its design and limitations, including its single-center setting, limited sample size, short 6-month follow-up period, and low event rate, which restrict the ability to fully assess the clinical implications of the results. Another limitation is the imbalance in trastuzumab use between the placebo and sacubitril-valsartan groups, with a higher rate observed in the placebo group. This difference could have influenced LVEF outcomes owing to the known cardiotoxic effects of trastuzumab. However, sensitivity analysis suggested that HER2 status did not significantly affect the primary outcome. In addition, exploratory analysis of the HER2 negative subgroup of patients showed beneficial effects of sacubitril-valsartan on GLS. Last, although the choice of a decline in GLS >15% as a primary end point may be questioned, it aligns with the 2002 European Society of Cardiology guidelines on cardio-oncology,[15] which recommend this criterion for monitoring cardiotoxicity owing to its predictive power for changes in LVEF.

Conclusions

The SARAH trial demonstrated that sacubitril-valsartan therapy significantly reduced the incidence of LV dysfunction, as assessed by LV GLS, in patients with elevated hs-cTnI levels after anthracycline administration. Our findings suggest that sacubitril-valsartan may play a potential role in preventing the progression of anthracycline-induced myocardial injury.

ARTICLE INFORMATION

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Supplemental Material

List of Safety Monitoring Committee
List of Investigators
Inclusion and exclusion criteria
Biomarkers Measurement
Echocardiography Assessment
Cardiac Magnetic Resonance Assessment
Other Methodological Aspects
List of Medications Used by Patients at Baseline
Figures S1–S4
Tables S1–S17
Protocol and Statistical Analysis Plan
References 30–62

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