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ORIGINAL RESEARCH ARTICLE

Sacubitril/Valsartan and Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy: The PRADA II Randomized Clinical Trial

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BACKGROUND: Anthracycline- and trastuzumab-associated cardiotoxicity may lead to cardiac dysfunction and dose reduction or halt of potentially life-saving adjuvant cancer therapy. Whether angiotensin receptor/neprilysin inhibitors can prevent cancer therapy–related cardiac dysfunction and injury remains to be established.

METHODS: PRADA II (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) was a randomized, parallel-group, placebo-controlled, double-blind, multicenter trial conducted at 4 academic medical centers in Norway that evaluated the cardioprotective effect of sacubitril/valsartan versus placebo administered concomitantly with anthracycline-containing breast cancer therapy and continued for 18 months. The target dose was 97/103 mg BID. The primary outcome was change in left ventricular ejection fraction by cardiovascular magnetic resonance from prior to initiation of chemotherapy to 18 months thereafter. Secondary outcomes included change in echocardiographic global longitudinal strain, circulating cardiac troponins, and NT-proBNP (N-terminal pro-B-type natriuretic peptide).

RESULTS: In total, 138 women (mean±SD age: 54.0±9.4 years) were randomized. The overall decline in left ventricular ejection fraction from baseline to 18 months was 2.2 percentage points (95% CI, 1.1 to 3.3) in the placebo group and 1.1 percentage points (95% CI, −0.01 to 2.2) in the sacubitril/valsartan group. The between-group difference was 1.1 percentage points (95% CI, −0.4 to 2.7; P=0.16). Left ventricular global longitudinal strain was normal and remained stable in the sacubitril/valsartan group throughout the study (change from baseline to 18 months, −0.3 [95% CI, −0.80 to 0.2]). In contrast, there was a progressive decline in the placebo group (change from baseline to 18 months, 0.5 [95% CI, 0.05 to 1.0]). The between-group difference was −0.9 (95% CI, −1.5 to −0.2). The mean increases in NT-proBNP and cardiac troponin I concentrations from baseline to 18 months were greater in the placebo group than in the sacubitril/valsartan group (log difference, 0.3 [95% CI, 0.05 to 0.6] for NT-proBNP and 0.5 [95% CI, 0.1to 1.0] for cardiac troponin I).

CONCLUSIONS: Anthracycline-based treatment for early breast cancer was associated with a reduction in left ventricular ejection fraction that was not significantly attenuated by sacubitril/valsartan.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03760588.

Key Words: anthracyclines ■ breast cancer ■ cardiotoxicity ■ global longitudinal strain ■ magnetic resonance imaging ■ troponin ■ ventricular ejection fraction

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Clinical Perspective

What Is New?

- The angiotensin receptor/neprilysin inhibitor sacubitril/valsartan is associated with favorable clinical outcomes compared with enalapril in heart failure with reduced ejection fraction, but whether sacubitril/valsartan can prevent cancer therapy–related cardiac dysfunction, injury, and stress remains unknown.
- Anthracycline-based treatment for early breast cancer is associated with a reduction in left ventricular ejection fraction, assessed by cardiovascular magnetic resonance, that was not significantly attenuated by sacubitril/valsartan.
- Sacubitril/valsartan prevented anthracycline-associated worsening in echocardiographic global longitudinal strain and attenuated chronic myocardial injury and stress, assessed by cardiac biomarkers.

What Are the Clinical Implications?

- The angiotensin receptor/neprilysin inhibitor sacubitril/valsartan may prevent cancer therapy–related chronic myocardial injury and stress, and larger randomized clinical trials are warranted to assess the effect on clinical end points.

Nonstandard Abbreviations and Acronyms

CMR	cardiovascular magnetic resonance
NT-proBNP	N-inal pro-B-type natriuretic peptide
PRADA	Prevention of Cardiac Dysfunction DuringAdjuvantBreastCancerTherapy

Contemporary treatment algorithms for early breast cancer are associated with markedly improved overall survival. Still, anthracycline- and trastuzumab-associated cardiotoxicity may lead to dose reduction or halt potentially life-saving adjuvant cancer therapy. Based on early studies suggesting that neurohormonal blockade may prevent or delay a reduction in left ventricular systolic function after anthracycline therapy,[1,2] several small-scale randomized clinical trials have recently tested the hypothesis that concomitant neurohormonal blockade may prevent or attenuate cardiotoxicity-induced myocardial injury and a subsequent reduction in cardiac function.[2–10] However, the results of recent trials have been generally disappointing, with modest or no significant effects reported.[3–9]

The angiotensin receptor/neprilysin inhibitor sacubitril/valsartan is associated with favorable clinical outcomes compared with enalapril in heart failure with reduced ejection fraction,[11] but so far, sparse randomized data exist concerning the effect of sacubitril/valsartan in the cardio-oncology setting. A recent meta-analysis suggests that, in patients with cancer therapy–induced heart failure with reduced ejection fraction, sacubitril/valsartan is associated with a favorable effect on functional class and echocardiographic indices of ventricular function compared with baseline values.[12] Moreover, experimental data suggest that sacubitril/valsartan may have favorable effects compared with angiotensin receptor blockers.[13,14] Accordingly, the PRADA II trial (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy II)[15] tested the hypothesis that sacubitril/valsartan, initiated concomitantly with adjuvant or neoadjuvant anthracycline-containing cancer chemotherapy with and without trastuzumab and maintained for 18 months, would prevent or attenuate cardiac injury and the development of cardiac dysfunction in patients with early breast cancer.

METHODS

Trial Design and Oversight

Data from the PRADA II trial cannot be publicly shared because of the risk of violating privacy, as regulated by the institutional data protection officer. PRADA II is a prospective, multicenter, randomized, placebo-controlled, double-blind, parallel-group clinical trial. The rationale and design have been described previously.[15] The PRADA II trial protocol was approved by the Regional Ethics Committee of South-Eastern Norway (2017/2411) and registered in the ClinicalTrials.gov registry (URL: https://www.clinicaltrials.gov; unique identifier: NCT03760588) before study initiation. Enrollment occurred between January 31, 2019, and January 30, 2023, with final follow-up on September 5, 2024. The trial complies with the Declaration of Helsinki, and all participants provided written informed consent before randomization. A data monitoring committee oversaw the conduct of the trial and performed analyses regularly to assess patient safety. A patient with previous breast cancer served as a user representative in the study steering committee and participated in the discussions concerning study design and conduct. The first draft of the manuscript was written by T.O. All authors participated in the interpretation of the data and critical review of the manuscript. T.O. and M.W.F. had full access to all data in the study and take responsibility for its integrity and the data analysis

Participants

Women ≥18 years of age with early breast cancer scheduled for (neo)adjuvant chemotherapy with epirubicin and cyclophosphamide were eligible for inclusion. A full list of eligibility criteria is provided in Table S1.

Study Randomization and Interventions

Eligible patients were randomly assigned at a 1:1 ratio in a double-blind fashion to receive sacubitril/valsartan or identical looking placebo tablets before initiation of anthracycline therapy. Study medications and matching placebo tablets were

provided by Novartis. The target dose was 97/103 mg BID. The randomization was stratified according to study sites and scheduled treatment with trastuzumab.

Study Procedures

Patients were examined before the start of (neo)adjuvant chemotherapy, after completion of anthracycline therapy (3 months), and 18 months after randomization. The study drug was initiated after baseline examinations but before chemotherapy. During each visit, patients were examined with cardiovascular magnetic resonance (CMR), echocardiography, and blood samples for biomarker assessment. The CMR, echocardiographic, and biochemical procedures performed, as well as the trial drug dose titration and procedure to assess compliance with use of the study drug, are described in the Supplemental Material. Figure S1 illustrates the study flow.

Outcome Measures

The primary outcome was change in left ventricular ejection fraction by CMR from randomization to 18 months. Secondary outcomes included change in echocardiographic global longitudinal strain; circulating concentrations of cardiac troponin I, cardiac troponin T, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) from baseline to 18 months; the incidence of a clinically significant reduction in systolic function, defined as a reduction in left ventricular ejection fraction >5% as assessed by CMR; and the incidence of (1) moderate or severe cancer therapy–related cardiac dysfunction and (2) mild cancer therapy–related cardiac dysfunction, as defined by the 2022 European Society of Cardiology guidelines on cardio-oncology.[16] Additional secondary outcome measures reported in the Supplemental Material include changes in left ventricular ejection fraction by CMR, echocardiographic global longitudinal strain, circulating concentrations of cardiac troponin I, cardiac troponin T, and NT-proBNP concentrations from baseline to the end of anthracycline therapy. Safety assessments included serious adverse events and adverse events that occurred during the trial period.

Sample Size Considerations

Based on the results from the initial PRADA trial, a decline in left ventricular ejection fraction, assessed by CMR, of 3.4% was assumed in the placebo group and 0.7% in the sacubitril/valsartan group, with a common SD of 4.7%. With 138 patients, the power for the primary outcome was approximately 92%.

In the original sample size calculation, the target sample size was 300 patients, resulting in >99% power for the primary outcome and assuring adequate power for relevant subgroups. After experiencing slow recruitment, in particular during the early phase of the COVID-19 pandemic, in September 2020, the steering committee decided to reduce the sample size target to 214 patients. This resulted in reduced power in the subgroups, whereas the power for the primary outcome was still ≈99%. However, the enrollment rate remained lower than originally projected, and the financial sponsor of the trial informed the steering committee that funding of the study would be halted by the end of 2024. Accordingly, the steering committee decided to stop the inclusion of patients after a total number of 158 patients had been included by January 2023.

Statistical Analysis

The statistical analyses follow the statistical analysis plan for PRADA II, version 1.0, published on the ClinicalTrials.gov page for the trial. All analyses were prespecified and performed on the full analysis set, corresponding to a modified intention-to-treat population, defined as all participants randomly assigned to a treatment group who had received at least 1 study treatment administration and 1 dose of anthracyclines after randomization and had completed at least the baseline CMR examination.

The primary outcome was analyzed with a linear mixed model, fitted to data from 3 time points (baseline, after the last epirubicin-cyclophosphamide administration, and 18 months after initiation of epirubicin-cyclophosphamide), with fixed effects for treatment, time point, treatment × time point interaction, and the factors used to stratify the randomization (study site and scheduled treatment with trastuzumab). A random intercept at the patient level was used. The primary effect estimate is the model-estimated between-group difference in mean change from baseline to 18 months with a 95% CI and a *P* value for the null hypothesis of a 0 difference.

Secondary continuous outcomes were measured at the same time points as the primary outcome and were analyzed in the same manner as the primary outcome, except that no hypothesis test for treatment effect was performed. Cardiac troponin I, cardiac troponin T, and NT-proBNP were heavily skewed to the right, and the outcome data were log transformed before fitting the linear mixed models. Secondary dichotomous outcomes were analyzed with logistic regression models, adjusted for study site and scheduled treatment with trastuzumab. The effect estimates are the differences between the predicted proportions (adjusted risk difference for sacubitril/valsartan minus placebo) of the dichotomous outcomes, calculated from the fitted models with the delta method.[17] Hosmer-Lemeshow goodness-of-fit tests were performed to assess whether the logistic regression models showed signs of poor fit.

Missing data in the primary and secondary continuous outcomes were handled by the linear mixed model under the assumption of missing at random. No patients had missing data for the primary outcome or the biomarker outcomes at all time points; however, 28 patients had missing values on global longitudinal strain for all 3 time points. The missing data on global longitudinal strain were imputed with multiple imputation before fitting the linear mixed model.

The widths of the CIs for secondary outcomes have not been adjusted for multiplicity and should not be used in place of hypothesis tests. Secondary outcomes should be interpreted as exploratory or supportive of the primary analysis. The statistical analyses were performed with Stata/SE 17 (StataCorp LLC, College Station, TX). Additional details are provided in the Supplemental Material, including descriptions of assumption checks and sensitivity analyses and more information on the handling of missing data.

RESULTS

In total, 138 women with breast cancer (69 randomized to sacubitril/valsartan and 69 to the placebo group) were included in the full analysis set (Figure 1). Patient characteristics according to randomization status are detailed in Table 1. Anthracycline dose, rate of trastuzumab treatment, and cardiometabolic comorbidities, including

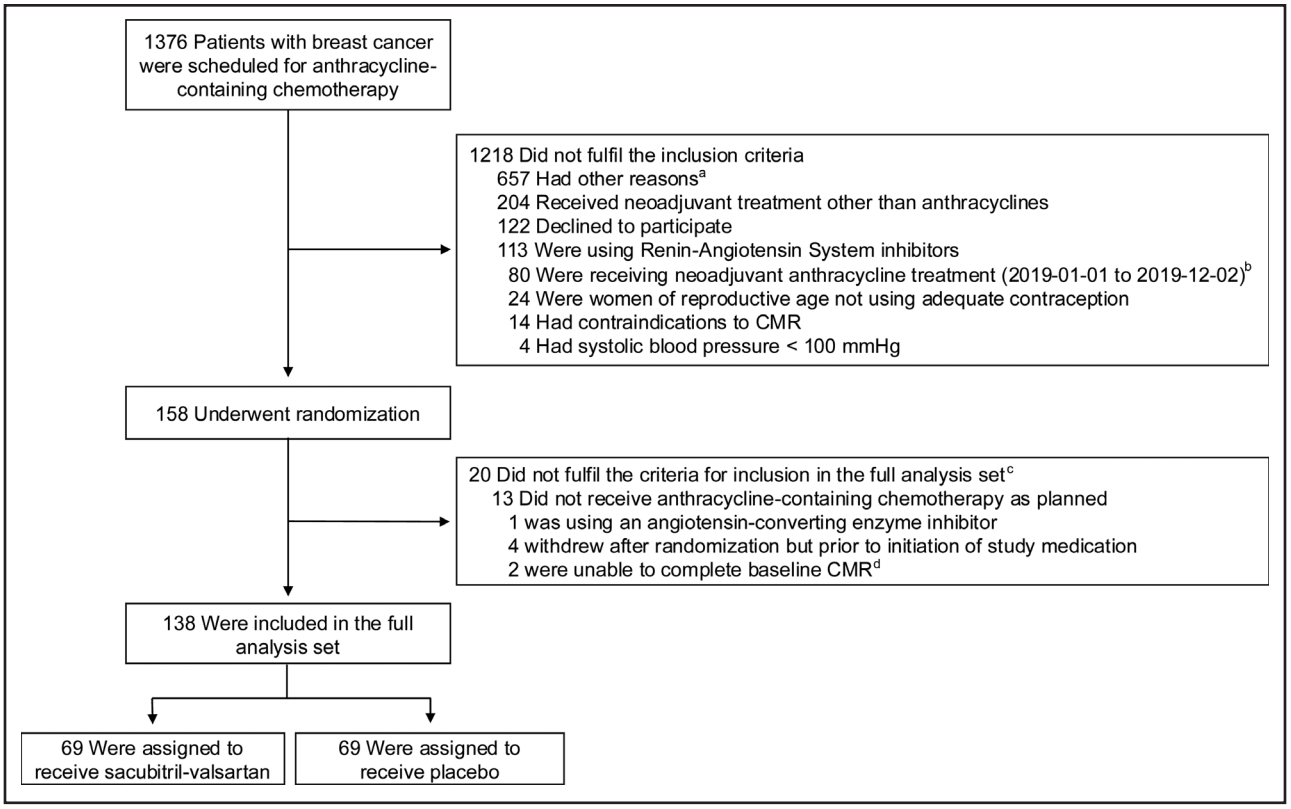

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.
[a]Other reasons included COVID-19, participation in other clinical trials, and language-related limitations. [b]Patients undergoing neoadjuvant anthracycline treatment were included from December 2, 2019. [c]Of the 20 patients who did not meet the criteria for inclusion in the full analysis set, 9 had been allocated to the placebo group and 11 to the sacubitril/valsartan group. [d]Attributable to contraindications or inability to undergo cardiovascular magnetic resonance. CMR indicates cardiovascular magnetic resonance.

hypertension and diabetes, were generally well balanced between groups but with numerically higher systolic blood pressure and rate of lipid-lowering treatment in the placebo group (Table 1).

Primary Outcome

Left ventricular ejection fraction, as assessed by CMR, was well balanced between groups at baseline (sacubitril/valsartan, 60.6 percentage points [95% CI, 59.4 to 61.7] versus placebo, 60.0 percentage points [95% CI, 58.8 to 61.1]) and remained relatively stable in the sacubitril/valsartan group throughout the study. In contrast, there was a mild, gradual decline in the placebo group. The overall decline in left ventricular ejection fraction from randomization to 18 months was 2.2 percentage points (95% CI, 1.1 to 3.3) in the placebo group and 1.1 percentage points (95% CI, −0.01 to 2.2) in the sacubitril/valsartan group. The between-group difference was 1.1 percentage points (95% CI, −0.4 to 2.7; P=0.16) (Table 2; Figures 2 and 3).

Prospectively Designed Subgroup Analyses

HER2 (Human epidermal growth factor 2) positivity and subsequent treatment with trastuzumab were a stratification variable and a prospectively defined subgroup, respectively. As in the primary analysis, left ventricular ejection fraction remained stable in the sacubitril/valsartan group throughout the study: 59.6 percentage points (95% CI, 56.7 to 62.5) at baseline versus 59.4 percentage points (95% CI, 56.3 to 62.4) after 18 months. In contrast, there was a progressive and more marked decline in the placebo group: 59.0 percentage points (95% CI, 56.0 to 62.0) at baseline versus 55.2 percentage points (95% CI, 52.2 to 58.2) after 18 months. The between-group difference in change from baseline to 18 months was 3.6 percentage points (95% CI, −0.4 to 7.7; Figure 2). Thus, despite the greater difference in the point estimates than in the overall cohort, the between-group difference in this subgroup was not significant.

Other prospectively defined subgroups included patients with baseline cardiac troponin concentrations above the level of detection. Thirty-three patients (24%) had cardiac troponin I concentrations above 1.6 ng/L, whereas 108 patients (78%) had cardiac troponin T concentrations above 3.0 ng/L. In the subgroup with detectable cardiac troponin T, the reduction in left ventricular ejection fraction was greater in the placebo than in the sacubitril/valsartan group; however, the CI for the

Table 1. Patient Characteristics at Baseline by Randomization Group

Characteristics	Sacubitril/valsartan (n=69)	Placebo (n=69)
Age, y	53.6±9.2	54.5±9.7
Ethnicity, No. (%)		
European	67 (97.1)	68 (98.6)
Asian	2 (2.9)	1 (1.4)
Weight, kg	75.0±14.1	77.7±15.4
Height, cm	168.0±5.1	166.3±5.8
Body mass index, kg/m^2	26.6±4.9	28.1±5.5
Smoking status, No. (%)		
Current	11 (15.9)	11 (15.9)
Previously	36 (52.2)	25 (36.2)
Never	22 (31.9)	33 (47.8)
Diabetes, No. (%)	3 (4.3)	1 (1.4)
Systolic blood pressure, mm Hg	127.0±15.6	132.4±19.3
Diastolic blood pressure, mm Hg	79.9±9.1	81.2±10.2
Heart rate, bpm	70.6±11.7	73.0±12.9
Antihypertensive treatment, No. (%)	5 (7.2)	5 (7.2)
Lipid-lowering treatment, No. (%)	3 (4.3)	8 (11.6)
Serum creatinine, μmol/L	61.0±11.6	64.0±10.4
eGFR, mL per min per 1.73 m^2	100±12.5	96.0±13.9
Anthracycline as planned with EC 90 mg/m^2 × 4, No. (%)	56 (81.2)	61 (88.4)
Reduced anthracycline dose*, No. (%)	13 (18.8)	8 (11.6)
Taxane treatment, No. (%)	45 (65.2)	43 (62.3)
Trastuzumab treatment, No. (%)	12 (17.4)	11 (15.9)
Radiation treatment, No. (%)	57 (82.6)	55 (79.7)
Side of radiation exposure, No. (%)		
Left side	29 (42.0)	24 (34.8)
Right side	25 (36.2)	31 (44.9)
Both sides	0 (0.0)	1 (1.4)
Tumor characteristics		
HER2 positive, No. (%)	12 (17.4)	11 (15.9)
Estrogen receptor positive, No. (%)	55 (79.7)	50 (72.5)
Progesterone receptor positive, No. (%)	47 (68.1)	44 (63.8)
Ki67 index, %	40.5 ± 20.4	45.9 ± 23.8

Plus-minus values are mean±SD.

bpm indicates beats per minute; EC, epirubicin cyclophosphamide; eGFR, estimated glomerular filtration rate (by Chronic Kidney Disease Epidemiology Collaboration creatinine 2021 version); and HER2, human epidermal growth factor receptor 2.

*A reduced anthracycline dose, including epirubicin cyclophosphamide 60, was given because of patient frailty or chemotherapy-related adverse effects (see details in the Supplemental Material).

between-group difference included 0: 1.6 percentage points (95% CI, −0.2 to 3.4). In the subgroup with detectable cardiac troponin I concentrations, no difference was observed.

Secondary Outcomes

Left ventricular systolic function, as assessed by echocardiographic global longitudinal strain, was normal and well balanced between groups at baseline (Table 2) and did not decline in the sacubitril/valsartan group throughout the study (change from baseline to 18 months, −0.3 [95% CI, −0.8 to 0.2]). In contrast, there was a progressive decline in echocardiographic global longitudinal strain in the placebo group (change from baseline to 18 months, 0.5 [95% CI, 0.05 to 1.0]). The between-group difference was −0.9 (95% CI, −1.5 to −0.2).

The incidence of a clinically significant reduction in left ventricular ejection fraction >5% by CMR was 42% in the placebo group and 33% in the sacubitril/valsartan group, with a between-group difference of 8.7% (95% CI, −7.3% to 24%).

Concentrations of both cardiac troponins and NT-proBNP at baseline were generally low. In both the placebo and sacubitril/valsartan groups, concentrations of cardiac troponins increased markedly after completion of anthracycline therapy, followed by a decline to the final study visit (Figure 4). In contrast, concentrations of NT-proBNP increased gradually from baseline to 18 months in the placebo group (Figure 4). From randomization to 18 months, increases in log-transformed concentrations of cardiac troponin I and NT-proBNP were greater in the placebo group than in the sacubitril/valsartan group, whereas cardiac troponin T concentrations did not differ between groups (Table 2). As logarithmically transformed values may not be intuitive to readers, the nontransformed observed mean change was 38 ng/L (NT-proBNP) and 2 ng/L (cardiac troponin I) greater in the placebo group than in the sacubitril/valsartan group. Detailed changes in primary and secondary outcomes from baseline to the end of anthracycline therapy are shown in Table S2.

Generally, there were few cases (2 in the placebo group and 0 in the sacubitril/valsartan group) of moderate or severe cancer therapy–related cardiac dysfunction as defined by the 2022 European Society of Cardiology Guidelines on Cardio-Oncology[16] (definitions are provided in the Supplemental Material). The incidence of mild cancer therapy–related cardiac dysfunction, defined by the 2022 European Society of Cardiology Guidelines on Cardio-Oncology as a new relative decline in global longitudinal strain >15% and/or increase in cardiac biomarkers above defined thresholds in asymptomatic patients with left ventricular ejection fraction greater or equal to 50%,[16] was 83% in the placebo group and 71% in the sacubitril/valsartan group, with a between-group difference of 12% (95% CI, −2.5% to 25%).

Medication Compliance and Safety

Anthracycline treatment details for participants deviating from the standard regimen are provided in Table S3. The

Table 2. Primary and Secondary Repeated Measures Outcomes Estimated Using Linear Mixed Models

Outcome	Baseline	End of anthracycline treatment	18 months	Change from baseline to 18 months	Between-group difference in change from baseline to 18 months
	Mean (95% CI)				
Left ventricular ejection fraction by CMR (%)					
Sacubitril/valsartan	60.6 (59.4 to 61.7)	59.7 (58.4 to 60.9)	59.5 (58.3 to 60.7)	−1.1 (−2.2 to 0.01)	1.1 (−0.4 to 2.7)
Placebo	60.0 (58.8 to 61.1)	58.5 (57.3 to 59.7)	57.8 (56.6 to 58.9)	−2.2 (−3.3 to −1.1)	
Global longitudinal strain by echocardiography					
Sacubitril/valsartan	−19.1 (−19.5 to −18.7)	−19.5 (−20.0 to −19.1)	−19.4 (−19.8 to −19.0)	−0.3 (−0.8 to 0.2)	−0.9 (−1.5 to −0.2)
Placebo	−19.0 (−19.4 to −18.6)	−18.7 (−19.2 to −18.3)	−18.5 (−18.9 to −18.1)	0.5 (0.05 to 1.0)	
Log-transformed high-sensitivity cardiac troponin I (log ng/L)					
Sacubitril/valsartan	0.03 (−0.2 to 0.3)	1.8 (1.6 to 2.1)	0.3 (0.009 to 0.5)	0.2 (−0.08 to 0.5)	−0.5 (−1.0 to −0.1)
Placebo	−0.3 (−0.5 to −0.04)	2.1 (1.9 to 2.3)	0.5 (0.2 to 0.7)	0.8 (0.5 to 1.0)	
Log-transformed high-sensitivity cardiac troponin T (log ng/L)					
Sacubitril/valsartan	1.2 (1.0 to 1.3)	2.4 (2.2 to 2.5)	1.6 (1.4 to 1.7)	0.4 (0.2 to 0.6)	−0.006 (−0.3 to 0.3)
Placebo	1.3 (1.1 to 1.5)	2.6 (2.4 to 2.7)	1.7 (1.6 to 1.9)	0.4 (0.3 to 0.6)	
Log-transformed NT-proBNP (log ng/L)					
Sacubitril/valsartan	3.9 (3.7 to 4.0)	3.7 (3.5 to 3.9)	3.9 (3.7 to 4.1)	0.06 (−0.1 to 0.2)	−0.3 (−0.6 to -0.06)
Placebo	3.9 (3.7 to 4.1)	4.1 (3.9 to 4.3)	4.2 (4.0 to 4.4)	0.4 (0.2 to 0.5)	

CMR indicates cardiovascular magnetic resonance; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

number and proportion of patients using different doses of sacubitril/valsartan and placebo at the final visit are shown in the Table S4. One hundred fifteen participants (83%) demonstrated compliance >70%. Among the 23 patients with lower compliance, 16 were in the sacubitril/valsartan and 7 in the placebo group. Ten participants did not complete the study and did not attend the final visit (visit 3), including 6 in the sacubitril/valsartan and 4 in the placebo group. Generally, the drug was well tolerated with no suspected unexpected serious adverse reactions. Adverse events were recorded systematically. A total of 29 serious adverse events were reported—13 in the sacubitril/valsartan and 16 in the placebo group (Table S5). Four patients, 2 in each study arm, experienced cancer recurrence. Of these, one patient in the placebo group died. One participant in the placebo group discontinued her anti-HER2 treatment because of a decline in left ventricular ejection fraction. Information detailing adverse events by randomization group is shown in Table S6. The most frequently occurring adverse events were muscle/joint pain (n=16), viral infection (n=13), symptomatic hypotension (n=11), and headache (n=9).

Information about the effect of the study intervention on systolic and diastolic blood pressure as well as serum creatinine is depicted in Figures S2 through S4).

DISCUSSION

In the current primary report of PRADA II, a randomized, multicenter, placebo-controlled, double-blind clinical trial of sacubitril/valsartan, an angiotensin receptor/neprilysin inhibitor, versus placebo, we report 4 main findings. First, contemporary adjuvant anticancer treatment for early breast cancer is associated with a modest but progressive

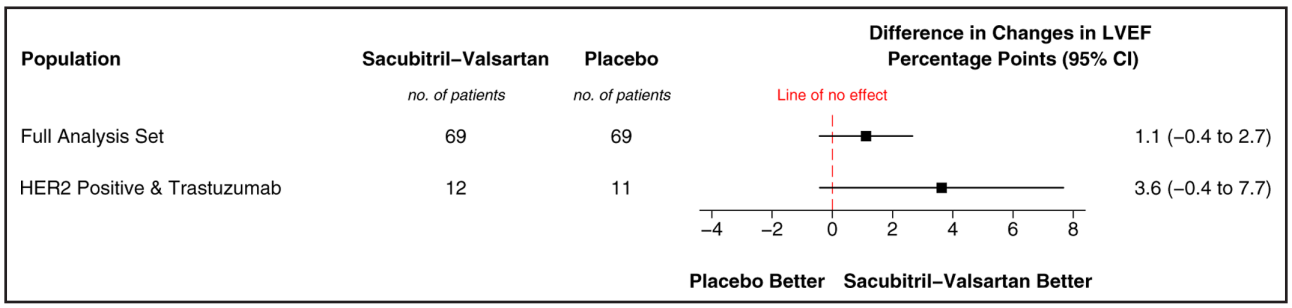

Figure 2. Forest plot showing between-group differences in the primary outcome measure, left ventricular ejection fraction from baseline to 18 months in the full analysis set and the subgroup of human epidermal growth factor 2–positive patients receiving trastuzumab.

HER2 indicates human epidermal growth factor 2; and LVEF, left ventricular ejection fraction.

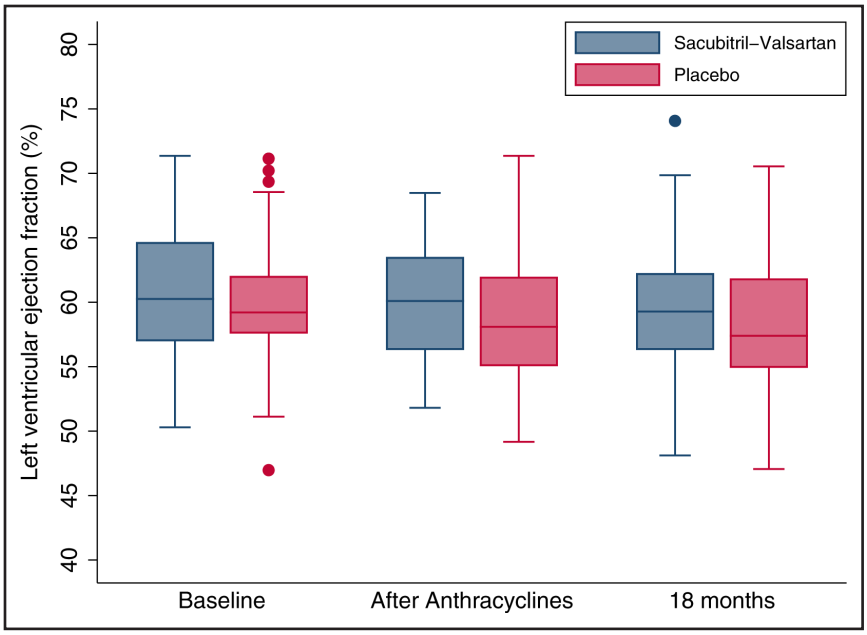

Figure 3. Temporal changes in the primary outcome measure by randomization group.
Boxplots show median with 25th and 75th percentiles (box) and outside values (dots) defined as above (or below) median ±1.5 times the interquartile range.

reduction in left ventricular systolic function over 18 months, as assessed by CMR and echocardiograpy. Second, although the reduction in the primary outcome measure, left ventricular ejection fraction, was not significantly attenuated by sacubitril/valsartan compared with placebo, the intervention prevented worsening in left ventricular echocardiographic global longitudinal strain, an early marker of decline in ventricular function,[18] and attenuated chronic myocardial injury and stress, as assessed by cardiac troponin I and NT-proBNP concentrations. Third, in a prespecified subgroup analysis of patients with HER2-positive cancers and subsequent trastuzumab therapy, left ventricular ejection fraction, assessed by CMR, remained stable in this group despite treatment with both anthracycline-containing chemotherapy and trastuzumab. In contrast, there was a more pronounced reduction in left ventricular function in the placebo group of HER2-positive cancer patients than in the placebo group of the overall study population. Finally, angiotensin receptor/neprilysin inhibition was well tolerated and not associated with an increased rate of serious adverse events. Collectively, the observed effect of sacubitril/valsartan on secondary outcomes, which include more sensitive imaging and biochemical markers of myocardial injury, stress, and dysfunction than left ventricular ejection fraction, raises the possibility that angiotensin receptor/neprilysin inhibition may represent a cardioprotective strategy in patients receiving anthracycline-containing cancer therapy. This hypothesis merits testing in well-powered multicenter trials, perhaps using a more sensitive primary outcome measure than left ventricular ejection fraction.

For patients with heart failure with reduced ejection fraction, sacubitril/valsartan, compared with enalapril, has convincingly been shown to reduce mortality and morbidity,[11] providing a rationale for angiotensin receptor/neprilysin inhibition to prevent ventricular dysfunction after cardiotoxic therapy. However, limited data exist concerning the effect of sacubitril/valsartan in the cardio-oncology setting. Case series reports and pilot studies have suggested clinical efficacy in patients with established cancer therapy–related cardiac dysfunction.[19–23] A recent meta-analysis showed that treatment with sacubitril/valsartan was associated with a favorable effect on functional class and echocardiographic indices of ventricular function compared with baseline values.[12] Experimental studies also indicate that sacubitril/valsartan may have favorable effects in preventing cardiotoxicity.[13,14]

PRADA II failed to reject the primary null hypothesis that the mean change in left ventricular ejection fraction, assessed by CMR from randomization to 18 months, is equal to sacubitril/valsartan and placebo. Several factors may have contributed to the observed lack of effect on the primary outcome. First, the unfortunate reduction in sample size and study power compared with the original plan may have contributed. Second, the observed decline in left ventricular ejection fraction in the control arm (2.2 percentage points) was less than anticipated in the power calculations. However, this is comparable with what has been observed in other recent clinical trials of anthracycline cardiotoxicity. For instance, in PRADA, the decline in left ventricular ejection fraction by CMR was 2.8 percentage points in the placebo-placebo group.[7] Similarly, in the Cardiac CARE study (High-Sensitivity Cardiac Troponin I–Guided Combination Angiotensin Receptor Blockade and Beta Blocker Therapy to Prevent Cardiac Toxicity in Cancer Patients Receiving Anthracycline Chemotherapy), the decline in CMR-assessed ejection fraction was 2.87% in the low-risk group.[3] Comparable reductions in ejection fraction were also reported in the PROACT (Preventing Cardiac Damage in Patients Treated for Breast Cancer and Lymphoma)[5] and SUCCOUR (Strain Surveillance of

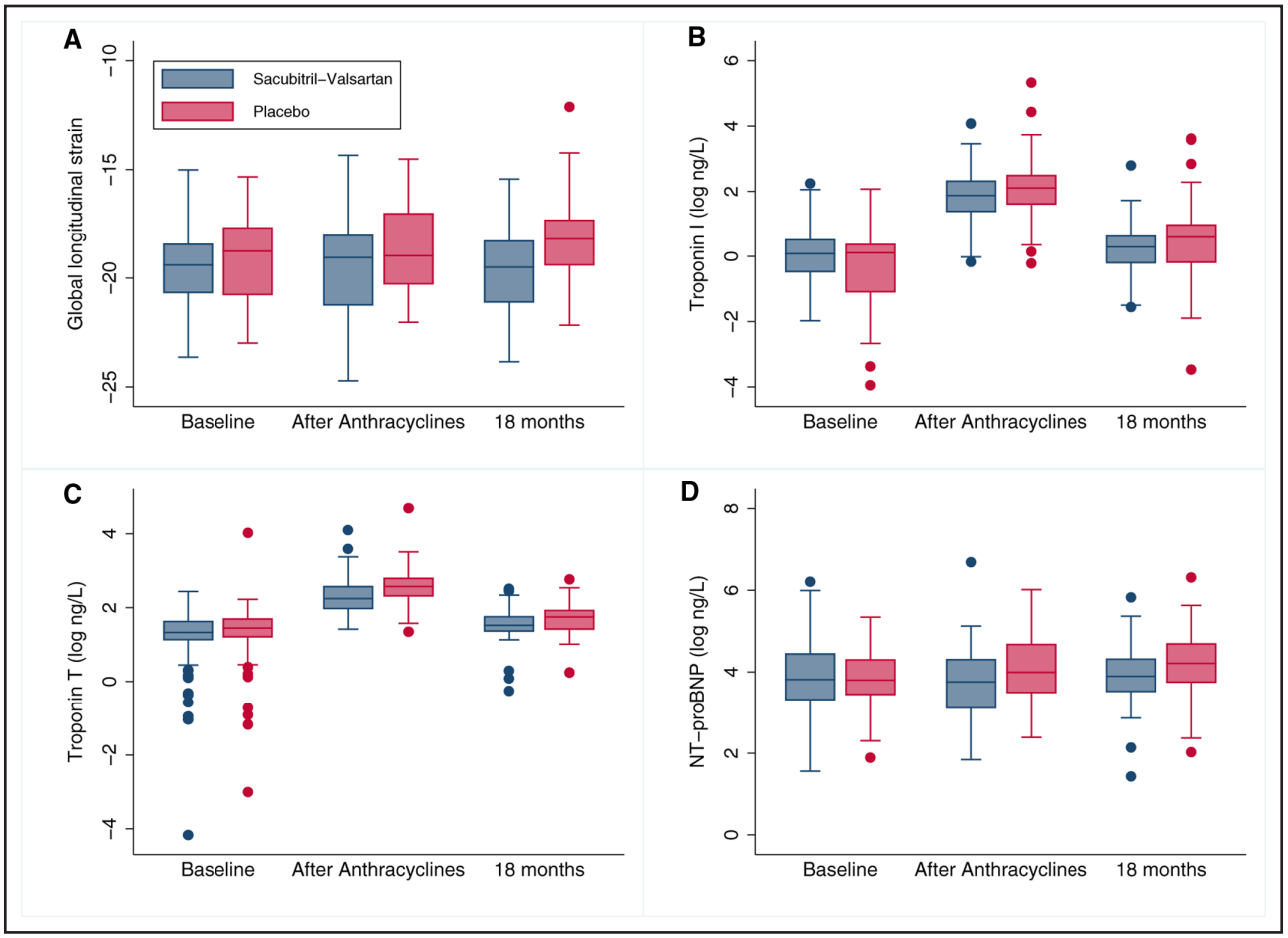

Figure 4. Temporal changes in continuous secondary outcome measures by randomization group.
Boxplots show median with 25th and 75th percentiles (box) and outside values (dots) defined as above (or below) median ±1.5 times the interquartile range. NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

Chemotherapy for Improving Cardiovascular Outcomes)[24] trials using transthoracic echocardiography, in which the reported decline ranged from 2 to 3 percentage points. Moreover, a drop in left ventricular ejection fraction may occur secondary to both myocellular dysfunction and increased end-systolic volumes[25,26] or reverse myocardial remodeling and declining end-diastolic volumes related to treatment with sacubitril/valsartan.[8,27] Accordingly, differential effects of the intervention on myocardial volumes may render left ventricular ejection fraction a less sensitive measure. In PRADA II, secondary outcome measures included echocardiographic global longitudinal strain, commonly considered to be a more sensitive and earlier sign of cancer therapy–related cardiac dysfunction than ejection fraction.[18] Additional secondary outcome measures included change in circulating sensitive biomarkers of chronic myocardial injury and stress.[28] Cardiac troponin release reflects myocardial injury, whereas natriuretic peptide release is a sensitive marker of cardiac stress. In the chronic state, small changes in circulating concentrations of these biomarkers, even within the normal range, are considered strong markers of future cardiovascular risk, in particular heart failure development.[29–32]

The enzyme neprilysin contributes to the degradation of natriuretic peptides and would therefore be expected to result in increased circulating concentrations of BNP. In PRADA II, the concentrations of NT-proBNP, which is degraded via mechanisms other than neprilysin, were measured.[33] Accordingly, the NT-proBNP concentration changes observed should be interpreted in the context of myocardial stress and not as secondary to pharmaceutical interference with NT-proBNP degradation. Although the NT-proBNP results are encouraging, a central question is whether the observed effects can be considered clinically relevant. Given that the Heart Failure Association of the European Society of Cardiology recently stated that an NT-proBNP concentration >75 ng/L in asymptomatic patients 50 to 75 years of age with risk factors means "rule in" for "heart stress," an increase in mean NT-proBNP concentration in the placebo group from 61 to 94 ng/L and an absolute between-group difference in change in NT-proBNP of 38 ng/L appears to be clinically relevant. The current NT-proBNP result, combined with the apparent prevention of the reduction in echocardiographic left ventricular global longitudinal strain and attenuation of the increase in cardiac troponin I, suggests that sacubitril/

valsartan may prevent chronic cardiac injury and stress induced by anthracyclines and potentially reduces the risk of transition from stage A to B heart failure. These observations appear to contrast with findings of recent randomized clinical trials of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors.[3,5] No significant effect of sacubitril/valsartan on cardiac troponin T concentration was observed. The reason for the different effect on cardiac troponin T and I is unclear but may be related to the stronger association between cardiac troponin I and changes in cardiac structure and function[34] and its apparent higher degree of cardiac specificity.[35]

Strengths of the PRADA II trial include the randomized, placebo-controlled, double-blind study design; the initiation of cardioprotective intervention before the start of cardiotoxic therapy; and the long intervention period, permitting evaluation of the temporal trends after the completion of cardiotoxic therapy. Moreover, the use of CMR, the reference method for assessment of cardiac anatomy and function, for assessment of change in the primary outcome measure; the multicenter organization of the trial; the use of highly competent centralized CMR and echocardiography core laboratories; as well as the use of an external, dedicated clinical trial unit for data analysis and trial monitoring are considerable strengths. Notable study limitations include the limited statistical power to detect differences in categorical end points, including clinical events. PRADA II did not reach its original inclusion target; however, the study still had reasonable power to detect differences in the primary outcome measure. The choice of a placebo-controlled trial design does not permit evaluation of whether a treatment effect is attributable to sacubitril or valsartan. Finally, the study population was generally at low to moderate cardiovascular risk and ethnically homogeneous.

In conclusion, adjuvant treatment for early breast cancer is associated with a reduction in left ventricular ejection fraction that was not significantly attenuated by sacubitril/valsartan.

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