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Dose-Response to Sacubitril/Valsartan in Patients With Heart Failure and Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Doses of sacubitril/valsartan (Sac/Val) achieved in clinical trials of heart failure with reduced ejection fraction (HFrEF) are often not reached in clinical practice.

OBJECTIVES The purpose of this study was to investigate associations among Sac/Val doses and changes in prognostic biomarkers, health status, and cardiac remodeling among individuals with HFrEF through 12 months of treatment with Sac/Val administered per usual care.

METHODS A total of 794 persons with HFrEF (ejection fraction [EF] ≤40%) were categorized according to average daily doses of Sac/Val divided into tertiles. Change from baseline to 12 months in biomarkers (N-terminal pro–B-type natriuretic peptide, high-sensitivity cardiac troponin T, soluble ST2, atrial natriuretic peptide, urinary cyclic guanosine monophosphate), Kansas City Cardiomyopathy Questionnaire-23 scores, and parameters of cardiac reverse remodeling (left ventricular EF, indexed left atrial and ventricular volumes, and E/e') were assessed.

RESULTS The average daily dose was 112 mg in Tertile 1 (low dose), 342 mg in Tertile 2 (moderate dose), and 379 mg in Tertile 3 (high dose). Similar changes in prognostic biomarkers were observed in all dose tertiles. Gains in Kansas City Cardiomyopathy Questionnaire-23 scores were comparable regardless of dose category. Consistent reverse cardiac remodeling in all dose categories occurred; the median absolute left ventricular EF improvement across HF dose groups was 9.3%, 8.7%, and 10.2%, for low, moderate, and high doses, respectively; similar improvements in left atrial and ventricular volumes and E/e' were also observed across dose categories.

CONCLUSIONS Among patients with HFrEF, similar improvement in prognostic biomarkers, health status, and cardiac remodeling were observed across various Sac/Val doses. (Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Outcomes [PROVE-HF]; NCT02887183 (J Am Coll Cardiol 2022;80:1529–1541)

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

ARNI = angiotensin receptor neprilysin inhibitor

GDMT = guideline-directed medical therapy

HFrEF = heart failure with reduced ejection fraction

hs-cTnT = high sensitivity cardiac troponin T

KCCQ-23 = Kansas City Cardiomyopathy Questionnaire-23

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Sac/Val = sacubitril/valsartan

In the medical treatment of patients with heart failure with reduced ejection fraction (HFrEF), clinical practice guidelines emphasize the importance of achievement of target doses of guideline-directed medical therapy (GDMT) whenever possible.[1,2] Although some GDMT for HFrEF has precedent data showing that higher doses reduced adverse risk and foster greater reverse remodeling (particularly evidence-based beta-blockers[3]), the data regarding benefit of higher vs lower doses tend to otherwise be mixed with most other therapies.[4,5] Nonetheless, titration to achieve target dose is an important exercise, because many individuals are undertreated for their HF.

Sacubitril/valsartan (Sac/Val), an angiotensin receptor/neprilysin inhibitor (ARNI), has been established as 1 of the 4 pillars of GDMT for HFrEF.[2,6] In the PARADIGM-HF[7] (Prospective Comparison of ARNI with Angiotensin-Converting-Enzyme Inhibitor [ACEI] to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, Sac/Val dosed at a target of 97/103 mg twice daily was superior to enalapril 10 mg twice daily. In an effort to ensure optimal administration of both drugs, a run-in period was used, only allowing those study participants able to reach the target doses of both treatments to be included. Thus, at randomization to treatment with Sac/Val, the dose administered was 97/103 mg twice daily, with superiority of Sac/Val demonstrated over enalapril. Notably, those requiring down-titration in dose postrandomization had higher event rates but similar risk reduction compared with enalapril.[8]

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Since its release and incorporation into clinical practice guidelines for the treatment of HFrEF, the doses of Sac/Val given in usual care have been considerably lower than those given in PARADIGM-HF, and relatively few patients in clinical practice reach the target GDMT doses similar to other GDMT.[9,10] For example, recent data showed that only 14%[11] of patients treated in usual care received Sac/Val at 97/103 mg twice daily. The gap between the evidence base supporting Sac/Val use at 97/103 mg twice daily and the usual care achievement of this dose has led to confusion about the benefit of the drug when used in doses below this target.[12,13]

In the PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sac/Val Therapy for Heart Failure; NCT02887183),[14] study participants with HFrEF were treated with Sac/Val per standard of care with a recommended target of 97/103 mg twice daily. The study protocol did allow for doses below the target based on clinician discretion or patient tolerance. We previously reported that among the 35% of study participants who did not reach 97/103 mg twice daily, similar degrees of reverse cardiac remodeling occurred by 12 months.[14] In this post hoc analysis, we sought to further expand this observation and more comprehensively evaluate mechanistic effects considered as a function of average Sac/Val dose over the duration of the PROVE-HF study. We hypothesized that mechanistic effects of Sac/Val would be largely consistent across Sac/Val dose categories.

METHODS

All study procedures were approved by local Institutional Review Boards.

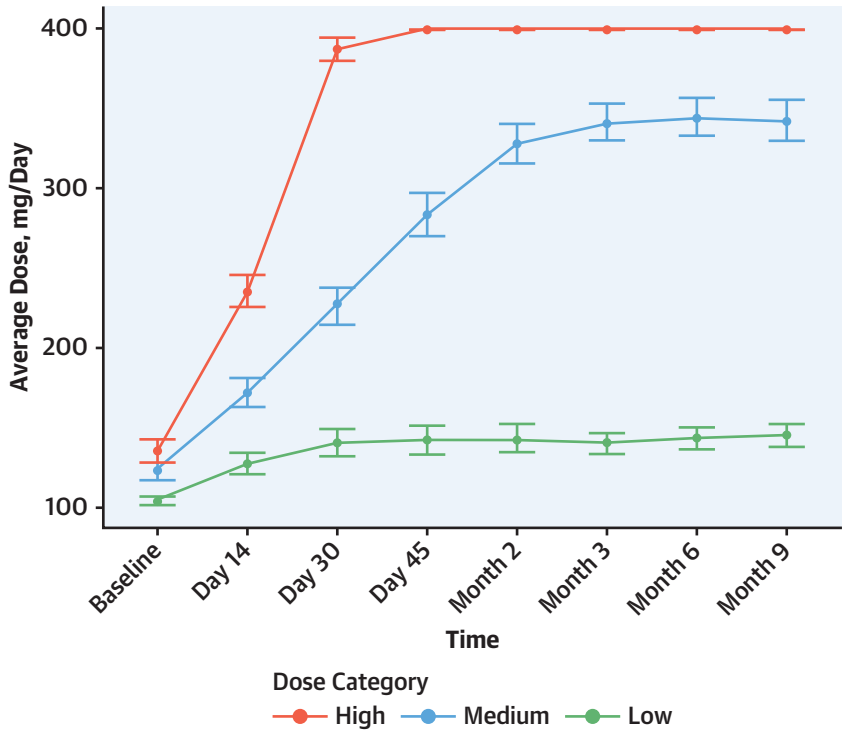
PROVE-HF STUDY DESIGN AND PARTICIPANTS. The rationale and design of the PROVE-HF study has been described previously.[15] Briefly, the study was a phase 4, 52-week, open-label, single-group study of participants with HFrEF (left ventricular ejection fraction [LVEF] ≤40%) initiated with Sac/Val treatment per usual care performed at 78 sites in the United States. After informed consent was obtained, angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) treatment was discontinued, and study participants were initiated on Sac/Val according to the U.S. prescribing information. Following Sac/Val initiation, study participants returned for study visits and drug titration approximately every 2 weeks through day 60, with a goal dose of Sac/Val of 97/103 mg twice daily (or highest tolerated dose). The dose could be reduced in the setting of drug-related adverse effects. Treatment continued for up to 12 months. At each study visit, a history and physical examination was performed, and blood samples and health status were obtained. All adverse events were recorded; suspected cases of angioedema were evaluated by a central adjudication panel according to protocol definitions.[15]

For the purposes of this study, we took advantage of the dosing information available across the study visits to calculate an average daily Sac/Val dose. This was calculated as follows:

$$\frac{\text{Total dose received across all study visits}}{\text{Total days in study}}$$

According to their average daily dose, participants were divided into dose tertiles.

FIGURE 1 Sacubitril/Valsartan Average Daily Dose Stratified by Dose Groups



The high-dose group had higher average daily dose of sacubitril/valsartan throughout the study period compared with the medium- and low-dose groups. **Error bars** represent 95% CI of average daily sacubitril/valsartan dose.

BIOMARKERS. At each study visit, a sample of blood was collected and sent to a central laboratory for measurement of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponin T (hs-cTnT) using electrochemiluminescence immunoassays (proBNP and Troponin T hs, Roche Diagnostics). Concentrations of soluble (s)ST2 were measured with an enzyme-linked immunosorbent assay (Critical Diagnostics). Spot urine was collected to measure urinary cyclic guanosine monophosphate (UcGMP) using an enzyme-linked immunosorbent assay (R&D Systems). For study participants consenting to inclusion in a labile biomarker substudy (n = 144), additional blood was drawn into tubes containing protease inhibitors (Becton Dickinson) to minimize protein degradation. From these samples, atrial natriuretic peptide (ANP) concentrations were measured using a radioimmunoassay using polyclonal antibodies (Phoenix Pharmaceuticals)[16] and B-type natriuretic peptide (BNP) was measured using a 2-site sandwich assay (Siemens Healthcare Diagnostics).

HEALTH STATUS. To assess health status, the Kansas City Cardiomyopathy Questionnaire (KCCQ)-23 was administered at baseline and then at subsequent study visits. For the purposes of this analysis, absolute change in the KCCQ-23 Overall Summary score was assessed, as were the percentages of study participants achieving previously identified and clinically meaningful thresholds for clinically significant change (≥5 points), large change (≥10 points), or very large change (≥20 points).

ECHOCARDIOGRAPHY. After enrollment, participants underwent 2-dimensional echocardiography at baseline and at approximately 6 and 12 months according to the study imaging protocol. Following completion, echocardiograms were transmitted in a secure fashion to a core laboratory where they were interpreted following completion of all study procedures in a temporally and clinically blinded fashion.

Measurements made from obtained images included left ventricular end-diastolic volume index (LVEDVi) (normal <76 mL/m^2), left ventricular end-systolic volume index (LVESVi) (normal <30 mL/m^2), and left atrial volume index (LAVi)

TABLE 1 Baseline Characteristics of the Study Population

	Average Dose Achieved			
	Tertile 1 (n = 286)	Tertile 2 (n = 272)	Tertile 3 (n = 236)	*P* Value for Trend
Age, y	66.37 ± 13.1	65.00 ± 11.6	63.76 ± 12.2	0.05
Male	190 (66.4)	205 (75.4)	173 (73.3)	0.05
Race				0.01
Asian	4 (1.4)	2 (0.7)	0 (0.0)	
Black	49 (17.1)	57 (21.0)	74 (31.4)	
Other	10 (3.5)	9 (3.3)	6 (2.5)	
White	222 (77.6)	203 (74.6)	156 (66.1)	
Ethnicity				0.08
Hispanic or Latino	55 (19.2)	37 (13.6)	25 (10.6)	
Not Hispanic or Latino	228 (79.7)	233 (85.7)	208 (88.1)	
NYHA functional class				0.63
II	208 (72.7)	193 (71.0)	184 (78.0)	
III	72 (25.2)	73 (26.8)	49 (20.8)	
IV	4 (1.4)	3 (1.1)	1 (0.4)	
New-onset HF	22 (7.7)	28 (10.3)	28 (11.9)	0.27
Time since diagnosis in months	84.2 ± 83.1	70.7 ± 73.4	71.1 ± 83.4	0.08
Ischemic HF etiology	127 (44.4)	117 (43.0)	124 (52.5)	0.07
Prior HF hospitalization	138 (48.3)	126 (46.3)	105 (44.5)	0.69
Body mass index, mL/kg^2	30.00 ± 6.6	31.37 ± 6.3	32.77 ± 7.5	<0.001
Medical history				
Hypertension	243 (85.0)	239 (87.9)	217 (91.9)	0.07
TIA	21 (7.3)	18 (6.6)	9 (3.8)	0.10
Stroke	25 (8.7)	37 (13.6)	24 (10.2)	0.31
Prior MI	129 (45.1)	113 (41.5)	87 (36.9)	0.16
Prior revascularization	143 (50.0)	127 (46.7)	106 (44.9)	0.49
Prior PCI	78 (27.3)	86 (31.6)	60 (25.4)	0.27
Prior CABG	82 (28.7)	58 (21.3)	50 (21.2)	0.06
Diabetes mellitus	121 (42.3)	126 (46.3)	114 (48.3)	0.37
Atrial fibrillation	102 (35.7)	91 (33.5)	75 (31.8)	0.64
Atrial flutter	13 (4.5)	19 (7.0)	4 (1.7)	0.02
Peripheral artery disease	2 (0.7)	0 (0.0)	1 (0.4)	0.40
Baseline GDMT use				
ACE inhibitor/ARB	193 (67.5)	220 (80.9)	189 (80.1)	<0.001
β-blocker	270 (94.4)	259 (95.2)	222 (94.1)	0.84
MRA	110 (38.5)	92 (33.8)	90 (38.1)	0.46
CRT-P or -D	1 (0.3)	1 (0.4)	2 (0.8)	0.67
CRT-D	55 (19.2)	44 (16.2)	19 (8.1)	0.001
ICD alone	94 (32.9)	75 (27.6)	57 (24.2)	0.08
Baseline vital signs				
Systolic BP	119.9 ± 14.4	125.6 ± 14.7	131.2 ± 16.8	<0.001
Diastolic BP	73.9 ± 9.5	75.9 ± 9.9	79.6 ± 10.3	<0.001
Heart rate	72.3 ± 10.7	72.6 ± 12.2	72.1 ± 11.3	0.90
Baseline laboratory results				
eGFR, mL/min/1.73 m^2	59.9 ± 20.5	65.2 ± 21.3	68.3 ± 18.2	<0.001
eGFR <60 mL/min/1.73 m^2	127 (44.4)	89 (32.7)	61 (25.8)	<0.001

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(a value ≥34 mL/m^2 is considered enlarged according to American Society of Echocardiography recommendations[17]). Doppler examinations included assessment of early diastolic filling velocity (E-wave) and early diastolic mitral annular velocity (e'); an E/e' ratio >14 is associated with elevated filling pressures. Additionally, left ventricular mass index (LVMi) (normal <89 g/m^2 in women and <103 g/m^2 in men) was calculated.

STATISTICAL ANALYSES. Mean ± SD or median (IQR), depending on normality of variables, and count (frequency) are used to show the distribution of the data for continuous and categorical variables, respectively. Comparisons of serial measures were

TABLE 1 Continued

	Average Dose Achieved			
	Tertile 1 (n = 286)	Tertile 2 (n = 272)	Tertile 3 (n = 236)	*P* Value for Trend
Baseline echocardiographic parameters				
LVEF, %	28.2 (24.3-32.5)	29.0 (23.7-33.3)	28.5 (25.2-33.3)	0.42
LVEDVi, mL/m^2	86.4 (74.9-100.4)	90.3 (76.7-102.9)	85.6 (76.6-98.4)	0.20
LVESVi, mL/m^2	61.6 (52.0-74.3)	63.4 (51.9-77.3)	59.8 (52.2-72.0)	0.24
LAVi, mL/m^2	36.9 (31.5-46.1)	39.5 (32.5-48.2)	36.5 (30.2-43.4)	0.02
E/e'	11.6 (8.2-15.7)	11.8 (8.8-16.5)	11.5 (8.9-15.2)	0.84
Achieved target dose	23 (8.0)	257 (94.5)	236 (100.0)	<0.001
Average dose	111.6 (100.0-183.3)	341.7 (250.0-362.8)	379.4 (379.4-380.4)	<0.001

Values are mean ± SD, n (%), or median (IQR). Tertile 1 dose range 48-196 mg daily. Tertile 2 dose range 200-371 mg daily. Tertile 3 dose range 372-400 mg daily.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ANP = atrial natriuretic peptides; BNP = B-type natriuretic peptides; BP = blood pressure; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; E/e' = transmitral E wave velocity/early diastolic mitral tissue Doppler velocity; eGFR = estimated glomerular filtration rate; GDMT = guideline-directed medical therapy; hs-cTnT = high-sensitivity troponin T; HF = heart failure; HTN = hypertension; ICD = implantable cardioverter-defibrillator; LAVi = left atrial volume index; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; sST2 = soluble suppressor of tumorigenicity-2; TIA = transient ischemic attack.

performed using analysis of variance and the chi-square test as appropriate. Statistics were performed using R version 3.5.5 (R Foundation for Statistical Computing). *P* values are 2-sided, with values <0.05 considered significant.

RESULTS

A total of 794 patients with HFrEF were included in this analysis; nearly all started at the 24/26 mg twice daily dose of Sac/Val.

The frequencies of average daily dose of Sac/Val during the study duration are shown in Supplemental Figure 1. Reasons given by the study investigators for not reaching 97/103 mg twice daily are listed in Supplemental Table 1.

Participants were categorized into 3 tertiles reflective of the average Sac/Val dose received during the study: low dose (112 mg daily dose), moderate dose (342 mg daily dose), and high dose (379 mg daily dose). The distributions of average daily doses during the study as well as by the end of the study are displayed in **Figure 1**.

Given the ability to examine variation in dose over the course of a year's time, we were able to evaluate the frequency of achieving the target dose of 97/103 mg twice daily during the course of the study; 23 (8%) patients in the lowest average dose (tertile 1) received target dose at least once during the course of study procedures, whereas 257 (94.5%) patients in tertile 2 and 236 (100%) patients in tertile 3 achieved target dose.

Baseline characteristics of study participants across average achieved dose tertiles are shown in **Table 1**. Patients in the highest average dose (tertile 3) were younger, were more likely to be men, had a higher body-mass index, and were more likely to take an ACE inhibitor/ARB at baseline and to have higher systolic and diastolic blood pressures. Black patients reached the target dose (97/103 mg twice daily) by month 12 at slightly higher rates (73.0%) than White (62.2%) or Hispanic (52.1%) patients (*P* value = 0.01). Additionally, those reaching higher doses had better kidney function and lower NT-proBNP. No differences in baseline echocardiographic parameters were found across the dose tertiles except for LAVi.

Changes in geometric mean biomarker concentrations stratified by average daily Sac/Val dose are shown in **Tables 2 and 3**. Study participants destined to receive the lowest cumulative doses had a higher baseline concentration of NT-proBNP than those destined to receive higher daily doses. Treatment with Sac/Val resulted in a greater absolute reduction of NT-proBNP in those receiving lower doses (Supplemental Table 2A), but relative NT-proBNP reduction was the same across dose categories (**Central Illustration**, Supplemental Table 2C). Patterns of decrease in hs-cTnT and sST2 were similar across dose tertiles. Absolute increase in ANP and BNP were greatest in those receiving moderate-dose Sac/Val (as was rise in UcGMP), but the relative increase of both was not significantly different across dose categories (Supplemental Tables 2B and 2C).

Table 4 shows the KCCQ-23 Overall Summary scores stratified by average dose achieved during the study. During 12 months of follow-up, increases in KCCQ-23 score were observed regardless of achieved dose categories. At the end of follow-up, no statistical

TABLE 2 Geometric Mean (95% CI) Biomarker Concentrations Across Study Visits Stratified by Sac/Val Dose

	NT-proBNP (pg/mL)				hs-cTnT (ng/L)			
	Tertile 1	Tertile 2	Tertile 3	*P* Value	Tertile 1	Tertile 2	Tertile 3	*P* Value
Baseline	907 (769-1,070)	834 (706-986)	582 (493-688)	0.007	16 (15-18)	18 (17-20)	15 (14-17)	0.06
Day 14	657 (553-780)	576 (489-679)	388 (325-464)	0.02	15 (13-17)	17 (15-18)	14 (13-15)	0.35
Day 30	629 (529-749)	550 (463-653)	402 (341-475)	0.008	14 (13-16)	17 (15-18)	14 (12-15)	0.72
Day 45	613 (511-735)	548 (459-653)	366 (310-433)	0.004	14 (13-16)	16 (15-18)	13 (12-15)	0.51
Month 2	610 (508-731)	580 (486-693)	377 (318-448)	0.04	14 (13-16)	16 (15-18)	13 (12-15)	0.11
Month 3	625 (521-751)	560 (468-671)	355 (299-421)	0.01	14 (12-15)	16 (14-18)	13 (12-14)	0.41
Month 6	599 (495-725)	481 (403-574)	336 (281-402)	0.01	14 (13-16)	15 (14-17)	13 (12-15)	0.38
Month 9	538 (445-649)	468 (386-568)	325 (271-390)	0.11	13 (12-15)	16 (14-18)	13 (12-15)	0.18
Month 12	527 (433-640)	448 (366-548)	308 (225-371)	0.03	14 (12-15)	15 (14-17)	13 (12-14)	0.11

Tertile 1 dose range 48-196 mg daily. Tertile 2 dose range 200-371 mg daily. Tertile 3 dose range 372-400 mg daily.
cGMP = cyclic guanosine monophosphate; other abbreviations as in Table 1.

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difference was seen between KCCQ-23 Overall Summary scores across dose tertiles. The results of KCCQ-23 Responder Analysis are shown in **Table 5**, which also details similar categorical changes in health status across dose tertiles: 71 (32.6%) patients in tertile 1, 79 (34.8%) patients in tertile 2, and 67 (32.8%) patients in tertile 3 had a ≥20 increase in KCCQ-23 score.

Echocardiographic measures stratified by average dose are shown in **Figure 2** and **Table 6**. These show consistent reverse cardiac remodeling in each achieved dose tertile, with similar rise in LVEF, reduction of left ventricular and left atrial volumes, lowering of E/e', and reduction in LVMi. For example, by 12 months of follow-up, LVEF was significantly increased across all the dose categories: from 28.7% to 38.0% in tertile 1, from 28.9% to 37.7% in tertile 2, and from 29.5% to 39.7% in tertile 3. The corresponding median absolute LVEF improvement across these categories by 12 months were 9.35% (IQR: 5.35%-13.63%), 8.80% (IQR: 4.40%-12.80%), and 9.55 (IQR: 5.67%-14.07%). These increases in LVEF were paralleled by a reduction in LVEDVi and LVESVi across all dose tertile categories in a similar pattern. In addition, LAVi, E/e', and LVMi improved in all dose tertile categories during the 12 months of follow-up (Supplemental Table 3).

Table 7 demonstrates safety outcomes: dizziness (22.4%), hypotension (27.6%), and hyperkalemia (13.3%) were significantly more reported in tertile 1. The 2 cases of adjudicated angioedema in the study occurred in average dose tertile 1.

DISCUSSION

In this post hoc analysis of the PROVE-HF study, patients were categorized according to the average dosage received over the duration of PROVE-HF. We found that patients who received the highest dose of Sac/Val were younger, were more likely to be men, and had higher blood pressure and better kidney function at baseline than the other dose tertiles; by day 45, all patients in this group reached the target dose. We also assessed associations between different Sac/Val dose tertiles on mechanistic measures and determined that regardless of dose category, relative improvement in cardiac stress biomarkers (ANP, BNP, NT-proBNP, hs-cTnT, and sST2) were generally similar across dose tertiles. Although differences existed in the absolute change of UcGMP from baseline, relative change was similar across dose tertiles. Moreover, we observed comparable improvement in health status and reversal of cardiac remodeling in all 3 tertiles of achieved Sac/Val dose. Side effects such as hypotension or dizziness were more common in those with the lowest average dose category, presumably explaining the need for lower total doses and lack of ability to titrate the medication. Although achieving target GDMT doses in HFrEF should always be attempted, these results suggest that for those unable to achieve maximum doses of Sac/Val, mechanistic benefits and improvement in health status may be expected, even at lower doses (eg, 24/26 mg twice daily) (**Central Illustration**).

In pharmaceutical development programs, phase 2 studies evaluate various doses in persons with the diagnosis of interest with a goal to identify the drug dose providing maximal mechanistic efficacy and safety. The 97/103 mg twice-daily Sac/Val dose was selected to achieve serum concentrations of valsartan equivalent to those achieved with previous formulations of the drug studied in the Val-HeFT (Valsartan Heart Failure Trial)[18] and VALIANT (Valsartan in Acute Myocardial Infarction Trial)[19] while simultaneously achieving 90% neprilysin inhibition

TABLE 2 Continued

sST2 (ng/mL)				Urinary cGMP (nmol/mmol)			
Tertile 1	Tertile 2	Tertile 3	*P* Value	Tertile 1	Tertile 2	Tertile 3	*P* Value
26 (25-28)	26 (25-27)	25 (24-27)	0.89	446 (396-503)	511 (451-578)	442 (387-505)	0.49
24 (23-25)	24 (23-25)	23 (22-25)	0.50	583 (514-661)	776 (692-871)	672 (589-767)	0.07
24 (23-25)	23 (22-25)	23 (22-24)	0.32	573 (507-649)	736 (650-835)	665 (573-771)	0.02
24 (23-25)	24 (23-25)	23 (22-24)	0.64	632 (556-719)	796 (704-899)	699 (614-796)	0.02
24 (22-25)	24 (23-25)	23 (22-25)	0.45	621 (548-704)	768 (680-867)	774 (677-884)	0.04
24 (23-26)	24 (23-26)	24 (22-25)	0.28	654 (582-733)	825 (731-931)	766 (674-871)	0.02
24 (23-25)	24 (23-26)	24 (23-25)	0.86	621 (548-704)	752 (664-852)	720 (634-818)	0.11
24 (23-25)	24 (22-25)	23 (22-24)	0.46	584 (513-663)	770 (682-869)	663 (574-766)	0.02
24 (23-25)	23 (22-25)	23 (22-25)	0.92	549 (480-629)	718 (634-813)	686 (604-779)	0.23

in normal individuals.[20] This dose also was associated with reduction in NT-proBNP and LAVi among individuals with HF and preserved EF treated in the Prospective Comparison of ARNI with ARB on Management of HF with Preserved EF trial.[21] However, no phase 2 clinical trial data were available regarding Sac/Val dose in HFrEF to inform expected mechanistic or health status benefits associated with doses lower than target. The design of PROVE-HF allowed for administration of Sac/Val per usual clinical care with most study participants averaging doses below those used in the PARADIGM-HF trial. In this study, the biomarker data, echo-demonstrated cardiac remodeling, and health status scores suggest that across all of the doses achieved in the study, significant clinical benefits would be expected, even in those only able to receive lowest Sac/Val doses.

The PARADIGM-HF trial established Sac/Val as a first-line renin-angiotensin inhibitor for HFrEF, yet the design of the trial has created ambiguity regarding value of lower doses of the drug because of its run-in period. Accordingly, the average daily Sac/Val dose administered in PARADIGM-HF is considerably higher than what is seen in usual care,[11] where it may be substantially harder to reach target goal doses for HFrEF GDMT, particularly for a treatment that is associated with greater lowering of blood pressure compared with ACE inhibitor or ARB. Recent data show that 14% receive 97/103 mg twice daily of Sac/Val and 51% receive the lowest dose of 24/26 mg twice daily.[11] Few data exist regarding expected benefit of lower doses of Sac/Val in chronic HFrEF.[22-25] Thus, the results of this analysis have relevance to the ongoing uncertainty about benefit of Sac/Val when a patient with HFrEF is unable achieve the highest dose of the drug.

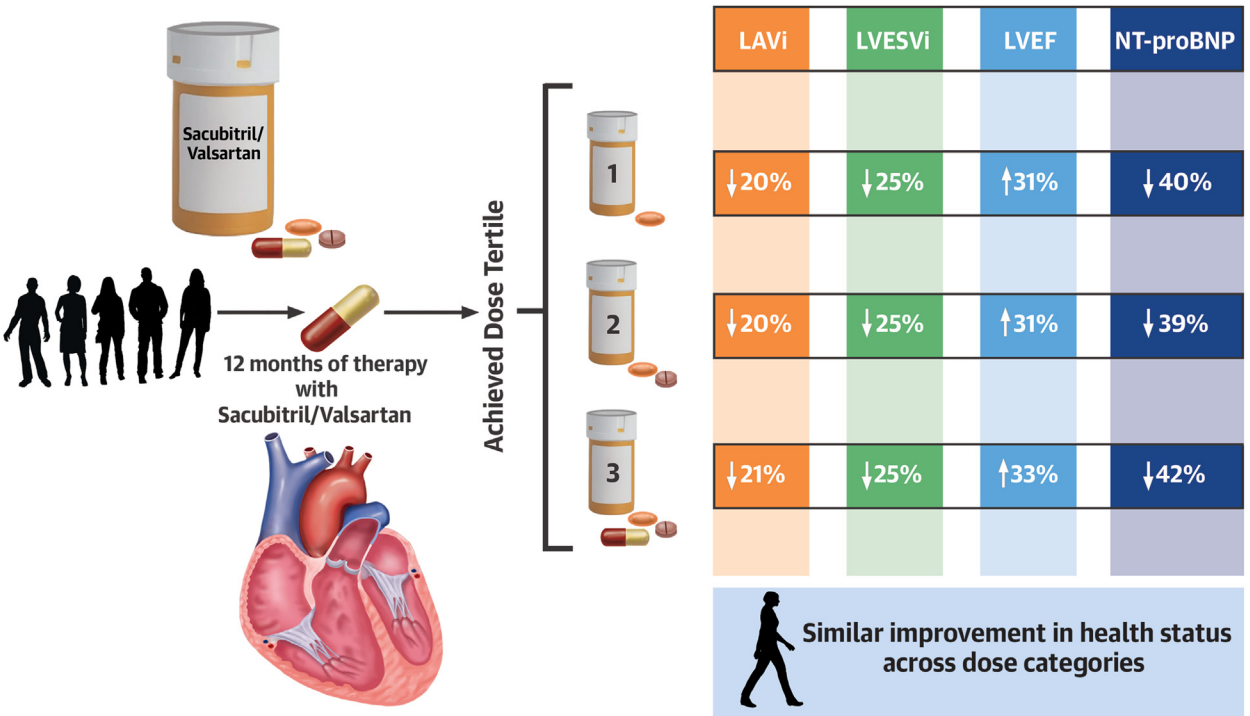
Among the dose tertiles, there was 1 group of patients who were least able to reach target dose. They were older, with a generally higher prevalence of medical conditions and frequency of intolerances that likely explain the need for lower doses. These individuals were much less likely to achieve 97/103 mg twice daily before adjustment to a lower achieved dose. These individuals are most reminiscent of those in PARADIGM-HF who did not get through the run-in phase. It is noteworthy that those in the lowest-dose tertile were least likely to have taken ACE inhibitor or ARB before enrollment,

TABLE 3 Geometric Mean (95% CI) Concentrations of ANP and BNP Across Study Visits Stratified by Sac/Val Dose in the Labile Biomarker Substudy Sample (n = 144)

	ANP (pg/mL)				BNP (pg/mL)			
	Tertile 1	Tertile 2	Tertile 3	*P* Value	Tertile 1	Tertile 2	Tertile 3	*P* Value
Baseline	94 (69-130)	125 (93-167)	73 (49-109)	0.29	117 (81-170)	146 (104-206)	90 (58-138)	0.04
Day 14	144 (103-203)	204 (149-280)	95 (62-144)	0.02	117 (79-174)	149 (101-222)	60 (36-102)	0.38
Day 30	136 (89-207)	226 (163-315)	117 (77-178)	0.05	131 (84-203)	157 (109-226)	65 (39-107)	0.37
Day 45	170 (119-242)	256 (183-358)	129 (82-203)	0.11	123 (81-188)	155 (106-228)	71 (43-119)	0.88
Month 2	151 (106-217)	262 (190-361)	146 (98-218)	0.04	116 (73-183)	173 (116-259)	88 (52-147)	0.85
Month 3	161 (113-229)	290 (205-411)	136 (88-210)	0.03	138 (89-212)	144 (96-215)	77 (48-122)	0.71
Month 6	172 (119-250)	205 (138-304)	144 (91-226)	0.45	117 (72-189)	123 (85-177)	75 (46-123)	0.78
Month 9	138 (90-211)	233 (156-348)	161 (107-243)	0.11	114 (70-185)	122 (80-188)	75 (43-132)	0.76
Month 12	151 (98-235)	240 (165-347)	120 (79-182)	0.04	118 (72-193)	122 (81-185)	69 (37-128)	0.56

Tertile 1 dose range 48-196 mg daily. Tertile 2 dose range 200-371 mg daily. Tertile 3 dose range 372-400 mg daily.
ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide.

CENTRAL ILLUSTRATION **Improvements in Cardiac Function Across Sacubitril/Valsartan Dose Categories**



Mohebi R, et al. J Am Coll Cardiol. 2022;80(16):1529–1541.

Improvements in cardiac biomarkers, health status, and reverse in cardiac remodeling were observed across all sacubitril/valsartan dose categories during 12 months of treatment with sacubitril/valsartan. LAVi = left atrial volume index; LVESVi = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction; NT-proBNP = N terminal pro-B-type natriuretic peptides.

indicating possible intolerances to other renin-angiotensin inhibitors. They were also most likely to have previously have implantation of cardiac resynchronization therapy device implantation.

TABLE 4 **KCCQ-23 Overall Summary Scores Stratified by Average Dose**

KCCQ-23 OS	Average Dose Achieved			*P* Value for Trend
	Tertile 1	Tertile 2	Tertile 3	
Baseline	63.12 ± 21.72	61.42 ± 23.54	63.76 ± 22.71	0.49
Day 14	68.16 ± 21.86	68.15 ± 22.18	70.05 ± 21.09	0.55
Day 30	68.85 ± 22.80	70.36 ± 22.00	71.89 ± 21.12	0.32
Month 2	70.38 ± 23.35	72.23 ± 22.07	73.83 ± 21.19	0.25
Month 3	71.78 ± 23.15	71.76 ± 22.11	74.38 ± 20.26	0.33
Month 6	69.78 ± 25.12	71.29 ± 24.68	74.86 ± 22.89	0.07
Month 9	69.29 ± 27.32	69.50 ± 25.56	74.27 ± 23.12	0.06
Month 12	68.80 ± 28.12	72.50 ± 25.49	73.11 ± 24.07	0.17

Values are mean ± SD. Tertile 1 dose range 48-196 mg daily. Tertile 2 dose range 200-371 mg daily. Tertile 3 dose range 372-400 mg daily.

KCCQ-23 OS = Kansas City Cardiomyopathy Questionnaire-23 overall summary score.

Despite both points, these individuals were nonetheless able to receive Sac/Val at a low dose and show significant improvement in cardiac stress biomarkers, substantial improvement in health status, and clinically meaningful reverse cardiac remodeling. All of these changes were comparable to those receiving higher doses of Sac/Val, despite differences in baseline characteristics.

A second group of study participants achieved a moderate average Sac/Val dose; many were able to reach the Sac/Val target, but some were down-titrated. Individuals in this dose group are reminiscent of those described in a post hoc analysis of PARADIGM-HF[8] where dose reductions were necessary in 42% after the run-in. Among those requiring dose reduction in PARADIGM-HF, the benefit on cardiovascular disease or HF hospitalization was similar to that of patients who remained on the target dose. In the current analysis, the middle-dose group had comparable improvement in biomarkers, health

TABLE 5 KCCQ-23 Responder Analysis

		Average Dose Achieved			
KCCQ-23 OS	All Groups	Tertile 1	Tertile 2	Tertile 3	P Value
Day 14					
≥5 increase	471 (64.5)	161 (63.1)	174 (67.2)	136 (63.0)	0.54
≥10 increase	292 (40.0)	99 (38.8)	111 (42.9)	82 (38.0)	0.50
≥20 increase	93 (12.7)	30 (11.8)	34 (13.1)	29 (13.4)	0.84
Day 30					
≥5 increase	488 (67.4)	164 (65.6)	177 (70.2)	147 (66.2)	0.49
≥10 increase	341 (47.1)	119 (47.6)	128 (50.8)	94 (42.3)	0.18
≥20 increase	151 (20.9)	53 (21.2)	58 (23.0)	40 (18.0)	0.40
Month 2					
≥5 increase	474 (69.4)	153 (66.5)	168 (70.9)	153 (70.8)	0.51
≥10 increase	333 (48.8)	109 (47.4)	114 (48.1)	110 (50.9)	0.73
≥20 increase	173 (25.3)	53 (23.0)	67 (28.3)	53 (24.5)	0.41
Month 3					
≥5 increase	500 (71.6)	171 (71.2)	173 (72.1)	156 (71.6)	0.98
≥10 increase	359 (51.4)	120 (50.0)	127 (52.9)	112 (51.4)	0.82
≥20 increase	184 (26.4)	58 (24.2)	72 (30.0)	54 (24.8)	0.28
Month 6					
≥5 increase	519 (74.2)	173 (73.9)	177 (72.5)	169 (76.5)	0.62
≥10 increase	390 (55.8)	138 (59.0)	133 (54.5)	119 (53.8)	0.48
≥20 increase	203 (29.0)	68 (29.1)	68 (27.9)	67 (30.3)	0.85
Month 9					
≥5 increase	497 (75.4)	166 (76.1)	169 (75.1)	162 (75.0)	0.95
≥10 increase	378 (57.4)	127 (58.3)	126 (56.0)	125 (57.9)	0.88
≥20 increase	210 (31.9)	78 (35.8)	70 (31.1)	62 (28.7)	0.27
Month 12					
≥5 increase	487 (75.0)	167 (76.6)	172 (75.8)	148 (72.5)	0.60
≥10 increase	365 (56.2)	120 (55.0)	131 (57.7)	114 (55.9)	0.85
≥20 increase	217 (33.4)	71 (32.6)	79 (34.8)	67 (32.8)	0.86
Any time					
≥5 increase	37 (59.7)	11 (61.1)	14 (60.9)	12 (57.1)	0.99
≥10 increase	26 (41.9)	8 (44.4)	9 (39.1)	9 (42.9)	0.94
≥20 increase	14 (22.6)	4 (22.2)	4 (17.4)	6 (28.6)	0.68

Values are n (%). Tertile 1 dose range 48-196 mg daily. Tertile 2 dose range 200-371 mg daily. Tertile 3 dose range 372-400 mg daily.
KCCQ-23 OS = Kansas City Cardiomyopathy Questionnaire-23 overall summary score.

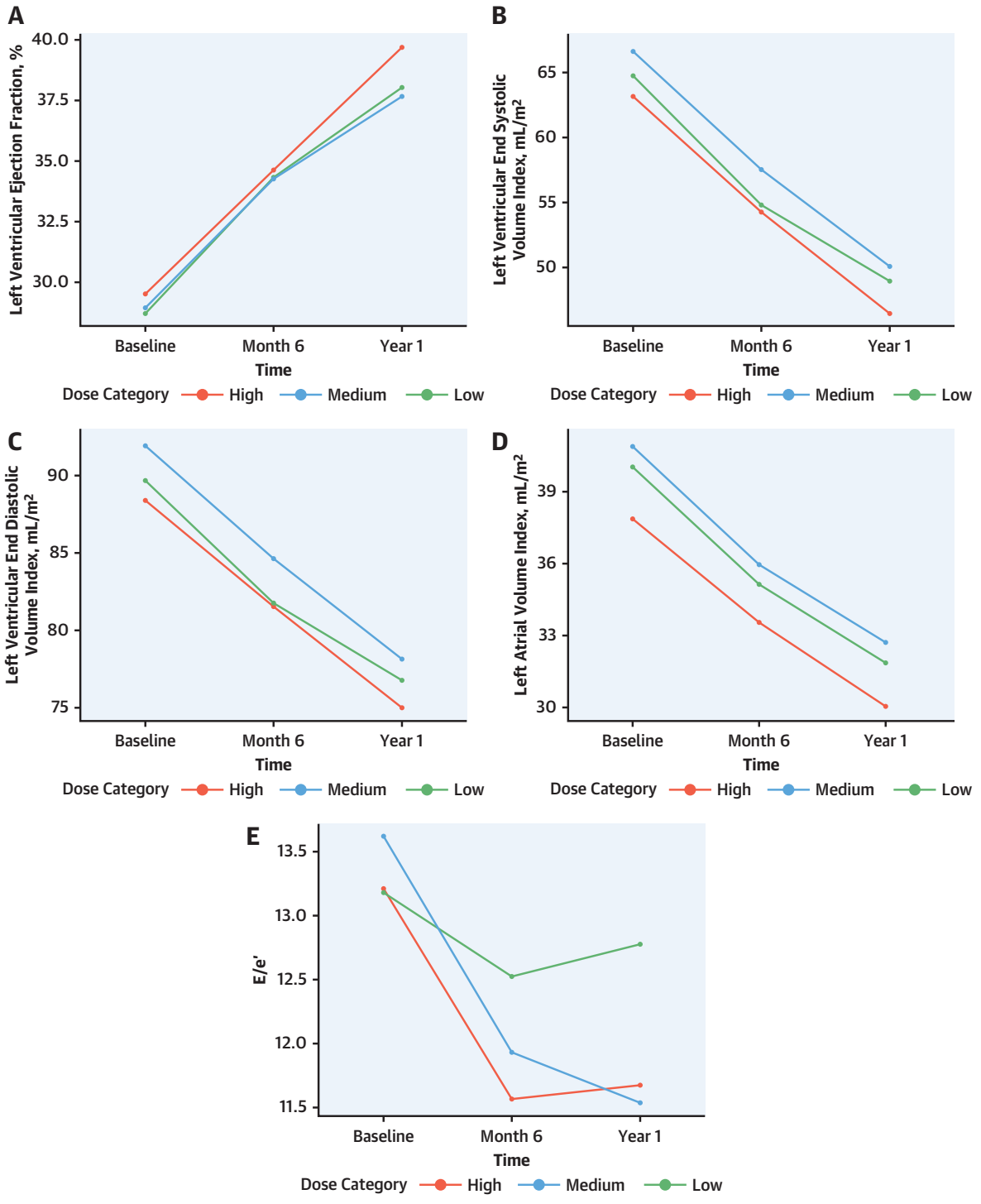
status, and reverse cardiac remodeling as those who reached and remained at target dose.

Study participants in the highest-dose tertile in this analysis rapidly ascended to the Sac/Val target within 45 days, with an average dose over the study period of nearly 97/103 mg twice daily. All achieved the target dose at least once, and nearly all remained at target dose for the duration of the study. These individuals were more likely to be younger and with higher blood pressures at baseline, and might be best viewed as being "PARADIGM-HF like." A close comparison reveals a similar age range, NYHA functional class, and prevalence of comorbidities in these PROVE-HF participants compared with those in PARADIGM-HF.

We previously showed that Sac/Val treatment resulted in a statistically significantly early rise in ANP concentrations,[16] with the speed and slope of ANP increase correlated with later UcGMP increase. Early ANP increase was also strongly associated with reverse cardiac remodeling by 12 months.[16] ANP binds the natriuretic peptide receptor-A (NPR-A) with higher affinity than BNP and results in the rise of UcGMP, an index of its biological activity.[26] In this post hoc analysis, increases in ANP levels were observed in all dose categories. Although moderate and higher Sac/Val doses were associated with larger absolute UcGMP increases, the relative change in UcGMP was similar across dose groups.

CLINICAL IMPLICATIONS. Our results have immediate applicability to recent clinical practice guidelines and consensus recommendations regarding application and titration of GDMT in HFrEF.[1,2,27] Recent guidelines and consensus documents[2,6] have evolved from recommending slower titration of medications to target before adding new therapies to now

FIGURE 2 **Echocardiographic Measures Stratified by Dose Tertiles**



All dose categories achieved a similar magnitude of reverse cardiac remodeling by echocardiographic parameters after initiation of sacubitril/valsartan, with consistent improvements in left ventricular ejection fraction **(A)** and reductions in indexed left ventricular end-systolic **(B)** and -diastolic **(C)** volumes and left atrial volume from baseline to month 12 **(D)**. Similarly, E/e' **(E)** (transmitral E-wave velocity/early diastolic mitral tissue Doppler velocity), a measure of intracardiac filling pressures, improved in all dose groups.

TABLE 6 Echocardiographic Measures Stratified by Average Dose

	Average Dose Achieved			
	Tertile 1	Tertile 2	Tertile 3	*P* Value for Trend
LVEF, %				
Baseline	28.72 ± 6.76	28.93 ± 6.65	29.53 ± 7.45	0.46
Month 6	34.33 ± 8.19	34.27 ± 8.27	34.62 ± 7.63	0.90
Month 12	38.04 ± 9.84	37.67 ± 9.64	39.70 ± 8.96	0.09
LVEDVi, mL/m^2				
Baseline	89.70 ± 20.32	91.95 ± 21.87	88.42 ± 19.66	0.16
Month 6	81.77 ± 19.68	84.61 ± 22.13	81.57 ± 19.51	0.19
Month 12	76.78 ± 20.10	78.11 ± 21.44	74.98 ± 19.69	0.28
LVESVi, mL/m^2				
Baseline	64.74 ± 18.83	66.60 ± 20.42	63.13 ± 18.29	0.14
Month 6	54.78 ± 18.83	57.50 ± 21.17	54.22 ± 18.15	0.14
Month 12	48.89 ± 19.39	50.04 ± 20.59	46.46 ± 17.86	0.15
LAVi, mL/m^2				
Baseline	40.02 ± 16.09	40.89 ± 11.82	37.87 ± 10.25	0.04
Month 6	35.10 ± 12.75	35.94 ± 11.26	33.52 ± 9.32	0.07
Month 12	31.82 ± 14.03	32.68 ± 11.06	29.99 ± 9.19	0.05
E/e'				
Baseline	13.18 ± 6.78	13.62 ± 7.73	13.21 ± 7.23	0.78
Month 6	12.53 ± 7.33	11.93 ± 6.22	11.56 ± 5.69	0.33
Month 12	12.77 ± 7.79	11.54 ± 6.01	11.67 ± 5.90	0.15

Tertile 1 dose range 48-196 mg daily. Tertile 2 dose range 200-371 mg daily. Tertile 3 dose range 372-400 mg daily.
LS = least square; other abbreviations as in Table 1.

suggesting the early addition of the 4 major classes of first-line GDMT (ARNI, evidence-based beta-blocker, mineralocorticoid receptor antagonist, and sodium-glucose cotransporter-2 inhibitor) at a low dose as an initial step. Following, individualized up-titration of medications to target is recommended according to the patient's symptoms, vital signs, functional status, tolerance, renal function, electrolytes, and comorbidities. When reaching target ARNI dose is not possible, our results suggest that favorable mechanistic outcomes may be expected from even low doses of Sac/Val, and provide reassurance that the most commonly used dose of the drug in clinical practice (24/26 mg twice daily) provides substantial clinical benefit. To our knowledge, these data are the most comprehensive examining important mechanistic outcome measures across doses of Sac/Val.

STUDY LIMITATIONS. First, although study participants were enrolled from 78 sites in the United States, more than 70% of study participants in this study were White and a minority were women. Future studies should strive to have recruitment goals aligned with recommendations for inclusion of minoritized individuals and equitable enrollment of women.[28] Second, to most rigorously study the benefit of different dose levels, randomized placebo-controlled phase 2-type dose ranging trials would be needed. As noted, such trials were not performed, and it is unlikely such studies would occur at this point. Despite the ongoing discussions around differences between dosing in PARADIGM-HF and usual clinical practice, some might argue that these results are not surprising because data are mixed regarding whether higher doses of renin-angiotensin inhibitors are necessarily associated with greater benefit.[4,29,30] In each case where higher doses were associated with better outcome, the ability to tolerate higher doses of GDMT might confound survival analyses caused by unmeasured variables. Third, we did not examine change in other GDMT in the course of the study. At baseline, we found no difference in frequency of other GDMT use (beta-blocker and mineralocorticoid receptor antagonist) across dose categories, and prior analyses from this data set have shown very little change in other GDMT; thus, change in other GDMT across dose categories is unlikely to explain similar findings across the Sac/Val categories. Last, we focused on mechanistic efficacy and improvements in quality of life associated with different Sac/Val doses, but we did not examine the impact of various doses on survival. In the PARADIGM-HF trial, those titrated to lower doses after completing the run-in phase of the study nonetheless had superior outcomes to those treated with enalapril.[8] More data in this regard are needed.

TABLE 7 Safety Outcomes

	Average Dose Achieved		
	Tertile 1	Tertile 2	Tertile 3
Dizziness	64 (22.4)	45 (16.5)	26 (11.0)
Hypotension (SBP <90 mm Hg)	79 (27.6)	43 (15.8)	17 (7.2)
Hyperkalemia (>5.3 mEq/L)	38 (13.3)	34 (12.5)	14 (5.9)
Worsening renal function[a]	4 (1.4)	7 (2.6)	8 (3.4)
Angioedema	2 (1.0)	0 (0.0)	0 (0.0)

Values are n (%). Tertile 1 dose range 48-196 mg daily. Tertile 2 dose range 200-371 mg daily. Tertile 3 dose range 372-400 mg daily. [a]Decrease in eGFR >35% from baseline, or an increase in creatinine >0.5 mg/dL from baseline with decrease in eGFR >25% from baseline at a given visit.

SBP = systolic blood pressure.

CONCLUSIONS

In this analysis from the PROVE-HF study, we characterized different Sac/Val dose trajectories in HFrEF, finding similar reduction in stress biomarkers, similar improvement in health status, and comparable reversal in cardiac remodeling process across all 3 dose categories. Further data are needed regarding the optimal dose of Sac/Val, including the degree of neprilysin and angiotensin receptor inhibition needed to accrue greatest benefits from the drug.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The efficacy of Sac/Val in lowering prognostic biomarkers, improving health status, and reversing cardiac remodeling in patients with HFrEF was similar across all dose categories tested.

TRANSLATIONAL OUTLOOK: Data from prospective dose-ranging trials would further inform dose selection for patients with impediments to a standard treatment regimen.

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APPENDIX For a supplemental figure and tables, please see the online version of this paper.