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Heart Failure Duration and Mechanistic Efficacy of Sacubitril/Valsartan in Heart Failure With Reduced Ejection Fraction

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ABSTRACT

Background: Although sacubitril/valsartan (Sac/Val) is indicated for the treatment of heart failure with reduced ejection fraction (HFrEF), gaps in care continue to exist for those with newer onset HFrEF vs those with longer durations of disease.

Methods and Results: We categorized 794 persons with HFrEF (EF of ≤40%) according to a HF duration of less than 12 months, 12−24 months, 24−60 months, and more than> 60 months. After the initiation of Sac/Val, concentrations of N-terminal pro-B type natriuretic peptide, high sensitivity cardiac troponin T, and soluble ST2 were measured, and Kansas City Cardiomyopathy Questionnaire 23 scores were obtained serially from baseline to 12 months. The left ventricular ejection fraction was measured by echocardiography. Significant decreases in the concentrations of N-terminal pro-B type natriuretic peptide, high sensitivity cardiac troponin T, and soluble ST2 were observed regardless of HF duration ($P < .001$). Comparable gains in Kansas City Cardiomyopathy Questionnaire 23 scores were achieved in all HF duration categories. Moreover, consistent reverse cardiac remodeling in all HF duration categories occurred, with the absolute left ventricular ejection fraction improvement by 12 months across HF duration groups of 12.2%, 6.9%, 8.5%, and 8.6% for HF duration of less than 12 months, 12−24 months, 24−60 months, and more than 60 months, respectively.

Conclusions: The initiation of Sac/Val decreases prognostic biomarkers, improves health status, and reverses cardiac remodeling processes, regardless of HF duration.

Brief lay summary: We categorized 794 persons with heart failure owing to a low ejection fraction according to disease duration into 4 groups: less than 12 months, 12−24 months, 24−60 months, and more than 60 months. After the initiation of sacubitril/valsartan (Entresto), we found that regardless of the duration of heart failure significant improvements occurred in cardiac biomarkers, patients felt better with improved health status and on testing with cardiac ultrasound examination, improvement in heart size, and function occurred. These results suggest that, regardless of heart failure duration, patients with a reduced ejection fraction would benefit from use of sacubitril/valsartan for their care. (*J Cardiac Fail 2022;00:1−10*)

Key Words: Heart failure, sacubitril/valsartan, cardiac remodeling, biomarker, echocardiography.

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Modulation of the renin–angiotensin system is one of the cornerstones for treatment of heart failure with reduced ejection fraction (HFrEF).[1] In the Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor (ARNI) with Angiotensin Converting Enzyme (ACE) Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF),[2] treatment with the ARNI sacubitril/valsartan (Sac/Val) significantly decreased cardiovascular mortality and HF hospitalization compared with the ACE inhibitor enalapril; treatment with Sac/Val also reduced concentrations of N-terminal pro-B type natriuretic peptide (NT-proBNP) and improved health status compared with enalapril.[3] Following the results of PARADIGM-HF, Sac/Val was incorporated into clinical practice guidelines and consensus documents as the preferred treatment even for those presumed stable on either ACE inhibitor or angiotensin II receptor blocker (ARB).[4-7] In PARADIGM-HF and comParIson Of sacubitril/valsartaN versus Enalapril on Effect on NT-proBNP in patients stabilized from an acute Heart Failure episode (PIONEER-HF), the benefits of Sac/Val seemed to be present regardless of HF duration[8] and irrespective of previous HF duration or ACE inhibitor or ARB pretreatment,[9] respectively. Similar results were found in the Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event (TRANSITION) study.[10] Despite this finding, prescription rates for Sac/Val remain low, particularly for those with new-onset HFrEF and patients with longer term HF.[11,12]

The reasons for the lower rates of initiation of Sac/Val in those with very short or longer duration HFrEF are likely complex. However, uncertainty has been created by clinical practice guidelines that suggest pretreatment with an ACE inhibitor or ARB for persons with newer onset HF before the change to Sac/Val,[5,7] as well as ambivalence regarding changing therapies for persons with more chronic HF exists, especially when such patients are perceived as being stable on an ACE inhibitor or ARB.[13] There might also be hesitancy regarding potential mechanistic benefits of Sac/Val, particularly in persons with more longstanding HF. For example, one benefit of renin–angiotensin inhibition in HFrEF is reverse cardiac remodeling, which might not be as robust after treatment with guideline-directed medical therapy (GDMT) in HFrEF of a more longstanding duration.[14] Last, concerns about risk for side effects in older persons with longer standing HFrEF may also explain low prescription rates in these individuals.

In the recent Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sac/Val Therapy for Heart Failure (PROVE-HF; NCT02887183),[15] treatment with Sac/Val resulted in substantial lowering of biomarkers of cardiac stress (including a significant decrease in NT-proBNP), improvement in health status, and robust reverse cardiac remodeling. In the present study, we sought to provide mechanistic insights and assess the safety and tolerability of Sac/Val across HFrEF duration categories. We hypothesized that the effects of Sac/Val would be largely consistent across HF duration groups.

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.[16] Briefly, the study was a phase IV, 52-week, open-label, single-group study of persons with HFrEF (left ventricular [LV]EF of $\leq$40%) initiated with Sac/Val treatment per standard of care performed at 78 sites in the United States. After informed consent was obtained, ACE inhibitor or ARB treatment was discontinued (if applicable), and study participants were initiated on Sac/Val according to the US prescribing information (which at the time was indicated to decrease the risk of cardiovascular death and hospitalization for adult patients with HFrEF). Specific to this post hoc analysis, study participants were categorized according to HF duration into 4 categories: (1) new-onset HF, less than 12 months, (2) 12–24 months, (3) 24–60 months, and (4) more than 60 months. After 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 the highest tolerated dose). The dose could be decreased 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 were obtained. All adverse events were recorded; suspected cases of angioedema were evaluated by a central adjudication panel according to protocol definitions. Consistent with the design of PROVE-HF, available data from study participants withdrawn from treatment because of adverse events were not excluded from analysis; no imputation for missingness was applied[16] (**Supplementary Table 1,** Figure 1).

Biomarkers

At each study visit, a sample of blood was sent to a central laboratory for measurement of plasma NT-

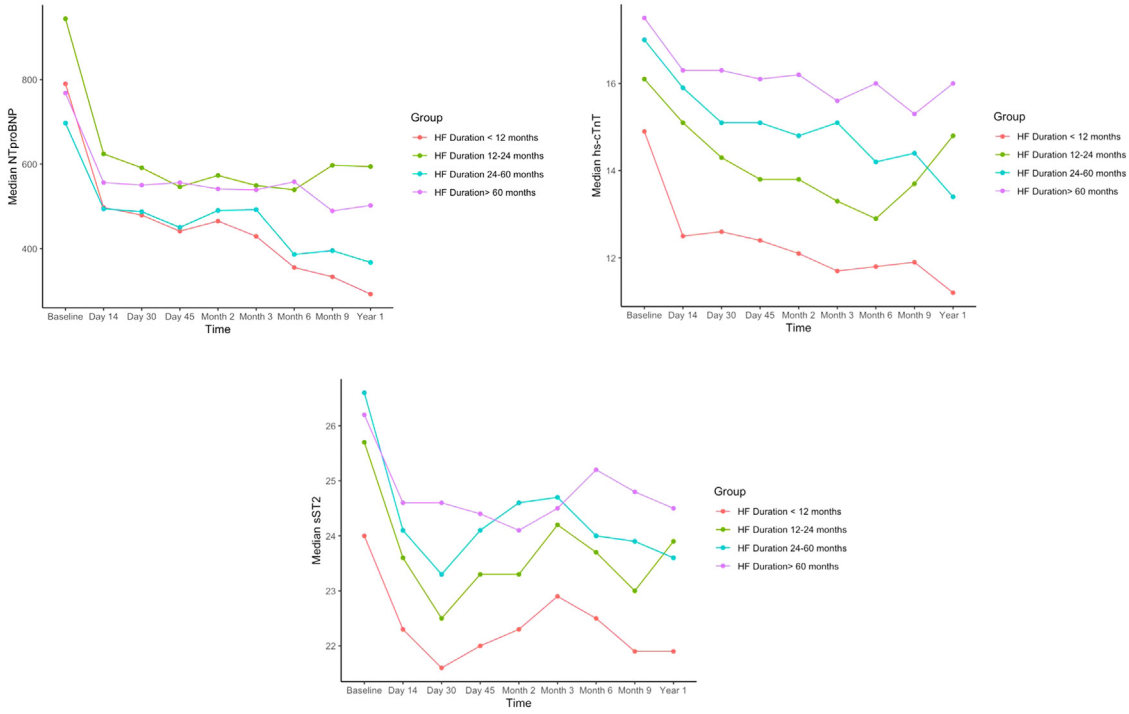


Figure 1. Changes in median biomarker concentrations stratified by heart failure (HF) duration. After treatment with sacubitril/valsartan, biomarker concentrations were decreased across all HF duration groups. NTproBNP, N-terminal pro-B type natriuretic peptide.

proBNP and high sensitivity cardiac troponin T using electrochemiluminescence immunoassays (Roche Diagnostics, Penzberg, Germany), and soluble ST2 was measured with an enzyme-linked immunosorbent assay (Critical Diagnostics, San Diego, CA).

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 was the percent of study participants achieving previously identified and clinically meaningful thresholds for significant change ($\geq$5 points), large change ($\geq$10 points), or very large change ($\geq$20 points).

Echocardiography

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

Measurements made from obtained images included LV end-diastolic volume index (reference values, $<$76 mL/m^2), LV end-systolic volume index (reference value, $<$30 mL/m^2), and left atrial volume index (a value of $\geq$34 mL/m^2 is considered enlarged according to American Society of Echocardiography recommendations[17]). Additionally, the LV mass index (LVMi; reference value, $<$89 g/m^2 in women and $<$103 g/m^2 in men) was calculated. Doppler examinations included assessment of early diastolic filling velocity (E wave) and early diastolic mitral annular velocity (e'); an E/e′ ratio of greater than 14 is associated with elevated filling pressures.

Statistical Analyses

The mean $\pm$ standard deviation or median (interquartile range) values, depending on the normality of variables, and count (frequency) are used to show the distribution of the data for continuous and categorical variables, respectively. Comparisons of baseline characteristics of study population and safety outcomes across HF duration groups were performed using analysis of variance and the χ^2 test as appropriate (Table 1 and Table 2). There were imbalances across the HF duration groups at baseline. Thus, analysis of covariance was performed to measure the effect of HF duration group on continuous dependent variables (ie, biomarkers, KCCQ-23, echocardiographic measures) while controlling the effects of confounders, including age, race, hypertension, diabetes, and myocardial infarction. Statistics were performed using R version 3.5.5 (The R

Table 1. Baseline Characteristics of the Study Population by Heart Failure Duration

	HF Duration <12 Months (n = 178)	HF Duration 12−24 Months (n = 80)	HF Duration 24−60 Months (n = 185)	HF Duration >60 Months (n = 351)	P Value
Age, years	61.8 ± 13.1	65.2 ± 14.6	64.3 ± 12.7	67.3 ± 10.7	<.001
Male	125 (70.2)	52 (65.0)	143 (77.3)	248 (70.7)	.17
Race					.02
Asian	4 (2.2)	0 (0.0)	2 (1.1)	0 (0.0)	
Black	35 (19.7)	19 (23.8)	54 (29.2)	72 (20.5)	
Other	7 (3.9)	5 (6.2)	7 (3.8)	6 (1.7)	
White	131 (73.6)	56 (70.0)	121 (65.4)	273 (77.8)	
Ethnicity					.29
Hispanic/Latino	22 (12.4)	17 (21.2)	26 (14.1)	52 (14.8)	
Not Hispanic/Latino	155 (87.1)	61 (76.2)	156 (84.3)	297 (84.6)	
Vital signs					
SBP, mm Hg	127 ± 16	125 ± 17	125 ± 16	124 ± 15	.28
DBP, mm Hg	77 ± 10	77 ± 10	77 ± 11	75 ± 10	.13
Pulse rate, beats/min	73 ± 13	72 ± 12	72 ± 12	72 ± 10	.82
NYHA functional class					.64
II	136 (76.4)	59 (73.8)	135 (73.0)	255 (72.6)	
III	39 (21.9)	18 (22.5)	48 (25.9)	89 (25.4)	
IV	2 (1.1)	1 (1.2)	1 (0.5)	4 (1.1)	
Months since HF diagnosis	4.44 ± 3.04	17.72 ± 3.07	41.47 ± 9.98	142.99 ± 77.32	<.001
Medical conditions					
Ischemic etiology	73 (41.0)	46 (57.5)	93 (50.3)	214 (61.0)	<.001
Prior HF hospitalization	94 (52.8)	34 (42.5)	79 (42.7)	162 (46.2)	.22
BMI	31.15 (6.43)	30.24 (7.02)	31.44 (7.62)	31.52 (6.62)	.48
Hypertension	142 (79.8)	73 (91.2)	167 (90.3)	317 (90.3)	.002
TIA	8 (4.5)	3 (3.8)	8 (4.3)	29 (8.3)	.41
Stroke	20 (11.2)	10 (12.5)	17 (9.2)	39 (11.1)	.78
Myocardial infarction	50 (28.1)	39 (48.8)	65 (35.1)	175 (49.9)	<.001
Coronary revascularization	64 (36.0)	42 (52.5)	83 (44.9)	187 (53.3)	.001
Prior PCI	41 (23.0)	28 (35.0)	49 (26.5)	106 (30.2)	.16
Prior CABG	28 (15.7)	20 (25.0)	40 (21.6)	102 (29.1)	.007
Diabetes Mellitus	64 (36.0)	33 (41.2)	81 (43.8)	183 (52.1)	.004
Atrial fibrillation	50 (28.1)	25 (31.2)	60 (32.4)	133 (37.9)	.13
Medications/devices					
ACEi/ARB	141 (79.2)	61 (76.2)	146 (78.9)	254 (72.4)	.22
Beta-blocker	166 (93.3)	78 (97.5)	173 (93.5)	334 (95.2)	.46
MRA	69 (38.8)	29 (36.2)	70 (37.8)	124 (35.3)	.86
CRT-P	0 (0.0)	2 (2.5)	1 (0.5)	1 (0.3)	.06
CRT-D	7 (3.9)	10 (12.5)	31 (16.8)	70 (19.9)	<.001
ICD-alone	18 (10.1)	24 (30.0)	59 (31.9)	125 (35.6)	<.001
Biomarkers, geometric					
NT-proBNP, pg/mL	790 ± 3.45	944 ± 3.89	697 ± 4.52	768 ± 3.80	.51
hs-TnT, ng/L	15 ± 2.41	16.2 ± 2.37	17.2 ± 2.30	17.5 ± 2.07	.59
sST2, ng/mL	24.3 ± 1.51	25.5 ± 1.51	26.6 ± 1.54	26.3 ± 1.48	.18
eGFR, mL/min/1.73 m^2	67 ± 20	66 ± 22	65 ± 21	60 ± 18	.004
eGFR <60 mL/min/ 1.73 m^2	51 ± 28.7	29 ± 36.2	63 ± 34.1	134 ± 38.2	.18
Echocardiography measures					
LVEF, %	30 (25, 33)	27 (21, 33)	28 (24, 33)	27 (24, 32)	.03
LVEDVi, mL/m^2	83 (74, 94)	93 (79, 103)	87 (76, 100)	88 (76, 104)	.001
LVESVi, mL/m^2	58 (50, 69)	65 (54, 79)	61 (51, 74)	63 (53, 79)	.001
LAEDVi, mL/m^2	35 (29, 42)	37 (32, 46)	38 (31, 46)	39 (32, 47)	<.001
E/e', ratio	10 (8, 15)	12 (9, 16)	10 (8, 15)	12.10 (9, 16)	.03
LV mass index, g/m^2	125 (105, 145)	121 (99, 150)	123 (105, 145)	125 (109, 150)	.32
Achieved target dose	122 (68.5)	49 (61.3)	135 (73.0)	210 (59.8)	.01

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; hs-TnT, high sensitive troponin T; ICD, implantable cardiac device; LAEDVi, left atrial end diastolic volume index; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end systolic volume index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptides; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; sST2, somatostatin receptor subtype 2; TIA, transient ischemic attack.

Values are mean ± standard deviation, number (%), or median, (Q1, Q3).

Table 2. Safety Outcomes

	HF Duration <12 Months (n = 178)	HF Duration 12–24 Months (n = 80)	HF Duration 24–60 Months (n = 185)	HF Duration >60 Months (n = 351)	P Value
Dizziness	24 (13.5)	15 (48.8)	22 (41.9)	74 (21.1)	.03
Hypotension	22 (42.4)	16 (20.0)	29 (5.7)	72 (20.5)	.10
Hyperkalemia	19 (10.7)	7 (8.8)	19 (40.3)	41 (41.7)	.88
WRF	2 (1.1)	3 (3.8)	2 (1.1)	12 (3.4)	.19
Angioedema	2 (1.1)	0 (0.0)	0 (0.0)	1 (0.3)	.29
Loss to follow-up/ death	16	14	39	57	<.001

HF, heart failure; WRF, worsening renal function.

Foundation for Statistical Computing). P values are 2-sided, with values of less than .05 considered significant.

Results

Baseline characteristics of the 794 study participants are shown by HF duration in Table 1. There were 178 study participants with a HF duration of less than 1 year, 80 with a HF duration of 12–24 months, 185 with a HF duration of 24–60 months, and 351 with a HF duration of more than 60 months (**Supplementary Figure 2**).

Study participants with a HF duration of 60 or more months tended to be older and to have greater medical complexity, with a higher prevalence of hypertension, diabetes mellitus, myocardial infarction, and ischemic etiology to their HF with prior coronary revascularization. There were no differences in the baseline cardiac biomarkers across the 4 HF duration groups, although those with more chronic HF had a slightly lower estimated glomerular filtration rate. With respect to prior HF management, all 4 HF duration groups were well-treated with GDMT at baseline with the similar use of ACE inhibitors and ARBs (>70% across all groups), beta-blockers (>90% across all groups), and mineralocorticoid receptor antagonists (>35% across all groups). Notably, nearly 20% of study participants with longest duration HF had received cardiac resynchronization therapy (CRT), more likely when compared with those with more recent onset of HFrEF (4%).

Across HF duration groups, significant differences existed with respect to baseline echocardiographic measurements. For example, those with newer onset HF had a slightly higher LVEF (30%) than the other groups, with correspondingly lower volumes. In contrast, study participants with a HF duration of more than 60 months had a slightly lower baseline EF (27%) with a correspondingly higher LV end-diastolic volume index (88 mL/m^2) and left ventricular end-systolic volume index (63 mL/m^2), but similar LVMi (125 g/m^2). Those with a longer duration of HF also had more dilated left atrium with higher left atrial volume index (39 mL/m^2).

After the initiation and titration of Sac/Val, each HF duration category was able to achieve a target dose of 97/103 mg twice daily in the majority of study participants; those with the longest standing HF duration were the least likely, achieving this dose in 59.8% of study participants, compared with 68.5%, 61.3% and 73.0% in the other three groups (P = .01).

Figure 1 **and Supplementary Table 2** show the changes in cardiac biomarkers during 12 months of treatment with Sac/Val. All 3 biomarkers decreased over time after treatment, with study participants in the shortest duration of HF group having greatest decrease in cardiac biomarkers. For example, the geometric mean NT-proBNP decreased from 790 pg/mL to 292 pg/mL during 1 year in patients with a HF duration of less than 12 months (absolute change 498 pg/mL). In patients with a HF duration of more than 60 months, NT-proBNP decreased from 768 pg/mL to 502 pg/mL (absolute change 266 pg/mL).

With respect to health status, Figure 2 **and Supplementary Table 3A** show the KCCQ-23 overall summary score stratified by HF duration groups. No significant differences in KCCQ-23 scores were observed between groups at baseline. During the 1-year of follow-up, regardless of the HF duration group, substantial improvements were observed in the KCCQ-23 overall summary score without significant differences across the groups. **Supplementary Table 3** shows the proportion of KCCQ-23 responders as a function of HF duration. This shows the percentage of study participants with 5-point or more, 10-point or more, or 20-point or more increases at each time point was comparable across HF duration categories. For example, by 12 months, the percentage of study participants with a 20-point or more increase was 26.6%, 25.0%, 24.8%, and 25.2% across HF durations of 12 months or less, 12–24 months, 24–60 months, and more than 60 months, respectively.

Echocardiographic measures stratified by HF duration groups from baseline to 12 months are detailed in Figure 3 with absolute changes detailed in **Supplementary Table 4**. These show consistent reverse

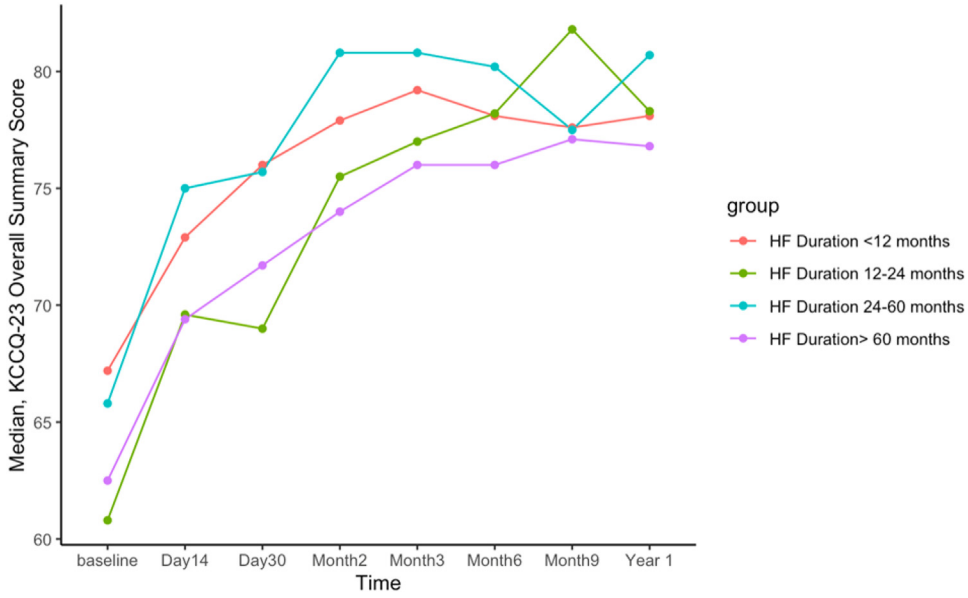


Figure 2. Kansas City Cardiomyopathy Questionnaire 23 (KCCQ-23) overall summary scores stratified by heart failure (HF) duration. After treatment with sacubitril/valsartan, we observed increases in KCCQ-23 score during the study period across all HF duration groups. hs-cTnT, high sensitivity cardiac troponin T; sST2, somatostatin receptor subtype 2.

cardiac remodeling in each HF duration category, with improved LVEF, reduced LV and left atrial volumes, lower E/e', and decreased LVMi. Nonetheless, although significantly better in each category, those with a longer HF duration had slightly smaller improvements. For example, by 12 months of follow-up, the LVEF was significantly increased across all the HF duration groups; from 30.1% to 41.7% in those with a HF duration of 12 months or less, from 27.2 to 36.4% in those with a HF duration of 12−24 months, from 28.9% to 36.7% in those with a HF duration of 24−60 months, and from 27.6% to 36.7% in those with a HF duration of more than 60 months. The corresponding median absolute LVEF improvement across these groups by 12 months were 12.2% (7.5%, 19.1%), 6.9% (4.1%, 12.0%), 8.5% (5.7%, 11.7%), and 8.6% (4.0%, 12.7%). These increases in the LVEF were paralleled by a decrease in the LV end-diastolic volume index and the left ventricular end-systolic volume index across all HF duration groups in a similar pattern. As well, the left atrial volume index improved in all 4 HF duration categories during the 12 months of follow-up with small (but significant) differences across the groups; E/e' showed the same pattern of improvement and distribution of change. Last, the LVMi was similar at baseline across all groups, with very similar decreases across all 4 groups (**Supplementary Table 4**). Further, stratifying HF duration categories by HF etiology (ischemic vs nonischemic) showed that, regardless of HF etiology, Sac/Val improved echocardiographic measures during 1 year follow-up (**Supplementary Table 5**). Table 2 demonstrates safety outcomes; Sac/Val was safe and well-tolerated without clear patterns based on HF duration. Excluding patients in whom Sac/Val was discontinued ($n = 140$) from the cohort did not change our findings (**Supplementary Tables 6−8**).

Discussion

In this post hoc analysis from the PROVE HF study, there are several major conclusions. First, those with a longer duration of HFrEF had more complex baseline medical histories with factors that might mitigate against a significant response to therapies with effects to reverse remodeling the heart (more ischemic heart disease, diabetes mellitus, worse kidney function, and a higher frequency of previous CRT). Second, those with a longer HF duration were slightly less likely to achieve target Sac/Val dose, but study investigators were able to titrate nearly 60% to this level; in doing so, Sac/Val was well-tolerated, generally comparable with other groups. Third, treatment with Sac/Val reduced concentration of prognostically relevant biomarkers across HF duration groups; individuals with a longer duration of HF tended to have a higher concentration of each biomarker, and the decrease was significant in each case. Fourth, treatment with Sac/Val was associated with substantial improvement in health status, regardless of HF duration. Last, and importantly, after the initiation and titration of Sac/Val, robust reverse cardiac remodeling (marked by an improved LVEF, reduced LV and left atrial volumes, improved myocardial relaxation, and reduced LVMi) was observed across HF duration categories. These findings emphasize the mechanistic benefit of ARNI

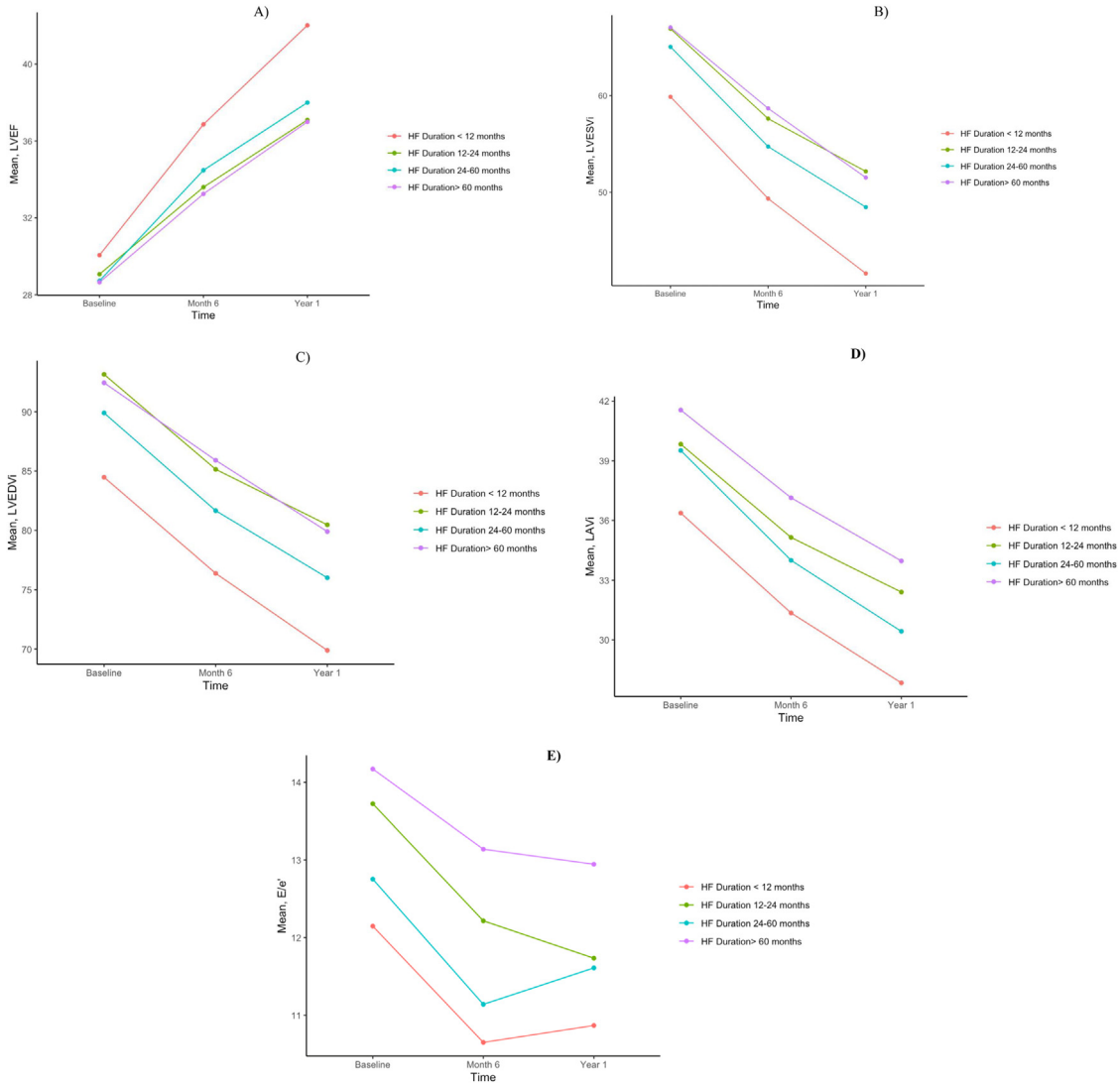


Figure 3. Echocardiographic measures stratified by heart failure (HF) duration, including (A) left ventricular ejection fraction (LVEF), (B) left ventricular end-systolic volume index (LVESVi), (C) left ventricular end-diastolic volume index (LVEDVi), (D) left atrial volume index (LAVi), and (E) E/e'. After treatment with sacubitril/valsartan, improvement in average measurement was observed across HF duration categories of less than 12 months, 12 to 24 months, 24 to 60 months, and more than 60 months.

therapy, regardless of duration in stable chronic HFrEF, underlining urgency to initiate the treatment in newer onset disease, while not delaying (or avoiding) change in those with longer duration HFrEF; both are ongoing issues after the single PARADIGM-HF trial results.

In patients with HFrEF, a fatal event may occur unexpectedly at any time, so time is of the essence in initiating therapies with proven superiority for treating the diagnosis. Two recent clinical trials[10,18] have shown the efficacy and safety of initiating Sac/Val after acute HF events even in hospital or shortly after discharge. Unfortunately, despite the initiation of Sac/Val in patients with HFrEF receiving class I recommendation from clinical practice guidelines and expert consensus documents[5,19] in different clinical settings, real-world data from a Medicare and Medicaid use and an associated spending registry[11] showed that a substantial proportion of patients with HFrEF were not prescribed the drug despite being eligible. Numerous reasons for gaps in optimal care exist, some of which are addressed through the mechanistic data in this analysis. Prescription patterns suggest a common trigger for the initiation of Sac/Val is worse clinical status and a lower LVEF, as well as frequent antecedent clinical events,[13] suggesting that the drug may be used as a bail out medication in a selective fashion. As well, most new-onset HFrEF is not treated with Sac/Val, and, in a similar fashion, more patients with chronic disease are also less likely to receive the drug. This factor may be due to lack of recognition of mechanistic benefit of the drug.

In newer onset HFrEF, one reason for not directly initiating Sac/Val relates to ambiguity created by clinical practice guidelines[5] that have variably suggested pretreatment with an ACE inhibitor or an ARB may be needed before obligate exchange to ARNI after an ambiguous period; even in the more declarative guidelines recommending ARNI as first line, ACE inhibitors and ARBs remain mentioned side by side with ARNIs. Delaying the indicated change of therapies early after diagnosis of HFrEF is associated with a failure to make changes later, exposing patients to unacceptable risk, particularly because the benefit of Sac/Val is observed early after treatment.[20] In addition, no biological reason exists to suggest pretreatment with ACE inhibitor or ARB would somehow make ARNI therapy more successful. In contrast, the data from this study suggest that those with newer onset HFrEF have a vigorous response to the effects of Sac/Val, with the greatest improvement in prognostic biomarker concentrations and most robust reverse cardiac remodeling, accompanied by substantial improvement in KCCQ-23 scores. This finding implies that patients with a shorter duration of HF have more plasticity and are more amenable to reverse remodeling.

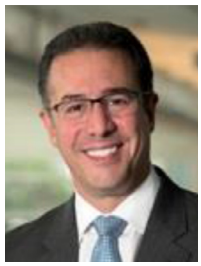
In contrast with those with newer onset HF, the reasons for not initiating Sac/Val in longer duration HFrEF might be more explainable by clinical inertia—the assumption that a patient chronically treated with an ACE inhibitor or ARB was stable enough to not be changed to an ARNI or that benefits from Sac/Val might not be observed in such individuals. However, in PARADIGM-HF, those with more chronic HFrEF (matched in the same HF duration categories in this analysis) accrued a significant decrease in risk from being changed to Sac/Val.[8] And yet, despite such results, the drug is underused in this category of patients. These results from PROVE-HF put a mechanistic emphasis on this fact: despite a baseline medical picture that might mitigate against robust reverse remodeling (including more chronic myocardial disease, already excellent GDMT, and more prior CRT), those with HFrEF for 5 years or more nonetheless showed a substantial lowering of biomarkers, improvement in KCCQ-23, and clinically relevant reverse cardiac remodeling. Given the tolerability of the therapy in this group, the results in totality suggest that, regardless of chronicity, treatment with Sac/Val would be expected to have significant benefits.

To our knowledge, few data exist about the effect of ARNI therapy and remodeling effects relative to chronicity. In a small study of 69 study participants with HFrEF,[21] treatment with Sac/Val in those with a disease duration of less than 8.5 years resulted in a significant improvement in symptoms, NT-proBNP concentration, LVEF, LVESV, and estimated pulmonary pressure at 12 months. In contrast, patients with a disease duration of more than 8.5 years had only a slight improvement only in LVEF, leading the authors to conclude that favorable LV remodeling effects of Sac/Val might only be observed among those with relatively short duration of HF. The results from this larger post hoc analysis from PROVE-HF contradict this conclusion; benefits were observed across the range of HF durations. This finding implies the importance of initiation of ARNI in those with HFrEF across the entire range of HF duration to improve outcomes through reduced cardiac stress and reversal of cardiac remodeling.

Last, we found a significant absolute increase in LVEF once switched to Sac/Val despite chronic HF and background therapy with ACE inhibitors and ARBs in most study participants. This finding is of importance for those chronic HF patients who may meet the indication for primary prevention implantable cardioverter-defibrillator (ICD). After the initiation of Sac/Val and subsequent improvement in LVEF, such individuals might not need an ICD. We previously published from PROVE-HF that up to 62% of study participants meeting the criteria for ICD implantation were no longer eligible after 12 months of treatment with Sac/Val.[22] Similarly, in the SAVE-ICD study,[23] Guerra et al found that Sac/Val improved LVEF after 6 months of treatment and prevented ICD implantation in 1 out of 4 patients with HFrEF. These data should be interpreted as hypothesis-generating but clearly support the need to optimize GDMT with Sac/Val before consideration of decision-making regarding ICD.

This study has several limitations. First, although the results from the present study suggest that the mechanistic and clinical benefits of Sac/Val are expected in those with more chronic HFrEF durations, this study cohort represented those with stage C HF and cannot be extrapolated to those with truly advanced or stage D HFrEF, where treatment with Sac/Val did not decrease the NT-proBNP or improve prognosis relative to valsartan.[24] In a sense, this finding further emphasizes the crucial need to initiate and titrate ARNI at earlier stages of HFrEF without delay, to prevent progression to HF stages that are considerably more difficult to treat. Second, PROVE-HF is a single observational group, open-label study. Given the lack of randomization and comparison group, one may assume these improvements in cardiac biomarkers, health status, and echocardiographic measures have occurred spontaneously or by chance although the magnitude of improvements and their parallel nature make it implausible the changes are due to regression to the mean or play of chance. Because of a class I clinical practice guideline recommendation for use of Sac/Val at the

time of the study,[4,5] randomization to receive ACE inhibitor or ARB for long-term treatment was deemed impossible. Third, our cohort may have been lower risk: approximately one-half of these patients had a history of hospitalization owing to acute HF. Thus, as noted elsewhere in this article, the results from this analysis might not necessarily apply to those with more severe or advanced disease. This finding again emphasizes the importance of early application of Sac/Val before disease progression to more advanced stages. Fourth, no intervention, such as implantation of CRT, transcatheter mitral valve edge-to-edge repair, or up-titration of other pillars of GDMT, occurred during the study period. Hence, the result of this study may be interpreted irrespective of other additional disease-modifying therapies in patients with LVEF. Fourth, there was a significant difference in the loss to follow-up rate across HF duration groups. We are unable to exclude the possibility that differential loss to follow-up may have influenced the safety and efficacy outcomes. Last, we followed our study participants serially for only 12 months. Future studies may need to investigate longer term impact of Sac/Val on mechanistic end points in a larger, more ethnically diverse population.



Conclusions

Across relevant categories of HFrEF duration, treatment with Sac/Val was associated with important improvements in stress biomarkers, health status, and cardiac remodeling parameters despite excellent background GDMT and device therapy even in those with longer duration of disease. These results provide an important and clear message that regardless of HF duration, in chronic HFrEF, ARNI initiation would be expected to produce significant benefit and should not be withheld.

Disclosures

Dr Felker has received research grants from NHLBI, American Heart Association, Amgen, Bayer Merck, Cytokinetics, Myokardia; he has acted as a consultant to Novartis, Amgen, BMS, Cytokinetics, Medtronic, Cardionomic, Boehringer-Ingelheim, American Regent, Abbott, Astra-Zeneca, Reprieve, and Sequana; and has served on clinical end point committees abd data safety monitoring boards for Amgen, Merck, Medtronic, EBR Systems, V-Wave, LivaNova, Siemens, and Rocket Pharma. Drs Prescott, Ward, and Meng are employees of Novartis Pharmaceuticals, Inc. Dr Piña has participated on advisory boards for Vifor and AstraZeneca, and is a steering committee member for Novartis. Dr Butler is a consultant for Abbott, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, CVRx, Eli Lilly, G3 Pharmaceutical, Impulse Dynamics, Innolife, Janssen, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Sequana, StealthPeptide, and Vifor. Dr Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, and Theracos; and has consulted for Akros, Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardior, Corvia, Cytokinetics, Gilead, GSK, Ironwood, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, and Tenaya. Dr Januzzi is a Trustee of the American College of Cardiology; a Board member of Imbria Pharmaceuticals; has received grant support from Abbott Diagnostics, Applied Therapeutics, Innolife, Novartis Pharmaceuticals, and Roche Diagnostics; consulting income from Abbott, Janssen, Novartis, Prevencio, and Roche Diagnostics; and participates in clinical end point committees and data safety monitoring boards for Abbott, AbbVie, Amgen, Bayer, CVRx, Janssen, MyoKardia, Takeda, and Vifor. The rest of the authors have no disclosures to report. Fig. 3

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.08.006.

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