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


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brief bullet points:

- Treatment with Sacubitril/Valsartan reduced concentration of prognostically relevant biomarkers across heart failure duration groups.

- Treatment with Sacubitril/Valsartan was associated with substantial improvement in health status across heart failure duration groups.

- Treatment with Sacubitril/Valsartan reversed cardiac remodeling (marked by improved LVEF, reduced LV and/or LA volumes, improved myocardial relaxation and reduced LVMi) across heart failure duration groups.
Heart Failure Duration and Mechanistic Efficacy of Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction

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\textbf{Short Title:} Effects of Sacubitril/Valsartan Stratified by HF duration

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Abstract

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

**Methods and Results:** 794 persons with HFrEF (EF≤40 %) were categorized according to HF duration <12 months, 12-24 months, 24-60 months, and > 60 months. Following initiation of Sac/Val, concentrations of N-terminal pro-B type natriuretic peptide (NT-proBNP), high sensitivity troponin T (hs-cTnT), and soluble ST2 were measured, and Kansas City Cardiomyopathy Questionnaire (KCCQ)-23 scores were obtained serially from baseline to 12 months. Left ventricular ejection fraction (LVEF) was measured by echocardiography. Significant reductions in concentrations of NT-proBNP, hs-cTnT, and soluble ST2 were observed regardless of HF duration (P <0.001). Comparable gains in KCCQ-23 scores were achieved in all HF duration categories. Moreover, consistent reverse cardiac remodeling in all HF duration categories occurred, with the absolute LVEF improvement by 12 months across HF duration groups of 12.2%, 6.9%, 8.5%, and 8.6% for HF duration <12 months, 12-24 months, 24-60 months, and > 60 months respectively.

**Conclusion:** Initiation of Sac/Val lowers prognostic biomarkers, improves health status, reverses cardiac remodeling processes, regardless of HF duration.

- Brief Lay summary:
We categorized 794 persons with heart failure due to a low ejection fraction according to disease duration into 4 groups; <12 months, 12-24 months, 24-60 months, and > 60 months. Following initiation of Entresto we found that regardless of duration of heart failure significant improvements occurred in cardiac biomarkers, patients felt better with improved health status and on testing with cardiac ultrasound, improvement in the heart size and function occurred. These results suggest that regardless of heart failure duration, patients with reduced ejection fraction would benefit from use of Entresto for their care.

**Trial Registration:** PROVE-HF; NCT02887183

**Keywords:** Heart failure, Sacubitril/valsartan, Cardiac remodeling, Biomarker, Echocardiography,

Abbreviations:

ACEi = angiotensin converting enzyme inhibitor

ARB = angiotensin receptor blocker

Sac/Val = sacubitril/valsartan

ARNI = angiotensin receptor neprilysin inhibitor

GDMT = guideline-directed medical therapy
HFrEF = heart failure with reduced ejection fraction

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

hs-cTnT = high sensitivity cardiac troponin T

KCCQ-23 = Kansas City Cardiomyopathy Questionnaire-23

LVEF = left ventricular ejection fraction
Introduction

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 angiotensin receptor/neprilysin inhibitor (ARNI) sacubitril/valsartan (Sac/Val) significantly reduced cardiovascular (CV) mortality and HF hospitalization compared to 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 to 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 ACEi or angiotensin II receptor blocker (ARB)(4-7). In PARADIGM-HF and PIONEER-HF (comParison Of sacubitril/valsartaN versus Enalapril on Effect on NT-proBNP in patients stabilized from an acute Heart Failure episode), the benefits of Sac/Val appeared to be present regardless of HF duration (8) and irrespective of previous HF duration or ACE inhibitor or ARB pre-treatment (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, prescription rates for Sac/Val remain low, particularly for those with new-onset HFrEF and patients with longer-term HF(11, 12).

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 pre-treatment with an ACE inhibitor or ARB for persons with newer-onset HF prior to 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 “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 following treatment with guideline-directed medical therapy in HFrEF of more longstanding duration (14). Lastly, 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 significant reduction of NT-proBNP), improvement in health status, and robust reverse cardiac remodeling. In the present study, we sought to provide mechanistic insights and assess safety/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 4, 52-week, open-label, single-group study of persons with HFrEF (left ventricular [LV] EF ≤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 reduce the risk of cardiovascular death and hospitalization for in adult patients with HFrEF). Specific to this post-hoc analysis, study participants were categorized according to HF duration into four categories: 1) new-onset HF, <12 months, 2) 12-24 months, 3) 24-60 months, and 4) > 60 months.

Following Sac/Val initiation, study participants returned for study visits and drug titration approximately every two 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 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-proBNP and high sensitivity cardiac troponin T (hs-cTnT) using electrochemiluminescence immunoassays (Roche Diagnostics, Penzberg, GE), while 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 (OSS) was assessed, as was the % of
study participants achieving previously identified and clinically meaningful thresholds for 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 approximately 6 months and 12 months, according to a study-specific 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 LV end-diastolic volume index (LVEDVi; normal <76 mL/m²), LV end-systolic volume index (LVESVi; normal <30 mL/m²), and left atrial volume index (LAVi; a value ≥34 mL/m² is considered enlarged according to American Society of Echocardiography recommendations(17)). Additionally, LV mass index (LVMi; normal <89 g/m² in women and <103 g/m² 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 greater than 14 is associated with elevated filling pressures.

**Statistical Analyses**

Mean (SD) or median (interquartile range [IQR]) 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 ANOVA and chi-square test as appropriate (Table 1 and Table 2). There were imbalances across the HF duration groups at
baseline. Thus, Analysis of Covariance (ANCOVA) was performed to measure the effect of HF duration group on continuous dependent variables (i.e. 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 (R Foundation). P values are 2-sided, with values less than 0.05 considered significant.

Results

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

Study participants with HF duration ≥ 60 months tended to be older, and to have a 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 baseline cardiac biomarkers across four 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 inhibitor/ARB (>70% across all groups), beta-blocker (>90% across all groups), and MRA (>35% across all groups). Notably, nearly 20% of study participants with longest duration HF had received cardiac resynchronization therapy (CRT), more likely when compared to those with more recent onset HFrEF (4%).

Across HF duration groups, significant differences existed with respect to baseline echocardiographic measurements. For example, those with newer-onset HF had slightly higher
LVEF (30%) than the other groups, with correspondingly lower volumes. In contrast, study participants with HF duration > 60 months had a slightly lower baseline EF (27%) with correspondingly higher LVEDVi (88 ml/m$^2$) and LVESVi (63 ml/m$^2$) but similar LVMi (125 g/m$^2$). Those with longer-duration HF also had more dilated LA with higher LAVi (39 ml/m$^2$).

Following initiation and titration of Sac/Val, each HF duration category was able to achieve target dose of 97/103 mg twice daily in the majority of study participants; those with longest standing HF duration were the least likely, achieving this dose in 59.8% of study participants, compared to 68.5%, 61.3% and 73.0% in the other three groups (P = 0.01).

**Figure 1 and Supplementary Table 2** show the change in cardiac biomarkers during 12 months of treatment with Sac/Val. All three biomarkers declined over time after treatment, with study participants in the shortest duration of HF group having greatest reduction in cardiac biomarkers. For example, geometric mean NT-proBNP was decreased from 790 pg/mL to 292 pg/mL during one year in patients with HF duration < 12 months (absolute change: 498 pg/mL). In patients with HF duration > 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 OSS stratified by HF duration groups. No significant differences in KCCQ-23 scores were observed between groups at baseline. During one year of follow-up, regardless of the HF duration group, substantial improvements were observed in the KCCQ-23 OSS without significant differences across the groups. **Supplementary Table 3B-C** shows the proportion of KCCQ-23 “responders” as a function of HF duration. This shows the percentage of study participants with ≥5, ≥10, or ≥20-point 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 rise was 26.6%, 25.0%, 24.8%, and 25.2% across HF durations of ≤12 months, 12-24 months, 24-60 months, and >60 months respectively.

Echocardiographic measures stratified by HF duration groups from baseline to 12 months are detailed in Figure 1 with absolute changes detailed in Supplementary Table 4. These show consistent reverse cardiac remodeling in each HF duration category, with improved LVEF, reduced LV and LA volumes, lower E/e’ and reduced LVMi. Nonetheless, though significantly better in each category, those with longer HF duration had slightly smaller improvements. For example, by 12 months of follow-up, LVEF was significantly increased across all the HF duration groups; from 30.1% to 41.7% in those with HF duration ≤12 months, from 27.2% to 36.4% in those with HF duration 12-24 months, 28.9% to 36.7% in those with HF duration 24-60 months, and from 27.6% to 36.7% in those with HF >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 LVEF were paralleled by reduction in LVEDVi and LVESVi across all HF duration groups in a similar pattern. As well, LAVi improved in all four 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. Lastly, LVMi was similar at baseline across all groups, with very similar reduction across all four groups (Supplementary Table 4). Further, stratifying HF duration categories by HF etiology (ischemic vs non-ischemic) 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 longer duration 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 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 to other groups. Third, treatment with Sac/Val reduced concentration of prognostically relevant biomarkers across HF duration groups; while individuals with longer duration HF tended to have higher concentration of each biomarker, reduction was significant in each case. Fourth, treatment with Sac/Val was associated with substantial improvement in health status, regardless of HF duration. Lastly and importantly, following initiation and titration of Sac/Val, robust reverse cardiac remodeling (marked by improved LVEF, reduced LV and LA volumes, improved myocardial relaxation and reduced LVMi) was observed across HF duration categories. These findings emphasize the mechanistic benefit of ARNI 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 following 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 following acute HF events even in hospital or shortly after discharge. Unfortunately, despite 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 Medicare and Medicaid utilization and 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 initiation of Sac/Val is worse clinical status, lower LVEF, as well as frequent antecedent clinical events (13), suggesting the drug may be used as a “bail out” in a selective fashion. As well, most new-onset HFrEF is not treated with Sac/Val, and in a similar fashion, more chronic patients are also less likely to receive the drug. This 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 “pre-treatment” with an ACE inhibitor or 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 ARNI. Delaying the indicated change of therapies early after diagnosis of HFrEF is associated with failure to make changes later, exposing patients to unacceptable risk particularly as benefit of Sac/Val is observed early after treatment (20). As well, no biological reason exists to suggest pre-treatment with ACE inhibitor or ARB would somehow make ARNI therapy more successful. On the contrary, 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
implies that patients with shorter duration of HF have more plasticity and more amenable to reverse remodeling.

In contrast to 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 significant reduction in risk from being changed to Sac/Val.(8) And yet, despite such results, the drug is under-utilized in this category of patient. 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 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 disease duration less than 8.5 years resulted in a significant improvement in symptoms, NT-proBNP concentration, LVEF, LVESV, and estimated pulmonary pressure at 12 months. On the contrary, patients with disease duration 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 duration. This 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.

Lastly, we found a significant absolute increase in LVEF once switched to Sac/Val despite chronic HF and background therapy with ACE inhibitor/ARB 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). Following initiation of Sac/Val and subsequent improvement in LVEF, such individuals might not need ICD. We previously published from PROVE-HF that up to 62% of study participants meeting 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 and colleague 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 prior to consideration of decision-making regarding ICD.

This study has several limitations. First, while the results from the present study suggest that 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/Stage D HFrEF, where treatment with Sac/Val did not reduce NT-proBNP or improve prognosis relative to valsartan (24). In a sense, this 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 harder to treat. Second, PROVE-HF is a single observational group, open-label study. Given 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 half had history of hospitalization due to acute HF. Thus, as noted previously, results from this analysis might not necessarily apply to those with more severe or advanced disease. This again emphasizes the importance of early application of Sac/Val prior to disease progression to more advanced stages. Fourth, no intervention—such as implantation of cardiac resynchronization therapy, 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 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 safety and efficacy outcomes. Lastly, we followed our study participant serially for only 12 months. Future studies may need to investigate longer-term impact of Sac/Val on mechanistic endpoints in a larger, more ethnically diverse population.

Conclusion

In conclusion, 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.

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Disclosures

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Author headshot photograph

• Brief Lay summary:
  
  o We categorized 794 persons with heart failure due to a low ejection fraction according to disease duration into 4 groups; <12 months, 12-24 months, 24-60 months, and > 60 months. Following initiation of Entresto we found that regardless of duration of heart failure significant improvements occurred in cardiac biomarkers, patients felt better with improved health status and on testing with cardiac ultrasound, improvement in the heart size and function occurred. These results suggest that regardless of heart failure duration, patients with reduced ejection fraction would benefit from use of Entresto for their care.
References


Table 1. Baseline characteristics of study population by heart failure duration.

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<th>HF Duration &lt;12 months N=178</th>
<th>HF Duration 12-24 months N=80</th>
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<td>121 (65.4)</td>
<td>273 (77.8)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, N (%)</td>
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<td>0.29</td>
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<tr>
<td>Hispanic/Latino</td>
<td>22 (12.4)</td>
<td>17 (21.2)</td>
<td>26 (14.1)</td>
<td>52 (14.8)</td>
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</tr>
<tr>
<td>Not Hispanic/Latino</td>
<td>155 (87.1)</td>
<td>61 (76.2)</td>
<td>156 (84.3)</td>
<td>297 (84.6)</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>127 (16)</td>
<td>125 (17)</td>
<td>125 (16)</td>
<td>124 (15)</td>
<td>0.28</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>77 (10)</td>
<td>77 (10)</td>
<td>77 (11)</td>
<td>75 (10)</td>
<td>0.13</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>73 (13)</td>
<td>72 (12)</td>
<td>72 (12)</td>
<td>72 (10)</td>
<td>0.82</td>
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<tr>
<td>NYHA, N (%)</td>
<td></td>
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<td>0.64</td>
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<tr>
<td>Class II</td>
<td>136 (76.4)</td>
<td>59 (73.8)</td>
<td>135 (73.0)</td>
<td>255 (72.6)</td>
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<tr>
<td>Class III</td>
<td>39 (21.9)</td>
<td>18 (22.5)</td>
<td>48 (25.9)</td>
<td>89 (25.4)</td>
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<tr>
<td>Class IV</td>
<td>2 (1.1)</td>
<td>1 (1.2)</td>
<td>1 (0.5)</td>
<td>4 (1.1)</td>
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</tr>
<tr>
<td>Months since HF diagnosis, mean (SD)</td>
<td>4.44 (3.04)</td>
<td>17.72 (3.07)</td>
<td>41.47 (9.98)</td>
<td>142.99 (77.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>73 (41.0)</td>
<td>46 (57.5)</td>
<td>93 (50.3)</td>
<td>214 (61.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior HF hospitalization</td>
<td>94 (52.8)</td>
<td>34 (42.5)</td>
<td>79 (42.7)</td>
<td>162 (46.2)</td>
<td>0.22</td>
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<tr>
<td>BMI</td>
<td>31.15 (6.43)</td>
<td>30.24 (7.02)</td>
<td>31.44 (7.62)</td>
<td>31.52 (6.62)</td>
<td>0.48</td>
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<tr>
<td>Hypertension</td>
<td>142 (79.8)</td>
<td>73 (91.2)</td>
<td>167 (90.3)</td>
<td>317 (90.3)</td>
<td>0.002</td>
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<tr>
<td>TIA</td>
<td>8 (4.5)</td>
<td>3 (3.8)</td>
<td>8 (4.3)</td>
<td>29 (8.3)</td>
<td>0.41</td>
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<tr>
<td>Stroke</td>
<td>20 (11.2)</td>
<td>10 (12.5)</td>
<td>17 (9.2)</td>
<td>39 (11.1)</td>
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<tr>
<td>Myocardial Infarction</td>
<td>50 (28.1)</td>
<td>39 (48.8)</td>
<td>65 (35.1)</td>
<td>175 (49.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary revasc</td>
<td>64 (36.0)</td>
<td>42 (52.5)</td>
<td>83 (44.9)</td>
<td>187 (53.3)</td>
<td>0.001</td>
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<tr>
<td>Prior PCI</td>
<td>41 (23.0)</td>
<td>28 (35.0)</td>
<td>49 (26.5)</td>
<td>106 (30.2)</td>
<td>0.16</td>
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<tr>
<td>Prior CABG</td>
<td>28 (15.7)</td>
<td>20 (25.0)</td>
<td>40 (21.6)</td>
<td>102 (29.1)</td>
<td>0.007</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>64 (36.0)</td>
<td>33 (41.2)</td>
<td>81 (43.8)</td>
<td>183 (52.1)</td>
<td>0.004</td>
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<tr>
<td>Atrial fibrillation</td>
<td>50 (28.1)</td>
<td>25 (31.2)</td>
<td>60 (32.4)</td>
<td>133 (37.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Medications/devices, N (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ACEi/ARB</td>
<td>141 (79.2)</td>
<td>61 (76.2)</td>
<td>146 (78.9)</td>
<td>254 (72.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>166 (93.3)</td>
<td>78 (97.5)</td>
<td>173 (93.5)</td>
<td>334 (95.2)</td>
<td>0.46</td>
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<tr>
<td>MRA</td>
<td>69 (38.8)</td>
<td>29 (36.2)</td>
<td>70 (37.8)</td>
<td>124 (35.3)</td>
<td>0.86</td>
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<tr>
<td>CRT-P</td>
<td>0 (0.0)</td>
<td>2 (2.5)</td>
<td>1 (0.5)</td>
<td>1 (0.3)</td>
<td>0.06</td>
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<tr>
<td>CRT-D</td>
<td>7 (3.9)</td>
<td>10 (12.5)</td>
<td>31 (16.8)</td>
<td>70 (19.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Biomarkers, Geometric mean, (SD)</td>
<td>ICD-Alone</td>
<td>24 (30.0)</td>
<td>59 (31.9)</td>
<td>125 (35.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>NT-proBNP, pg/ml</td>
<td>790(3.45)</td>
<td>944(3.89)</td>
<td>697(4.52)</td>
<td>768(3.80)</td>
<td>0.51</td>
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<tr>
<td>hs-TnT, ng/L</td>
<td>15(2.41)</td>
<td>16.2(2.37)</td>
<td>17.2(2.50)</td>
<td>17.5(2.07)</td>
<td>0.59</td>
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<tr>
<td>sST2, ng/mL</td>
<td>24.3(1.51)</td>
<td>25.5(1.51)</td>
<td>26.6(1.54)</td>
<td>26.3(1.48)</td>
<td>0.18</td>
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<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>67 (20)</td>
<td>66 (22)</td>
<td>65 (21)</td>
<td>60 (18)</td>
<td>0.004</td>
</tr>
<tr>
<td>eGFR&lt;60, mL/min/1.73m²</td>
<td>51 (28.7)</td>
<td>29 (36.2)</td>
<td>33 (34.1)</td>
<td>134 (38.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>Echocardiography measures, Median, (Q1, Q3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LVEF, %</td>
<td>30 (25, 33)</td>
<td>27 (21, 33)</td>
<td>28 (24, 33)</td>
<td>27 (24, 32)</td>
<td>0.03</td>
</tr>
<tr>
<td>LVEDVi, ml/m²</td>
<td>83 (74, 94)</td>
<td>93 (79, 103)</td>
<td>87 (76, 100)</td>
<td>88 (76, 104)</td>
<td>0.001</td>
</tr>
<tr>
<td>LVESVi, ml/m²</td>
<td>58 (50, 69)</td>
<td>65 (54, 79)</td>
<td>61 (51, 74)</td>
<td>63 (53, 79)</td>
<td>0.001</td>
</tr>
<tr>
<td>LAEDVi, ml/m²</td>
<td>35 (29, 42)</td>
<td>37 (32, 46)</td>
<td>38 (31, 46)</td>
<td>39 (32, 47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/e', Ratio</td>
<td>10 (8, 15)</td>
<td>12 (9, 16)</td>
<td>10 (8, 15)</td>
<td>12.10 (9, 16)</td>
<td>0.03</td>
</tr>
<tr>
<td>LV Mass Index, g/m²</td>
<td>125 (105, 145)</td>
<td>121 (99, 150)</td>
<td>125 (105, 145)</td>
<td>125 (109, 150)</td>
<td>0.32</td>
</tr>
<tr>
<td>Achieved target dose, N (%)</td>
<td>122 (68.5)</td>
<td>49 (61.3)</td>
<td>135 (73.0)</td>
<td>210 (59.8)</td>
<td>0.01</td>
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</table>

Table 2. Safety outcomes.

<table>
<thead>
<tr>
<th></th>
<th>HF Duration &lt;12 months N=178</th>
<th>HF Duration 12-24 months N=80</th>
<th>HF Duration 24-60 months N=185</th>
<th>HF Duration &gt;60 months N=351</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>24 (13.5)</td>
<td>15 (48.8)</td>
<td>22 (41.9)</td>
<td>74 (21.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypotension</td>
<td>22 (42.4)</td>
<td>16 (20.0)</td>
<td>29 (5.7)</td>
<td>72 (20.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>19 (10.7)</td>
<td>7 (8.8)</td>
<td>19 (40.3)</td>
<td>41 (41.7)</td>
<td>0.88</td>
</tr>
<tr>
<td>WRF</td>
<td>2 (1.1)</td>
<td>3 (3.8)</td>
<td>2 (1.1)</td>
<td>12 (3.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Angioedema</td>
<td>2 (1.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Loss to follow-up/Death</td>
<td>16</td>
<td>14</td>
<td>39</td>
<td>57</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HF: heart failure, WRF: worsening renal function
Figure 1. Changes in median biomarker concentrations stratified by HF duration. Following treatment with sacubitril/valsartan, biomarker concentrations were decreased across all HF duration groups.
Figure 2. KCCQ-23 Overall Summary Scores Stratified by HF Duration. Following treatment with sacubitril/valsartan, we observed increases in KCC1-23 score during the study period across all HF duration groups.
**Figure 3. Echocardiographic Measures Stratified by HF Duration.** This includes A) left ventricular ejection fraction (LVEF), B) left ventricular end diastolic volume index (LVEDVi), C) left ventricular end systolic volume index (LVESVi), D) left atrial volume index (LAVi), and E) E/e'. Following treatment with sacubitril/valsartan, improvement in average measurement was observed across HF duration categories of <12 months, 12-24 months, 24-60 months, and >60 months.
B)
D)
**Graphical abstract:** Improvement in cardiac remodeling across all heart failure duration categories as evident by the increase in left ventricular ejection fraction and decrease in cardiac biomarker, left atrial volume index and left ventricular end-systolic volume index during 12 months treatment with Sacubitril/Valsartan.