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FASTTRACK CLINICAL RESEARCH
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Cardiovascular biomarkers in patients with acute decompensated heart failure randomized to sacubitril-valsartan or enalapril in the PIONEER-HF trial

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Aims Circulating high-sensitivity cardiac troponin (hsTn) and soluble ST2 (sST2) reflect myocardial stress in patients with heart failure (HF). Production of cyclic guanosine 3′5′ monophosphate (cGMP) in response to activation of natriuretic peptide receptors reduces cardiac afterload and preload. We assessed the effects of sacubitril/valsartan on these biomarkers in patients with reduced ejection fraction and acute decompensated HF (ADHF).

Methods and results PIONEER-HF was a randomized, double-blind trial of sacubitril/valsartan vs. enalapril in hospitalized patients with ADHF following haemodynamic stabilization. We measured circulating hsTnT, sST2, and urinary cGMP at baseline, 1, 2 (sST2, cGMP), 4, and 8 weeks ($n = 694$ with all baseline biomarkers). Ratios of geometric means (timepoint/baseline) were determined and compared as a ratio for sacubitril/valsartan vs. enalapril. Compared with enalapril, sacubitril/valsartan led to a significantly greater decline in hsTnT and sST2. This effect emerged as early as 1 week for sST2 and was significant for both at 4 weeks with a 16% greater reduction in hsTnT ($P < 0.001$) and 9% greater reduction in sST2 ($P = 0.0033$). Serial urinary cGMP increased with sacubitril/valsartan compared with enalapril ($P < 0.001$, 1 week). The significant differences between treatment groups for each biomarker were sustained at 8 weeks. In an exploratory multivariable-adjusted analysis of cardiovascular death or HF-rehospitalization, the concentrations of hsTnT, sST2 at week 1 were significantly associated with subsequent outcome.

Conclusion Biomarkers of myocardial stress are elevated in patients with ADHF and associated with outcome. Compared with enalapril, sacubitril/valsartan reduces myocardial injury and haemodynamic stress as reflected by biomarkers, with an onset that is apparent within 1–4 weeks.

Clinical trials registration NCT 02554890 clinical.trials.gov

Keywords Biomarkers • Acute heart failure • Troponin

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Introduction

Sacubitril/valsartan is an angiotensin receptor-neprilysin inhibitor indicated for patients with symptomatic heart failure (HF) with reduced ejection fraction (HFrEF). In outpatients with chronic HFrEF, sacubitril/valsartan improves survival and reduces the rate of hospitalizations for HF.[1] Moreover, in mechanistic studies among outpatients with chronic HF, at 1 month or longer after initiation, sacubitril-valsartan favourably impacted circulating biomarkers of haemodynamic stress[2,3] and myocardial injury,[4,5] as well as a biochemical secondary messenger of its action.[1,5]

Until recently, the efficacy and safety of sacubitril/valsartan in patients hospitalized for acute decompensated HF (ADHF) was unknown. In the randomized, double-blind Comparison of Sacubitril/valsartan vs. Enalapril on Effect on N-terminal pro-brain natriuretic peptide (NT-proBNP) in Patients Stabilized from an Acute HF Episode (PIONEER-HF) trial, sacubitril/valsartan, started in-hospital and administered for 8 weeks, was well tolerated, achieved a greater reduction in NT-proBNP concentration, the primary endpoint, and reduced the exploratory composite of cardiovascular death or rehospitalization for HF.[6,7] Analyses of additional biomarkers reflecting possible mechanistic pathways of benefit were pre-specified in the trial design.[8]

In patients with HF, cardiovascular biomarkers can reflect haemodynamic stress and myocardial injury resulting from the interplay of neurohormonal, inflammatory, and biochemical insults to cardiac myocytes, the cardiac interstitium, or both.[9] High-sensitivity measurement of cardiac troponin (hsTn) can quantify cardiomyocyte injury resulting from these insults and hsTn values strongly correlate with prognosis in patients with HF.[10,11] Soluble ST2 (sST2), induced and released by stretched myocytes, reflects ventricular wall stress and is also a robust prognostic marker in ADHF.[12] Sacubitril inhibits neprilysin which degrades biologically active natriuretic peptides (NPs), including BNP, and thereby augments NP-induced generation of cyclic guanosine 3′5′ monophosphate (cGMP). Increased production of cGMP in response to activation of NP receptors mediates the favourable effects of NPs on cardiac afterload, preload, myocardial function, remodelling, as well as cardiorenal interactions.[13,14]

In this sub-study from PIONEER-HF, we examined the early- and near-term effects of initiating sacubitril/valsartan vs. enalapril on these mechanistic biomarkers (hsTnT, sST2, and cGMP) along with NT-proBNP in haemodynamically stabilized patients with ADHF.

Methods

Study population

The trial design has been reported.[8] PIONEER-HF was a multi-centre, randomized, double-blind, double-dummy, active-controlled trial of in-hospital initiation of sacubitril/valsartan compared with enalapril in patients stabilized after hospital admission for ADHF. Eligible patients were to have a left ventricular ejection fraction ≤40% and signs and symptoms of HF along with an NT-proBNP concentration ≥1600 pg/mL or BNP concentration ≥400 pg/mL. Patients were enrolled ≥24 h and up to 10 days after initial presentation while still hospitalized and were to be haemodynamically stable as defined by a systolic blood pressure ≥100 mm Hg for the preceding 6 h, with no increase in intravenous diuretics or use of intravenous vasodilators during that period, and no intravenous inotropes administered within the prior 24 h. Key exclusion criteria potentially relevant to this analysis included acute coronary syndrome, cardiac surgery or percutaneous coronary revascularization within the prior month, or severe renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m^2). This study complies with the Declaration of Helsinki. The protocol, including biomarker testing, was approved by the institutional review board at each participating hospital and all participants provided written informed consent.

Study therapy

Blinded study medication, sacubitril/valsartan or matched placebo and enalapril or matched placebo, was administered orally for an 8-week blinded study period, with the initial dosing selected based on the systolic blood pressure at randomization and titrated towards a target of sacubitril/valsartan 97/103 mg twice daily, or enalapril 10 mg twice daily according to a protocol-based algorithm using systolic blood pressure along with the investigator's assessment of tolerability.[8] Patients randomized to sacubitril/valsartan received placebo for the initial two doses to ensure a minimum 36-h washout period of any past angiotensin converting enzyme inhibitor prior to initiation of active sacubitril/valsartan with the 3rd dose of study drug.

Biomarkers

Blood and spot urine samples were collected at randomization (baseline), and visits at 1, 2, 4, and 8 weeks for biomarker analysis. Serum and plasma were isolated and initially maintained, along with urine, at -20°C or colder at the local site until shipment to the central laboratory. Frozen samples were shipped to the central laboratory (Clinical Reference Laboratory, Lenexa, KS) where they were stored at -80°C. All assays were performed by laboratory personnel blinded to treatment allocation, and clinical outcomes.

We measured circulating hsTnT, sST2, and urinary cGMP (ucGMP) at each timepoint with exception that hsTnT was not performed at 2 weeks. Plasma NT-proBNP was measured at all timepoints by a sandwich immunoassay (proBNP II; Roche Diagnostics) with a reporting range of 25–35 000 pg/mL and a coefficient of variation (CV) <5% across the assay range. Serum cTnT was measured using a high-sensitivity electrochemiluminescence immunoassay (Troponin T hs; Roche Diagnostics) with a lower limit of detection of 5 ng/L and a 99th percentile upper reference limit of 14 ng/L, with a CV <3% at that concentration. sST2 was measured using an enzyme-linked immunosorbent assay (Presage; Critical Diagnostics) with a reporting range of 3.1–200 ng/mL and CV <4.0% across the assay range. ucGMP was measured using a competitive enzyme immunoassay (Parameter; R&D Systems) with a reporting range of 42–200 000 nmol/L and CV <11% across the assay range.

Statistics

The primary objective of this prospectively nested biomarker sub-study was to assess the effect of sacubitril/valsartan vs. enalapril on the change in concentration from baseline of the biomarkers of interest. For each biomarker, ratios of the geometric means from baseline to each timepoint are presented. Values below the lower limit of the assay were imputed (NT-proBNP <25 pg/mL as 24.9 pg/mL, hsTnT <5 ng/L as 4.9 ng/L, and ucGMP <42 nmol/L as 41.9 nmol/L). Analyses at each timepoint included patients with values at baseline and the timepoint of interest. The proportional change in each biomarker was analysed from baseline in a logarithmic scale using a mixed model analysis of covariance (ANCOVA) adjusting for the baseline biomarker value, treatment, visit, and the treatment by visit interaction as fixed effects. Two-sided 95% confidence intervals (CIs) from the ANCOVA model are provided.

Additional analyses were performed to assess the relationship between the biomarkers of interest and the rate of cardiovascular death or rehospitalization for HF. For clinical endpoints, cumulative event rates were determined using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios (HRs) with associated CIs were calculated using a Cox proportional hazards model. The proportional hazards assumption was met. A landmark analysis of outcomes starting from the Week 1 sampling was also performed to assess the association with biomarker values at this timepoint.

Statistical significance for all analyses was assessed using a two-sided alpha level of 0.05 without adjustment for multiple comparisons. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Among patients with all biomarkers available at baseline ($n = 694$), the median age was 62 years and 73% were male, and 35% self-identified as black. The median time from presentation to randomization was 68 h (25th, 75th percentile: 48, 98). Baseline characteristics were similar between the two study treatment groups (*Table 1*). Baseline biomarker concentrations are reported in Supplementary material online, *Table S1*.

Effect of sacubitril/valsartan

Compared with enalapril, treatment with sacubitril/valsartan led to a significantly greater decline in hsTnT and sST2 (*Figure 1*) that paralleled the decline in NT-proBNP reported previously.[6] This effect on hsTnT was significant by 4 weeks with a 16% greater reduction in hsTnT ($P < 0.001$) with sacubitril/valsartan. Similarly, a 9% greater reduction in sST2 with sacubitril/valsartan was evident already by 1 week ($P < 0.001$, *Figure 1B*). The significant differences between treatment groups for both biomarkers were sustained at 8 weeks (*Figure 1*). The relative effects of sacubitril/valsartan vs. enalapril are summarized in *Take home figure* and the details at each timepoint are shown in Supplementary material online, *Figure S1* and are observed to be increasing through the first 4 weeks with a stably sustained advantage over enalapril at Week 8.

Considering ucGMP as a measure of the biological effect of sacubitril/valsartan on NP-mediated activation of NP receptors, serial measurement of ucGMP revealed an increased concentration in patients treated with sacubitril/valsartan (within-group change $P < 0.001$ at each timepoint) compared with a decline in ucGMP concentration in the enalapril group ($P < 0.001$ for sacubitril/valsartan vs. enalapril at 1 week through 8 weeks, *Figure 2*).

A graded dose-related association was apparent between the achieved dose of sacubitril/valsartan vs. enalapril at 4 weeks and the

Table 1 Baseline characteristics among patients with complete baseline biomarker data

Variables	Sacubitril/valsartan ($n = 342$)	Enalapril ($n = 352$)
Age, median (25th, 75th), years	61 (50.5, 71)	63 (53, 71)
Female sex, no. (%)	81 (23.7)	107 (30.4)
Race, no. (%)		
Black	117 (34.2)	124 (35.2)
White	206 (60.2)	202 (57.4)
BMI, median (25th, 75th), kg/m^2	30.4 (25.9, 36.9)	30.1 (25.9, 36.7)
Medical history of heart failure,[a] no. (%)	222 (64.9)	211 (59.9)
Medication history,[a] no. (%)		
ACEi/ARB	152 (44.4)	170 (48.3)
Beta-blocker	196 (57.3)	205 (58.2)
MRA	36 (10.5)	28 (8.0)
NYHA class,[a] no. (%)		
I	3 (0.9)	4 (1.1)
II	77 (22.5)	98 (27.8)
III	219 (64.0)	216 (61.4)
IV	32 (9.4)	30 (8.5)
Not assessed	11 (3.2)	4 (1.1)
SBP, median (25th, 75th), mm Hg	119 (111, 134)	119 (109, 132)
Pulse, median (25th, 75th), b.p.m.	82 (72, 91)	79 (70, 90)
LVEF, median (25th, 75th)	0.24 (0.18, 0.30)	0.24 (0.19, 0.30)
Estimated GFR,[b] median (25th, 75th), mg/dL	59.3 (48.5, 72.3)	58.9 (47.4, 71.9)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; b.p.m., beats per minute; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure.
[a]Prior to index hospitalization.
[b]At randomization.
$P > 0.05$ for each.

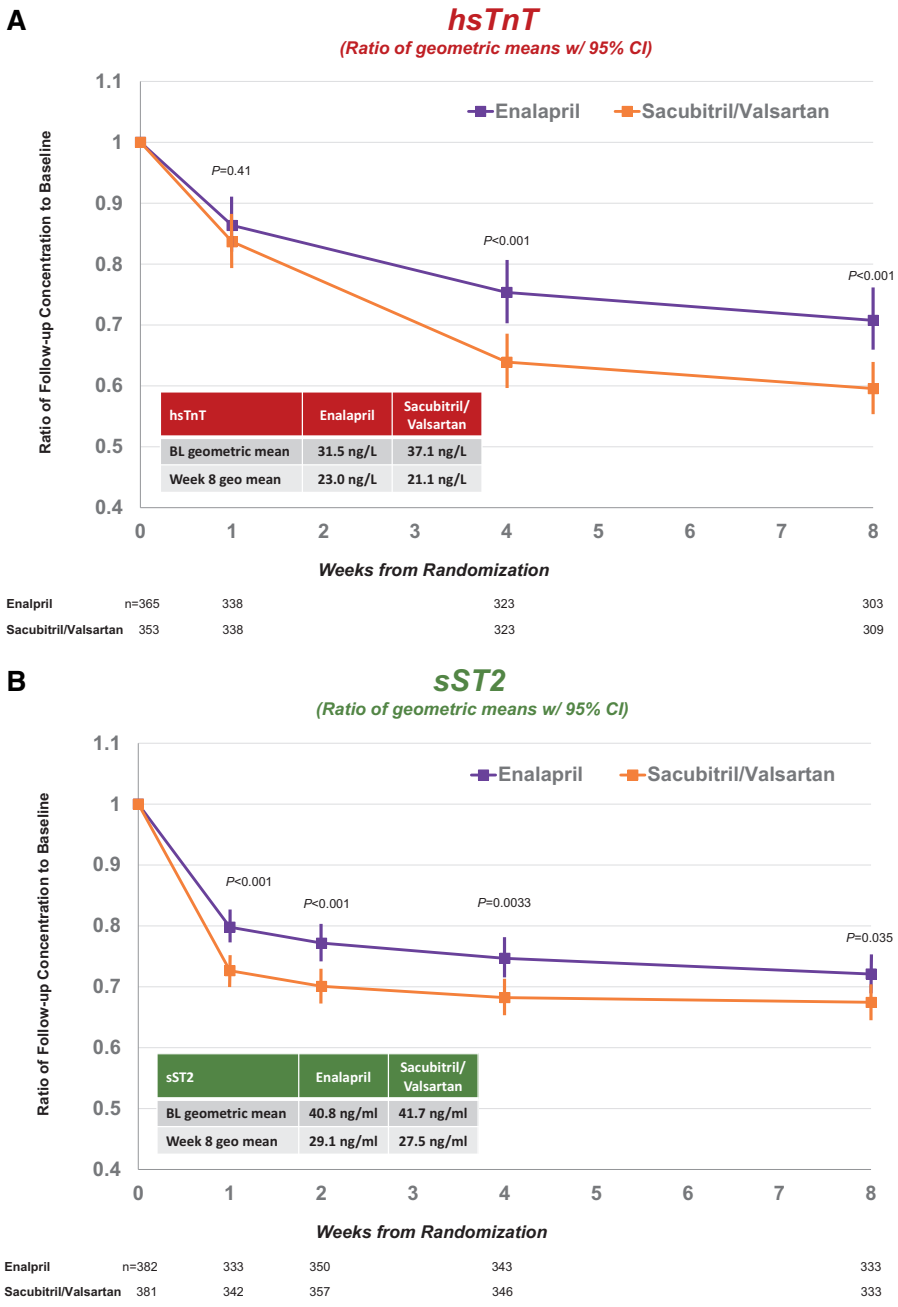


Figure 1 Ratio of the geometric mean concentration of hsTnT (*A*) and sST2 (*B*) at baseline (BL) and each subsequent timepoint compared with the baseline value and stratified by randomized treatment group with associated 95% confidence intervals. The reported *P*-values are for the comparison between changes with sacubitril/valsartan vs. enalapril.

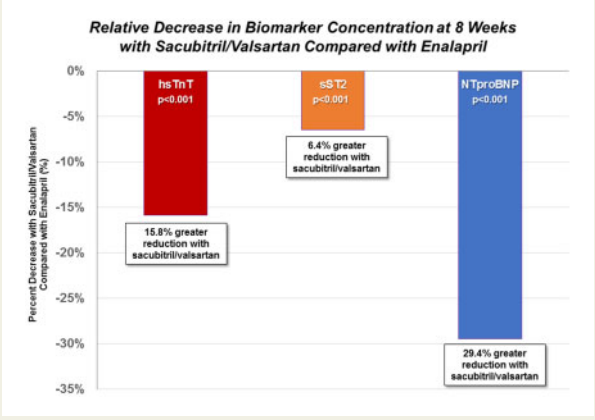
concentration of ucGMP at 8 weeks (*Table 2*). However, a greater reduction in NT-proBNP was achieved with sacubitril/valsartan vs. enalapril irrespective of the achieved dose level (*Table 2*). Moreover, there were only weak correlations (ρ = -0.08 to 0.22) between ucGMP and the other biomarkers apparent across any of the visits (Supplementary material online, *Table S2*). There was no significant difference in the dose tier achieved with sacubitril/valsartan vs. enalapril (Supplementary material online, *Table S3*).

Relationship with cardiovascular outcomes

Among enalapril treated patients, the baseline concentrations of hsTnT, sST2, and NT-proBNP were significantly associated with the rates of adverse clinical outcomes. In the enalapril group, each log-increase in baseline concentration hsTnT was associated with a 46% higher risk of cardiovascular death or rehospitalization for HF (*Table 3*). Similarly, baseline sST2 was associated with an 89% higher

risk of death or hospitalization for HF for each log-increase in the biomarker. These risk relationships for hsTnT and sST2 were not statistically significant among patients allocated to sacubitril/valsartan. However, interaction testing did not demonstrate formal heterogeneity of these risk relationships based on treatment group (*P*-interaction = 0.70 for hsTnT and 0.23 for sST2, *Table 3*). The rates of cardiovascular death or rehospitalization for HF with sacubitril/valsartan vs. enalapril stratified by baseline concentration of hsTnT, sST2, and NT-proBNP are shown in *Figure 3*.

In an exploratory analysis assessing the multivariable-adjusted risk of cardiovascular death or rehospitalization for HF, the concentrations of hsTnT, sST2, and NT-proBNP at week 1 were each significantly associated with subsequent outcome (*Table 4*).



Take home figure Relative effect of sacubitril/valsartan vs. enalapril on hsTnT, sST2 and NT-proBNP calculated from the ratio of the geometric means from baseline to week 8 for each biomarker.

Discussion

Sacubitril/valsartan reduces cardiovascular death or hospitalization for HF both in patients with chronic HFrEF and patients stabilized during hospitalization for ADHF.[1,7] We now demonstrate in this double-blind, randomized study against active control in stabilized patients hospitalized with ADHF that sacubitril/valsartan reduces myocardial injury and haemodynamic stress early after initiation as reflected by circulating biomarkers. Moreover, in exploratory analyses, we found that both the baseline and achieved concentrations of hsTnT, sST2, and NT-proBNP were associated with subsequent clinical outcome.

Early effects of sacubitril/valsartan in stabilized acute decompensated heart failure

In the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF,[15] sacubitril/valsartan is recommended to replace angiotensin-converting enzyme inhibitors in ambulatory HFrEF patients who remain symptomatic despite optimal therapy. However, the recommendation[15] is limited to patients who fit the profile of the population studied in the pivotal clinical trial in chronic HFrEF,[1] which excluded patients with current ADHF.

In this prospectively planned analysis among haemodynamically stabilized patients with reduced ejection fraction and ADHF from the PIONEER-HF trial, we found that the effect of sacubitril/valsartan on its target pathway is manifest by increases in ucGMP detectable by 1 week after in-hospital initiation and that the observed favourable effects on biomarkers of myocardial stress and injury begin to emerge

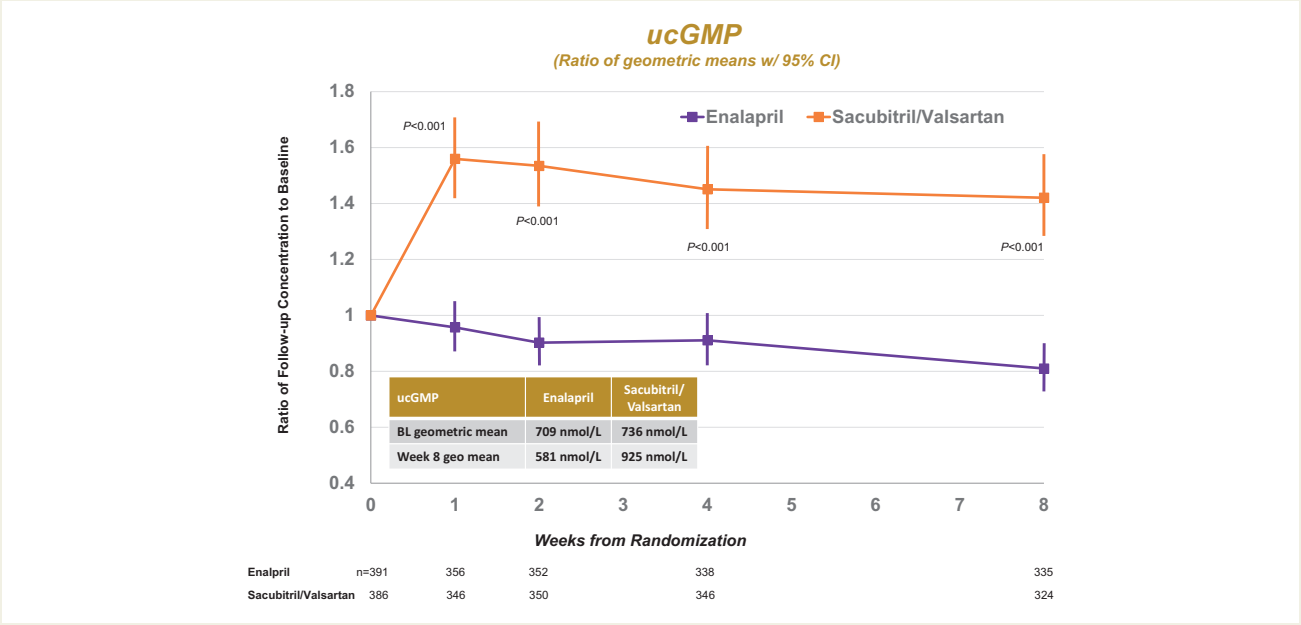


Figure 2 Ratio of the geometric mean concentration of urinary cyclic guanosine 3′5′ monophosphate at each timepoint compared with baseline and stratified by randomized treatment group with associated 95% confidence intervals. The reported *P*-values are for the comparison between changes with sacubitril/valsartan vs. enalapril.

Table 2 Ratio of geometric means at week 8 vs. baseline stratified by dose level at week 4

	Enalapril (*N* = 441)			Sacubitril|valsartan (*N* = 440)			Sacubitril|valsartan vs. enalapril	
Dose level	***n***	**Ratio of geometric means [95% CI]**	***P*-value**	***n***	**Ratio of geometric means [95% CI]**	***P*-value**	**Ratio for S/V vs. enalapril [95% CI]**	***P*-value**
ucGMP								
1	54	1.01 [0.73, 1.4]	0.9493	58	1.28 [0.93, 1.76]	0.127	1.27 [0.80, 2.01]	0.31
2	70	0.75 [0.56, 1.01]	0.0569	78	1.48 [1.13, 1.95]	0.005	1.97 [1.32, 2.94]	0.001
3	187	0.76 [0.63, 0.90]	0.0021	167	1.49 [1.24, 1.80]	<0.0001	1.97 [1.52, 2.56]	<0.0001
NT-proBNP								
1	56	0.70 [0.54, 0.92]	0.0116	64	0.40 [0.31, 0.52]	<0.0001	0.57 [0.39, 0.83]	0.0035
2	75	0.63 [0.49, 0.79]	0.0001	84	0.46 [0.37, 0.58]	<0.0001	0.74 [0.54, 1.03]	0.072
3	193	0.58 [0.50, 0.67]	<0.0001	176	0.40 [0.34, 0.46]	<0.0001	0.69 [0.56, 0.87]	0.0007
hsTnT								
1	47	0.76 [0.62, 0.94]	0.0107	58	0.63 [0.52, 0.76]	<0.0001	0.83 [0.63, 1.09]	0.18
2	66	0.65 [0.55, 0.78]	<0.0001	73	0.55 [0.47, 0.65]	<0.0001	0.85 [0.67, 1.08]	0.17
3	167	0.71 [0.64, 0.80]	<0.0001	162	0.53 [0.48, 0.60]	<0.0001	0.75 [0.64, 0.87]	0.0002
sST2								
1	53	0.69 [0.61, 0.79]	<0.0001	62	0.59 [0.52, 0.66]	<0.0001	0.85 [0.71, 1.01]	0.071
2	71	0.67 [0.60, 0.75]	<0.0001	78	0.63 [0.57, 0.70]	<0.0001	0.95 [0.81, 1.11]	0.51
3	185	0.73 [0.68, 0.78]	<0.0001	171	0.69 [0.64, 0.74]	<0.0001	0.95 [0.86, 1.05]	0.33

This table reports the change in concentration of each biomarker from baseline expressed as a ratio of the geometric mean concentration at week 8 vs. baseline for enalapril (column 3) and sacubitril/valsartan (column 6). Data are stratified by dose tier. Dose tier 1 = sacubitril/valsartan 24/26 mg BID or enalapril 2.5 mg BID; dose tier 2 = sacubitril/valsartan 49/51 mg BID or enalapril 5 mg BID; dose tier 3 = sacubitril/valsartan 97/103 mg BID or enalapril 10 mg BID. Column 8 presents the relative effect of sacubitril/valsartan vs. enalapril as a ratio of columns 3 and 6. For example, for NT-proBNP sacubitril/valsartan in dose tier 1 had a 43% (1–0.57) greater effect than enalapril.
CI, confidence interval.

Table 3 Association between baseline biomarker concentration and the incidence of cardiovascular death or rehospitalization for heart failure

Treatment	Biomarker (log_e-transformed)	Hazard ratio (95% CI)	*P*-value	Interaction *P*-value
Enalapril	hsTnT	1.46 (1.03, 2.08)	0.036	0.70
	sST2	1.89 (1.21, 2.94)	0.005	0.23
	NT-proBNP	1.51 (1.12, 2.03)	0.007	0.34
	ucGMP	1.23 (0.91, 1.66)	0.18	0.21
Sacubitril/valsartan	hsTnT	1.32 (0.89, 1.97)	0.17	
	sST2	1.17 (0.63, 2.21)	0.62	
	NT-proBNP	1.88 (1.35, 2.60)	<0.001	
	ucGMP	0.91 (0.64, 1.29)	0.60	

CI, confidence interval.

as early as 1 to 4 weeks after initiation of therapy in this population. These observations lend additional support for (i) favourable biochemical effects of combined angiotensin receptor blockade and neprilysin inhibition vs. angiotensin converting enzyme inhibition; and (ii) a rapid decline in biomarkers reflecting haemodynamic stress and myocardial injury with sacubitril/valsartan that weigh in favour of in-hospital initiation after presentation and haemodynamic stabilization with ADHF. These data complement the clinical data supporting an early reduction in cardiovascular death or rehospitalization for HF observed in this population.[6,7] The effects on hsTn and sST2 that occur by as early as 1 week (sST2) are intriguing in the context of longer-term effects of sacubitril/valsartan on biomarker indicators of extracellular matrix remodelling.[16] Notably, the binding of NPs to the particulate guanylyl cyclase A receptor has been linked not only to arterial vasodilation and natriuresis but also to anti-apoptotic, anti-hypertrophic, and lusitropic effects.[14] These effects of sacubitril/valsartan on myocardial injury and haemodynamic stress in patients hospitalized with ADHF in PIONEER-HF extend similar evidence at

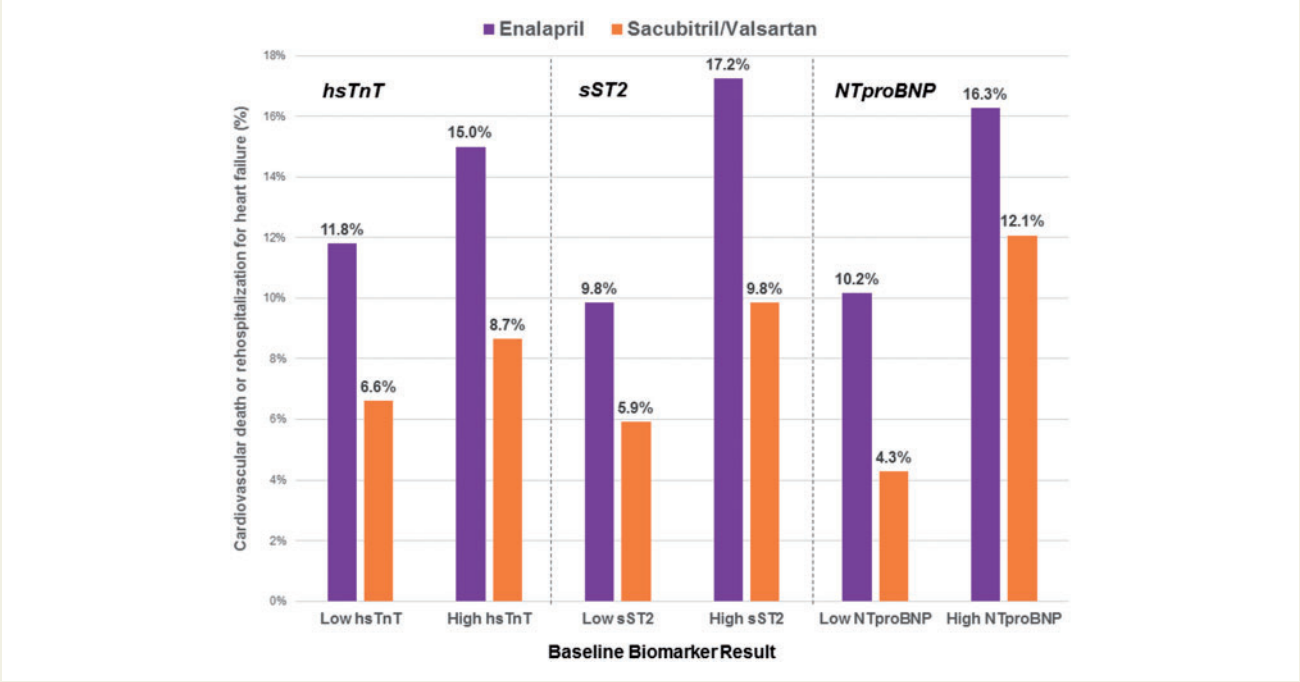


Figure 3 Kaplan–Meier-estimated rates at week 8 of cardiovascular death and rehospitalization for heart failure (84 events) with sacubitril/valsartan or enalapril using an intention-to-treat analysis stratified by baseline hsTnT, sST2, and NT-proBNP concentration ≥ median (high) vs. < median (low).

Table 4 Absolute (log_e-transformed) biomarker concentration at week 1 and the adjusted risk of subsequent cardiovascular death or rehospitalization for heart failure through 8 weeks

	Adjusted HR (95% CI)[a]	*P*-value
hsTnT		
	1.34 (1.001, 1.81)	0.049
sST2		
	2.13 (1.31, 3.45)	0.002
NT-proBNP		
	1.87 (1.46, 2.40)	<0.001

[a]Each biomarker was analysed individually in a model adjusting for age, sex, BMI, history of heart failure prior to enrolment, ejection fraction, and eGFR.
HR, hazard ratio.

1 month or longer after outpatient initiation of therapy in patients with chronic HF.[1–5]

In addition to revealing these differential effects of sacubitril/valsartan on biomarkers of myocardial injury and haemodynamic stress, this study provides additional data regarding the natural history of these biomarkers after presentation with ADHF. These findings build on prior studies that demonstrate a strong relationship between clinical outcomes and biomarkers of myocardial injury and haemodynamic stress measured at presentation and serially in patients with ADHF.[10–12,17,18] As an example, in a randomized trial of serelaxin in patients with ADHF, baseline and very early changes in hsTnT and NT-proBNP were associated with outcomes in this population. In this previous study, baseline hsTnT values were associated with a 41% increase in all-cause mortality at 6 months for any doubling of hsTnT levels and increases from baseline to days 2, 5, and 14 were associated with a higher rate of death.[18] Similarly, we found that patients in PIONEER-HF with higher baseline concentrations of hsTnT, sST2, and NT-proBNP were at higher absolute risk of cardiovascular death or rehospitalization for HF and that the subsequent achieved concentrations during follow-up were also associated with subsequent cardiovascular death or rehospitalization for HF.

Limitations

There are limitations to this study. First, although the demonstration of an effect of sacubitril/valsartan in this blinded, randomized trial is robust, it is not possible to definitively establish that these effects on biomarkers are in the causal pathway for the observed clinical effects. Second, testing for heterogeneity in the effect of sacubitril/valsartan across subgroups defined by achieved dose tier are observational analyses without the protection of randomization and may also be underpowered. These analyses should be interpreted as exploratory. Third, the analyses of the relationships between the achieved biomarker values and outcomes are at risk for unknown confounding and are regarded as exploratory in nature. Nonetheless, our findings are consistent with studies of sacubitril/valsartan in chronic HF[2,4] and their clinical relevance is supported by very robust external evidence for the prognostic relevance of hsTnT, sST2, and NT-proBNP in acute and chronic HF.[19] Moreover, they are concordant with the

observed exploratory evaluation of clinical outcomes in PIONEER-HF.[6,7] These results should be interpreted in light of the entry criterion for the trial, including the exclusion of patients with an eGFR <30 mL/min/1.73 m^2 and patients with significant hepatic disease.

Conclusion

Biomarkers of myocardial injury and haemodynamic stress are elevated in patients with ADHF and associated with cardiovascular death or rehospitalization for HF. Compared with enalapril, treatment with sacubitril/valsartan results in reduced myocardial injury and haemodynamic stress as reflected by such biomarkers with an onset that is apparent within 1–4 weeks and appears present across a range of doses.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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