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Integrating High-Sensitivity Troponin T and Sacubitril/Valsartan Treatment in HFpEF

The PARAGON-HF Trial

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ABSTRACT

OBJECTIVES This study examined the relationship among high-sensitivity troponin-T (hs-TnT), outcomes, and treatment with sacubitril/valsartan in patients with heart failure (HF) and preserved ejection fraction (HFpEF).

BACKGROUND hs-TnT is a marker of myocardial injury in HF.

METHODS The PARAGON-HF trial randomized 4,796 patients with HFpEF to sacubitril/valsartan or valsartan. We compared the risk of the composite outcome of cardiovascular death (CVD) and total HF hospitalization (HHF) according to hs-TnT. We also assessed the effect of allocated treatment on hs-TnT.

RESULTS hs-TnT was available in 1,141 patients (24%) at run-in (median value: 17 ng/L) and 1,260 (26%) at randomization, with 58.3% having hs-TnT >14 ng/L (upper limit of normal). During a median follow-up of 34 months, there were 393 outcome events (82 CVD, 311 HHF). Adjusting for demographics, comorbidities, left ventricular ejection fraction (LVEF), and N-terminal pro B-type natriuretic peptide (NT-proBNP), log-hs-TnT at randomization was an independent predictor of the composite outcome (HR: 1.38; 95% CI: 1.19-1.59; $P < 0.001$). Compared with valsartan, sacubitril/valsartan significantly reduced hs-TnT by 9% at week 16 ($P < 0.001$). Patients whose hs-TnT decreased from randomization to 16 weeks to at or below the median value of 17 ng/L subsequently had a lower risk of CVD/HHF compared with those with persistently elevated hs-TnT ($P = 0.046$). Patients with higher baseline hs-TnT (>17 ng/L) appeared to have a greater benefit from sacubitril/valsartan treatment when accounting for other potential effect modifiers (P interaction = 0.07).

CONCLUSIONS Higher baseline hs-TnT was associated with increased risk of CVD/HHF, whereas hs-TnT decrease at 16 weeks led to lower subsequent risk of CVD/HHF compared with those who had persistently elevated values. Sacubitril/valsartan significantly reduced hs-TnT compared with valsartan. hs-TnT may be helpful in identifying patients with HFpEF who are more likely to benefit from sacubitril/valsartan. (J Am Coll Cardiol HF 2021;9:627-635) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular death

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HHF = heart failure hospitalization

HFrEF = heart failure with reduced ejection fraction

hs-TnT = high-sensitivity troponin-T

LOD = limit of detection

LOQ = limit of quantitation

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for one-half of HF cases, is rising in prevalence, and is associated with increased morbidity and mortality (1–4). In the PARAGON-HF (The Prospective Comparison of ARNI [angiotensin receptor-neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction) trial, sacubitril/valsartan resulted in modest reductions in total HF hospitalizations (HHF) and cardiovascular death (CVD) compared with valsartan alone (rate ratio [RR]: 0.87, 95% CI: 0.75-1.01; $P = 0.06$) (5), with greater benefit in those with left ventricular ejection fraction (LVEF) below the median and in women (6,7).

High-sensitivity troponin (hs-Tn) predicts development of HF (8,9), reflects ongoing myocardial damage in HF, and is often elevated in HFpEF and reduced ejection fraction (HFrEF) (10–14). In addition, according to previous data on HFrEF, higher concentrations of hs-Tn predicted deleterious left-ventricular remodeling, whereas low or decreasing hs-Tn were associated with better reverse cardiac remodeling (15–17). Sacubitril/valsartan has been shown to reduce hs-Tn in HF with HFrEF in the PARADIGM (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial and in patients with HFpEF in the phase 2 PARAMOUNT (Prospective comparison of ARNi with ARB on Management Of heart failUre with preserved ejectioN fraction) trial (Supplemental Table 1) (12,18,19). The prognostic value of hs-TnT in HFpEF, and whether hs-Tn modifies the treatment response to sacubitril/valsartan, remains uncertain. To address these questions, we assessed the relationship among hs-TnT, outcomes, and the efficacy of treatment with sacubitril/valsartan in the PARAGON-HF trial.

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METHODS

STUDY DESIGN AND PATIENT POPULATION. The PARAGON-HF trial was a multicenter, randomized, double-blind trial comparing sacubitril/valsartan with valsartan in patients with chronic HF, LVEF ≥45%, elevated NT-proBNP levels, and evidence of structural heart disease (20). Inclusion criteria included age ≥50 years, New York Heart Association (NYHA) functional class II to IV, either left ventricular hypertrophy or left atrial enlargement by echocardiogram, and diuretic use for at least 30 days. Screening visit N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) level >200 ng/L for patients with HF hospitalization in the previous 9 months and >300 ng/L for patients who had not been hospitalized; these thresholds were increased 3-fold for patients with atrial fibrillation on screening visit electrocardiogram. All patients in the PARAGON-HF trial provided written informed consent. Local ethics committees and institutional review boards at each participating site approved the study protocols.

Patients were entered into sequential valsartan and sacubitril/valsartan run-in periods before randomization. During the 1- to 2-week valsartan run-in, valsartan 40 mg or 80 mg was administered twice daily; patients receiving the lower dose initially were increased to 80 mg twice daily. Patients tolerating valsartan were then exposed to a 2- to 4-week run-in period during which they received sacubitril/valsartan 49/51 mg twice daily. Only patients who tolerated both study drugs were eligible for randomization. At randomization, doses were increased to sacubitril/valsartan 97/103 mg twice daily or valsartan 160 mg twice daily.

CLINICAL ENDPOINTS. The primary efficacy endpoint was a composite of total (first and recurrent) HHF and CVD. A blinded clinical events committee at Brigham and Women's Hospital (Boston, Massachusetts) adjudicated these endpoints.

HS-TROPONIN T MEASUREMENTS. Plasma hs-Tn was analyzed in the biomarker subset of the trial and was measured using the high-sensitivity Roche Elecsys assay (Roche Diagnostics GmbH) at a central laboratory (Clinical Reference Laboratory, Cambridge, United Kingdom). All samples were stored at -80 °C and analyzed in a batch.

In the biomarker subset of the trial, hs-TnT was available in 1,141 patients (24%) at first run-in visit before administration of valsartan; 1,243 pre-sacubitril/valsartan run-in visit (26%); 1,260 patients

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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(26%) at randomization; 1,205 (25%) patients at week 16; and 1,120 patients (24%) at week 48.

The 99th percentile normal reference range for the hs-TnT assay is 14 ng/L. Reporting range uses the limit of detection (LOD) as lowest reported value and LOD is equal to 5 ng/L. The limit of quantitation (LOQ) for the assay is 13 ng/L (21). In the current study, the percentage of patients with hs-TnT values lower than the LOD before run-in was 1.1%.

STATISTICAL ANALYSIS. Patients were categorized according to quintiles of hs-TnT at randomization. Clinical characteristics were compared across these 5 groups. All variables were assessed for normality via visual inspection. Troponin and NT-proBNP were natural log-transformed before analyses. Non-normally distributed continuous variables were summarized using median and interquartile interval. Continuous normally distributed variables were expressed as mean ± SD and compared with a trend test, whereas categorical variables were compared using a chi-square test. Using a stepwise procedure, we evaluated predictors for hs-TnT at randomization, at 16 weeks, and for its change between randomization and 16 weeks.

Incidence rates of the composite of total (first and recurrent) HHF and CV death according to the randomization value of log-hs-TnT and to quintiles of randomization hs-TnT were calculated with the semiparametric proportional rates method of Lin et al (22). Models were adjusted for age, sex, race, body mass index (BMI), systolic blood pressure, heart rate, estimated glomerular filtration rate (eGFR), LVEF, NT-proBNP, NYHA functional class, atrial fibrillation at randomization, history of hypertension, diabetes mellitus, stroke, HF hospitalization, myocardial infarction, therapies (diuretics, mineralocorticoid

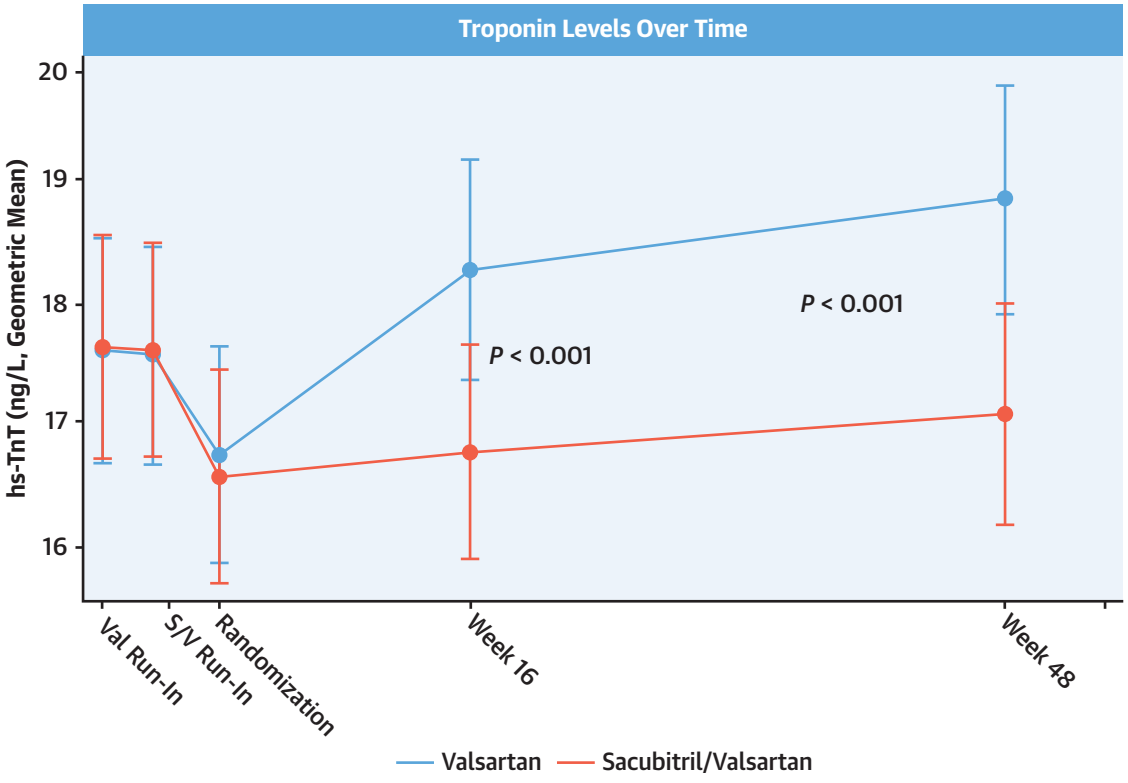
TABLE 1 Baseline Characteristics According to Quintiles of hs-TnT (At Randomization)

	Overall (N = 1,260)	I Quintile of hs-TnT (n = 274)	II Quintile of hs-TnT (n = 252)	III Quintile of hs-TnT (n = 254)	IV Quintile of hs-TnT (n = 234)	V Quintile of hs-TnT (n = 246)	*P* Value for Trend
Age (y)	73.6 ± 7.9	70.7 ± 7.5	73.1 ± 7.4	73.7 ± 7.4	75.0 ± 7.9	75.9 ± 8.5	<0.001
Women, (%)	649 (52)	209 (76)	154 (61)	124 (49)	95 (41)	67 (27)	<0.001
Race, (%)							0.10
White	1,162 (92)	249 (91)	233 (93)	238 (94)	215 (92)	227 (92)	
Asian	43 (3)	11 (4)	9 (4)	7 (3)	10 (4)	6 (2)	
Black	18 (1)	1 (0)	2 (1)	3 (1)	3 (1)	9 (4)	
Other	37 (3)	13 (5)	8 (3)	6 (2)	6 (3)	4 (2)	
Systolic blood pressure	131 ± 15	130 ± 15	130 ± 14	132 ± 15	131 ± 16	130 ± 17	0.46
Heart rate	70 ± 12	70 ± 12	71 ± 13	70 ± 12	69 ± 13	69 ± 12	0.39
BMI	31 ± 5	30 ± 5	31 ± 5	32 ± 5	31 ± 5	31 ± 5	0.035
eGFR	60 ± 18	68 ± 19	64 ± 17	58 ± 16	56 ± 16	53 ± 17	<0.001
eGFR <60 mL/min/1.73 m^2	671 (53)	96 (35)	113 (45)	143 (56)	144 (62)	175 (71)	<0.001
LVEF	57.2 ± 7.5	57.9 ± 7.4	57.3 ± 7.6	56.7 ± 7.0	57.1 ± 8.0	57.1 ± 7.5	0.52
Screening NT-proBNP	942 (505-1,551)	671 (414-1,281)	842 (458-1,434)	950 (506-1,449)	1,073 (620-1,705)	1,230 (684-2,077)	<0.001
NYHA functional class							0.036
I	34 (3)	12 (4)	6 (2)	5 (2)	3 (1)	8 (3)	
II	952 (76)	214 (78)	197 (78)	197 (78)	173 (74)	171 (70)	
III	272 (22)	48 (18)	49 (19)	52 (21)	58 (25)	65 (26)	
IV	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	
Hypertension	1,210 (96)	261 (95)	246 (98)	241 (95)	223 (95)	239 (97)	0.39
Diabetes mellitus	523 (42)	81 (30)	89 (36)	111 (44)	116 (50)	126 (51)	<0.001
Atrial fibrillation	413 (33)	78 (29)	85 (34)	83 (33)	75 (32)	92 (38)	0.28
Stroke	137 (11)	20 (7)	22 (9)	32 (13)	29 (13)	34 (14)	0.07
HF hospitalization	455 (36)	98 (36)	78 (31)	80 (32)	89 (38)	110 (45)	0.009
Myocardial infarction	265 (21)	40 (15)	52 (21)	52 (21)	62 (27)	59 (24)	0.015
Diuretics	1,222 (97)	261 (95)	239 (95)	247 (97)	230 (98)	245 (100)	0.008
Previously on ACE-I or ARB	1,107 (88)	249 (91)	227 (90)	225 (89)	207 (89)	199 (81)	0.005
MRA	303 (24)	60 (22)	57 (23)	59 (23)	64 (27)	63 (26)	0.59
Beta blockers	1,044 (83)	241(88)	211 (84)	213 (84)	195 (83)	184 (75)	0.002

Values are mean ± SD, n (%), or median (interquartile range).

ACE-I: angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; BMI = body mass index; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

CENTRAL ILLUSTRATION **Effect of Randomized Treatment on hs-TnT**



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Geometric mean hs-TnT concentration with 95% CIs are shown for patients with available hs-TnT measurement at different time points. hs-TnT = high-sensitivity troponin; S/V = sacubitril/valsartan; Val = valsartan.

receptor antagonists, beta blockers, angiotensin converting enzyme inhibitors [ACE-Is], or angiotensin receptor blockers [ARBs]), and randomization log-hs-TnT or quintiles of randomization hs-TnT.

We evaluated the association between hs-TnT change from randomization to 16 weeks and the risk of the combined endpoint, splitting the population into 4 groups, irrespective of the treatment arm: hs-TnT higher than the median (>17 ng/L) at both randomization and at 16 weeks (reference), hs-TnT high at randomization and low (≤17 ng/L) at 16 weeks, hs-TnT low at randomization and high at 16 weeks, and hs-TnT low at randomization and at 16 weeks.

The influence of elevated hs-TnT (above the median, >17 ng/L) on the effect of sacubitril/valsartan on the primary endpoint and its components was assessed by Kaplan-Meier curves and through the interaction term between high hs-TnT and sacubitril/valsartan (vs valsartan) treatment allocation stratifying for region, with adjustment for other known effect modifiers (sex and LVEF). We performed statistical analysis using STATA software v14.1 (StataCorp). A 2-sided *P* value <0.05 was considered significant.

RESULTS

Characteristics of patients in the biomarker subset (n = 1,260) of the PARAGON-HF trial with available hs-TnT measurements were older, more frequently white, obese, had lower eGFR, fewer previous HF hospitalizations, and higher use of loop diuretic agents and beta blockers compared with patients without hs-TnT (Supplemental Table 2) but similar in other respects. In patients with available hs-TnT, mean age was 74, 52% were women, and mean LVEF was 57% (**Table 1**). The median hs-TnT value was 17 ng/L (interquartile range [IQR]: 11-26 ng/L) at first run-in visit. The hs-TnT values were respectively 20 ng/L (IQR: 14-31 ng/L) in men and 13 ng/L (IQR: 9-19 ng/L) in women. Higher levels (highest quintile)

of hs-TnT at randomization were associated with older age, male sex (73% male in the highest quintile; 24% male in the lowest quintile), worse NYHA functional class, and higher NT-proBNP. Patients with higher levels of hs-TnT were more likely to have diabetes mellitus, worse renal function, history of myocardial infarction, and previous HHF, and were less likely to use beta blockers and renin-angiotensin-system inhibitors at baseline (**Table 1**). In addition, clinical correlates of higher hs-TnT at randomization were male sex, older age, higher BMI, diabetes mellitus, high BNP, and creatinine, whereas atrial fibrillation, beta blockers, and previous use of renin-angiotensin-system inhibitors were associated with lower values (Supplemental Table 3).

As shown in the **Central Illustration**, hs-TnT levels were stable during the valsartan run-in period, whereas they were reduced during the sacubitril/valsartan run-in. After randomization, hs-TnT values remained stable in the sacubitril/valsartan group, whereas hs-TnT increased in patients randomized to valsartan, resulting in significantly lower relative hs-TnT in the sacubitril/valsartan group by 9% (5%, 12%) at week 16 and 10% (6%, 13%) at week 48 ($P < 0.001$ for both) (**Central Illustration**). Similarly, the percentage of patients with hs-TnT >14 ng/L (ie, > 99° of the normal reference range) after randomization was lower in patients allocated to treatment with sacubitril/valsartan compared with valsartan, both at week 16 and week 48 (respectively, 55.9% vs 64.4%; $P = 0.002$; 59.0% vs 66.4%; $P = 0.010$) (**Table 2**). The effect of sacubitril/valsartan on hs-TnT was not modified by sex (P interaction = 0.76 for the effect of sex on hs-TnT at 48 weeks).

During a median follow-up of 34 months, there were 393 primary outcome events (82 CVD, 311 HHF). In a model adjusted for the baseline covariates shown in **Table 1**, log-hs-TnT at randomization was associated with higher risk of either the primary combined outcome or its components (**Table 3, Figure 1**). Concordantly, patients in the highest quintile of hs-TnT at randomization were at higher risk of the primary combined outcome compared with those in the lowest quintile (RR: 3.64, 95% CI: 1.82-7.26; $P < 0.001$) (**Figure 1**). Of note, the association of hs-TnT with outcomes was not modified by sex (P interaction, respectively, 0.86 for the association with CVD and 0.49 with HHF). In a landmark analysis, patients with hs-TnT decrease from randomization to 16 weeks to a value lower than the median (≤17 ng/L) subsequently had a lower risk of the composite outcome compared with those with a persistently elevated hs-TnT value ($P = 0.046$) (**Figure 2**). There was a weak signal of effect modification with patients with higher hs-TnT at baseline (above the median, >17 ng/L), appearing to have a greater treatment effect than those with lower hs-TnT at baseline after accounting for other potential effect modifiers, such as sex and LVEF (P interaction = 0.07) (Supplemental Figure 1).

DISCUSSION

In PARAGON-HF, higher hs-TnT—a marker of myocardial injury in HF—was associated with a greater risk of CVD and HHF in patients with HFpEF. hs-TnT was reduced by sacubitril/valsartan compared with valsartan, and this reduction was sustained. Patients with hs-TnT decrease from randomization to 16 weeks to a value to at or below the median value of 17 ng/L subsequently had lower risk of the composite outcome compared with those who had persistently elevated hs-TnT values.

PARAGON-HF confirms and extends previous evidence regarding the association between troponin elevation and adverse outcomes (**Figures 1 and 2**) (11,13,23). Patients with both higher hs-TnT at randomization and with increase in hs-TnT at 16 weeks had worse prognoses compared with those who had troponin decreases or in whom troponin remained persistently low. Importantly, our data are strengthen by an individual patient data meta-analysis, mostly considering patients with HFrEF, which identified a similar hs-TnT cutoff as the optimal threshold for prediction of outcome in chronic HF (24). Of note, high-sensitivity troponin is best recognized for its fundamental role in defining myocardial injury in patients with coronary syndromes. Nevertheless, the elevated levels of high-sensitivity troponin encountered in the setting of HFpEF are not usually associated with chest pain or myocardial infarction (11–13), and patients with active ischemic heart disease were excluded from the PARAGON trial (5). Thus, elevated troponin likely identifies a subgroup of patients with HFpEF who have ongoing myocardial injury, higher wall stress, or impaired microcirculation. Moreover, the

TABLE 2 Percentage of Patients With hs-TnT Values Higher Than 99th Percentile (or > 14 ng/L), According to Treatment Allocation

Time Point	Sacubitril/Valsartan and hs-TnT Value >14 ng/L	Valsartan and hs-TnT Value >14 ng/L	*P* Value
Before valsartan run-in	62.3	61.0	0.65
Randomization	57.5	59.0	0.58
Week 16	55.9	64.4	0.002
Week 48	59.0	66.4	0.010

Values are %, unless otherwise indicated.

TABLE 3 Association Between hs-TnT and Outcomes

	Patients Including Rate per 100 py	Unadjusted HR (95% CI) *P* Value	Adjusted HR (95% CI) *P* Value
Primary endpoints: cardiovascular death, HF hospitalization	393 (25.0) 11.4 per 100 py	1.64 (1.41–1.91) <0.001	1.38 (1.19–1.59) <0.001
HF hospitalization	311 (19.8) 9.0 per 100 py	1.62 (1.38–1.90) <0.001	1.34 (1.14–1.57) <0.001
Cardiovascular death	82 (6.5%) 2.4 per 100 py	1.73 (1.46–2.05) <0.001	1.43 (1.11–1.85) 0.006

Values are n (%) rate per 100 patient-year (py), unless otherwise indicated. Adjusted for all variables in Table 1.

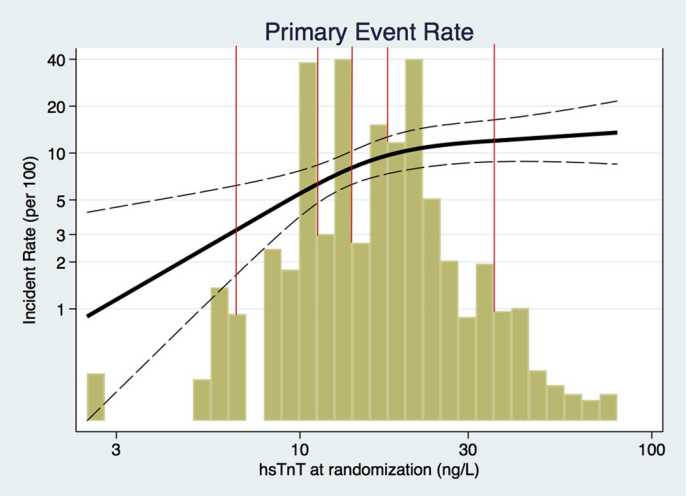
relationship between falling troponin and outcomes was similar after adjusting for recent hospitalization.

We found a higher proportion of women in the lowest compared with the highest quintile of hs-TnT, likely because normal cutoff values for hs-TnT are established to be higher in men than women (25). However, as different cutoffs have been approved worldwide (25), we preferred to use the single cutoff provided by the manufacturer. In our analysis, neither the association of hs-TnT with outcomes, nor the effect of sacubitril/valsartan on hs-TnT, was modified by sex, and sex was not a clinical correlate of hs-TnT change from randomization to 16 weeks.

Importantly, sacubitril/valsartan therapy reduced troponin values compared with valsartan. Although the exact mechanism for troponin release in HFpEF and for troponin reduction with sacubitril/valsartan are unknown and deserve further study, the known relationship between troponin elevation, elevation in natriuretic peptides, and measures of cardiac structure—such as myocardial mass and volumes—suggests that elevated diastolic wall stress may be a mechanism common to elevation of both biomarkers (12). Other possible suggested mechanisms include increased myocardial fibrosis (26), inflammation, and repetitive bouts of ischemia (27,28). Recent mechanistic studies show an association among congestion, intracardiac pressures, increased oxygen supply, and troponin elevation (29). Sacubitril/valsartan may counteract these abnormalities by virtue of neurohormonal modulation, reduced wall stress, and antifibrotic effects (30,31).

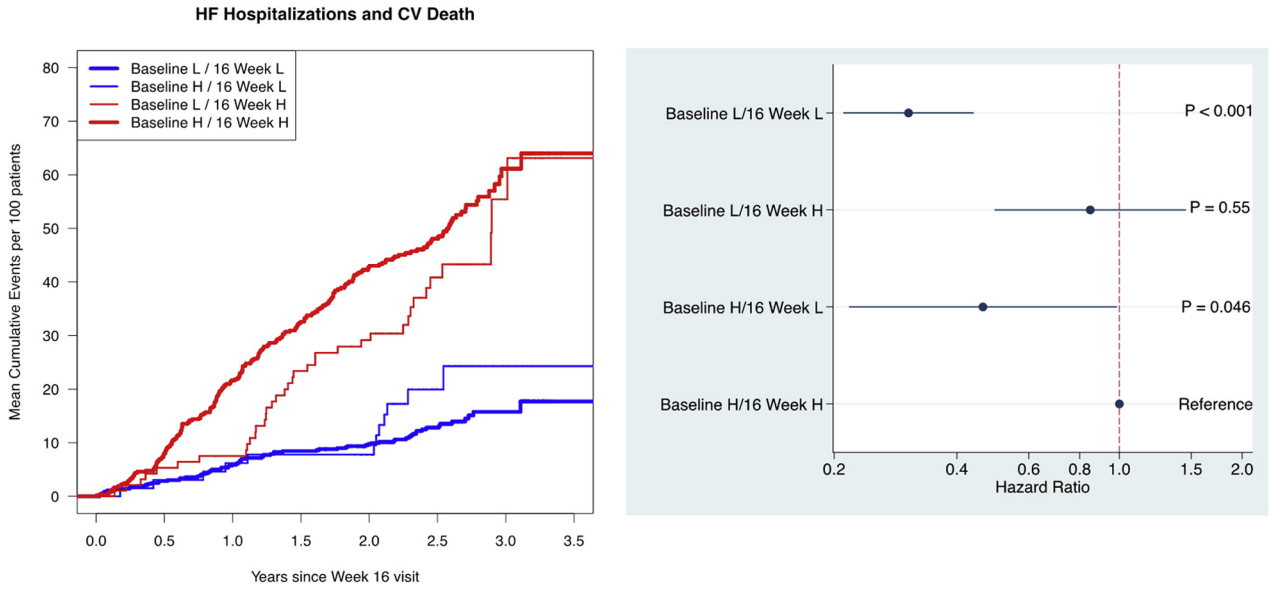
The hs-TnT reduction associated with sacubitril/valsartan was early and sustained over 48 weeks postrandomization (Supplemental Table 4). In fact, this reduction was already manifested during the sacubitril/valsartan run-in phase that averaged 3 weeks of treatment. Following randomization hs-TnT remained stable in those randomized to sacubitril/valsartan and significantly increased in those randomized to valsartan. As troponin reduction with sacubitril/valsartan was early, it is possible that troponin monitoring before and early after initiation of the drug might indicate patients more likely to benefit from therapies. Moreover, we found that higher pretreatment hs-TnT levels may have modestly modified the treatment effect of sacubitril/valsartan, accounting for other effect modifiers. This result should be considered hypothesis generating but suggests that troponin may identify patients with HFpEF who may be more likely to benefit from sacubitril/valsartan (32). Importantly, the strategy of using elevated plasma concentrations of natriuretic peptide (NP) for patient selection in HFpEF trials is questioned by the lack of benefit of irbesartan in patients with HFpEF and higher baseline NP values, the lower benefit of spironolactone observed in the group with higher levels of NP in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, and the absence of sacubitril/valsartan treatment effect modification according to baseline NP in PARAGON-HF (33–35). Conversely, our results might suggest that elevated levels of high-sensitivity troponin, a biomarker more related to injury than congestion, could be used to select high-risk patients more likely to benefit from drug therapy in HFpEF trials. These data reaffirm the heterogeneity of HFpEF (36,37). The absence of a strong correlation between NP and troponin changes in PARAGON (Supplemental Figure 2) does support the concept of using a panel of biomarkers, such as

FIGURE 1 Primary Outcome Event Rate According to hs-TnT at Randomization



The histogram represents hs-TnT at randomization (**red lines** separate quintiles of hs-TnT) visit. The **solid line** represents the estimated primary endpoint incidence rate. The **dashed lines** represent the 95% CIs for the estimated incidence rate. hs-TnT = high-sensitivity troponin T.

FIGURE 2 Association Between hs-TnT Change (Randomization vs 16 Weeks) and Rate of Subsequent Total HF Hospitalizations and CV Death



This figure displays the rate of total HF hospitalizations and CV death subsequent to 16 weeks, respectively, in 4 groups of patients: patients with elevated hs-TnT (>17 ng/L) at both randomization and 16 weeks (reference); patients with elevated hs-TnT only at randomization (with a low value at 16 weeks, ≤17 ng/L); patients with low hs-TnT at randomization (≤17 ng/L) and elevated hs-TnT (>17 ng/L) at 16 weeks; and patients with low hs-TnT (≤17 ng/L) both at randomization and at 16 weeks. (L means hs-TnT ≤17 ng/L; H means hs-TnT >17 ng/L.) CV = cardiovascular. HF = heart failure.

troponin and NP, to help to identify the appropriate patient for treatment (Supplemental Figure 3).

STUDY LIMITATIONS. We note several factors that might limit the generalizability of this analysis. PARAGON-HF excluded patients with severe renal impairment, and virtually all patients had some degree of elevation in NP levels. Also, only one-quarter of PARAGON-HF patients contributed samples to the biorepository (Supplemental Table 2). However, characteristics of patients with available hs-TnT measurements were similar to those without hs-TnT with respect to sex, LVEF, NT-proBNP, and history of myocardial infarction. The arbitrary choice of the prognostic cutoff and the model for multivariable analysis represent study limitations. Nonetheless, an individual patient data meta-analysis, mostly considering patients with HFrEF, identified a similar hs-TnT cutoff as the optimal threshold for prediction of outcome in chronic HF (21).

CONCLUSIONS

Higher hs-TnT, a marker of myocardial damage in HF, was associated with increased risk the composite outcome of CVD and HHF in patients with HFpEF, and this marker of myocardial injury was reduced by sacubitril/valsartan compared with valsartan. hs-TnT may be helpful in identifying patients with HFpEF more likely to benefit from sacubitril/valsartan.

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The PARAGON-HF trial was sponsored by Novartis. Dr Gori has received consulting fees from Novartis, Menarini, and Boehringer Ingelheim. Dr Senni has received consulting fees from Novartis, Bayer, Abbott, Merck, Vifor, AstraZeneca, and Boehringer Ingelheim. Dr Claggett has received consulting fees from AO Biome, Biogen, Boehringer Ingelheim, Corvia, Gilead, Myokardia, and Novartis. Dr Jhund's employer, the University of Glasgow, has been remunerated by Novartis for his work on the PARADIGM-HF and PARAGON-HF trials. His employer, the University of Glasgow, has been remunerated by AstraZeneca for his work on the DAPA-HF and DELIVER trials. Dr Jhund has received speaker fees and advisory board fees from Novartis; has received speaker fees from AstraZeneca; and a grant from Boehringer Ingelheim. Dr Packer has received consulting fees from Abbvie, Akcea, Actavis, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi-Sankyo, Johnson & Johnson, Lilly, Novartis, NovoNordisk, ParatusRx, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. Dr Rouleau has received consulting fees from Novartis, AstraZeneca, MyokardiaAbbott, and Sanofi. Dr Zannad has received steering committee personal fees from Applied Therapeutics, Bayer, Boehringer, Boston Scientific, Novartis, Janssen, and CVRx; advisory-board personal fees from AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Merck, and Owkin; stock options from G3Pharmaceutical; and is the founder of CardioRenal and CVCT. Dr Pfeffer has received grants

from Novartis and personal fees for consulting from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Alliance, DalCor, GlaxoSmithKline, Novartis, Novo Nordisk, Inc, Peerbridge, and Sanofi; and owns stock options of DalCor. Dr McMurray has received grants to his institution from Novartis, Bayer, Cardiorentis, Amgen, Oxford University, Theracos, Abbvie, DalCor, Pfizer, Merck, AstraZeneca, GlaxoSmithKline, Bristol Myers Squibb, and Kings College Hospital. Dr Zile has received fees for serving on steering committees from Abbott and Ironwood Pharma; consulting fees from Boston Scientific and MyoKardia; grant support and fees for serving on a steering committee from CVRx and Medtronic; fees for serving on an eligibility committee from EBR Systems and V-Wave; fees for serving on a clinical events committee from Endotronics; and fees for serving on a data and safety monitoring board from Merck. Dr van Veldhuisen has received fees for serving on a steering committee and has received travel support from ARCA Biopharma and Corvia Medical. Dr Pieske has received fees for serving on a steering committee, fees for serving on an advisory board, and lecture fees from Bayer HealthCare Pharmaceuticals and MSD; lecture fees from AstraZeneca; fees for serving on an advisory board and lecture fees from Bristol Myers Squibb; fees for serving on an advisory board for Daiichi-Sankyo; and lecture fees and honoraria from Medscape. Dr Lam has received grant support and fees for serving on an advisory board from Boston Scientific and Roche Diagnostics; grant support, fees for serving on an advisory board, and fees for serving on steering committees from Bayer; grant support from Medtronics; grant support and fees for serving on a steering committee from Vifor Pharma; fees for serving on an advisory board and fees for serving on steering committees from AstraZeneca and Novartis; fees for serving on an advisory board from Amgen, Boehringer Ingelheim, and Abbott Diagnostics; consulting fees from Merck and Stealth BioTherapeutics; fees for serving on a steering committee from Janssen Research and Development; lecture fees and consulting fees from Menarini; and fees for serving on a scientific committee from Corvia Medical; and is holding a pending patent (PCT/SG2016/050217) on a methodregarding diagnosis and prognosis of chronic heart failure. Dr Maggioni has received consulting fees from Novartis and fees for serving on study committees from Bayer and Fresenius. Drs Lefkowitz, Prescott, and Shi are employees of Novartis Pharmaceuticals Corporation. Dr Solomon has received grants paid to his institution from Alnylam, Amgen, AstraZeneca, Bayer, Bellerophon, Bristol Myers Squibb, Celladon, Cytokinetics, Gilead, Eidos, GlaxoSmithKline, Ionis, Lone Star Heart, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Novartis, Sanofi Pasteur, and Theracos; and consulting fees from Alnylam, Amgen, AoBiome, AstraZeneca, Bayer, Bristol Myers Squibb, Cardiac Dimensions, Corvia, Cytokinetics, Daichi-Sankyo, Gilead, GlaxoSmithKline, Ironwood, Janssen, Merck, MyoKardia, Novartis, Quantum Genomics, Roche, Takeda, Tenaya, and Theracos. Dr Liu has reported that he has no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this analysis of patients with HFpEF enrolled in PARAGON-HF, elevated high-sensitivity troponin at baseline was associated with increased risk of the composite outcome of CVD and HHF: in particular, when persistently elevated at 16-week follow-up. Sacubitril/valsartan determined a significant reduction of high-sensitivity troponin compared with valsartan. Patients with higher baseline troponin appeared to have a greater benefit (lower risk of CVD/HHF) from sacubitril/valsartan treatment.

TRANSLATIONAL OUTLOOK: These data suggest that troponin elevation might identify a subgroup of patients with HFpEF who may be more likely to respond to therapy; this hypothesis would need to be tested prospectively.

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KEY WORDS HFpEF, high-sensitivity troponin, sacubitril/valsartan

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