ORIGINAL RESEARCH

High-Sensitivity Troponin I in Hospitalized and Ambulatory Patients With Heart Failure With Preserved Ejection Fraction: Insights From the Heart Failure Clinical Research Network

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***Background*—**We sought to study the prevalence of high-sensitivity troponin and its association with cardiac structure and outcomes in ambulatory and hospitalized patients with heart failure with a preserved ejection fraction (HFpEF).

***Methods and Results*—**A post hoc analysis utilized data from HFpEF patients: DOSE (Diuretic Optimization Strategies Evaluation) and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) enrolled patients hospitalized with acute HFpEF, and RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction) enrolled ambulatory patients with HFpEF. High-sensitivity troponin I (hs-TnI) was measured in hospitalized patients at baseline, at 72 to 96 hours, on day 7, and on day 60. In ambulatory patients hs-TnI was measured at baseline and at week 24. In the ambulatory cohort, correlations between hs-TnI and cardiac structure and function were assessed. The association between hs-TnI and a 60-day composite of emergency room visits, readmissions, and death was assessed for hospitalized patients using multivariable Cox proportional hazard models. The study population included 139 hospitalized and 212 ambulatory patients with HFpEF and hs-TnI measured at baseline. The median (25th, 75th percentiles) baseline troponin was 17.6 (11.1, 41.0) ng/L in hospitalized patients and 9.5 (5.3, 19.7) ng/L in ambulatory patients ($P<0.001$). The prevalence of elevated hs-TnI (>99% percentile upper reference limit was 86% in hospitalized patients and 53% among ambulatory patients, with stable elevation in ambulatory patients during follow-up. HFpEF patients with a hs-TnI above the median were older with worse left ventricular hypertrophy and diastolic dysfunction. Continuously valued hs-TnI (per doubling) was associated with increased risk of composite end point (adjusted hazard ratio 1.20, 95% confidence interval 1.00-1.43; $P=0.042$).

***Conclusions*—**Hs-TnI is commonly elevated among both hospitalized and ambulatory patients with HFpEF. Increased hs-TnI levels are associated with worse cardiac structure and increased risk of adverse events. **(*J Am Heart Assoc*. 2018;7:e010364. DOI: 10.1161/JAHA.118.010364)**

Key Words: clinical outcomes • heart failure with preserved ejection fraction • high-sensitivity troponin

Cardiac stress, as evidenced by elevated or rising levels of troponin, may play a central role in the pathophysiologic progression of heart failure (HF), irrespective of underlying etiology (ie, ischemic versus nonischemic) or systolic function (ie, reduced versus preserved).[1] Elevated troponin levels during hospitalization have been associated with increased in-hospital and postdischarge mortality.[2-4] The introduction of high-sensitivity assays now allows the accurate detection of very low levels of circulating cardiac troponins. A recent analysis of a mixed HF population in the RELAX-AHF (Efficacy

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Accompanying Table S1 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010364

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Clinical Perspective

What Is New?

- The majority of patients' cardiac high-sensitivity troponin I (hs-TnI) levels were elevated above the 99th percentile of the upper reference limit (86% in hospitalized patients and 53% among ambulatory patients).
- In initially hospitalized patients, levels of hs-TnI remained elevated over the course of the first days up to a week, with a statistically significant drop after a few months, whereas in ambulatory patients with heart failure with preserved ejection fraction, the concentrations of hs-TnI remained unchanged over the study follow-up.

What Are the Clinical Implications?

- Because higher concentrations of hs-TnI were associated with worse cardiac remodeling, diastolic dysfunction, and an increased risk for adverse 60-day clinical outcomes, future work is needed to define the diagnostic and prognostic value of prospective single-time-point and serial measurement of hs-TnI in routine practice.

and Safety of Relaxin for the Treatment of Acute Heart Failure) trial reported that high-sensitivity troponin was abnormal (ie, defined as greater than the 99th percentile of the upper reference limit) in more than 90% of patients admitted for acute HF in the absence of clinical suspicion for acute coronary syndrome.[5] Similarly, a high proportion of ambulatory patients with heart failure and reduced ejection fraction have been shown to display elevated high-sensitivity troponin levels.[6]

Much less is known regarding the prevalence or clinical significance of troponin elevation in HF with preserved ejection fraction (HFpEF). Although the prevalence of HFpEF is increasing, HFpEF remains an incompletely understood clinical entity with a high adverse event rate and limited disease-modifying therapies.[7-12]

The Heart Failure Clinical Research Network (HFN) database provides a unique opportunity to study the diagnostic and prognostic implications of high-sensitivity troponin I (hs-TnI) given that (1) the study population includes ambulatory and hospitalized HFpEF patients, (2) deep phenotyping was performed on all patients including other biomarkers, cardiac imaging (ie, echocardiography and magnetic resonance imaging [MRI]), and functional testing (ie, cardiopulmonary exercise testing and 6-minute walk test), and (3) serum samples were processed at a core laboratory. Thus, the objectives of this novel analysis of the HFN database were to describe (1) the prevalence of elevated hs-TnI, (2) the association of hs-TnI with clinical characteristics, other biomarkers, and cardiac imaging, and (3) the relationship between hs-TnI and adverse events among ambulatory and hospitalized HFpEF patients.

Methods

Overview

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

This post hoc analysis was performed using pooled data from the National Heart, Lung, and Blood Institute (NHLBI)-sponsored HFN DOSE (Diuretic Optimization Strategies Evaluation), CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), and RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trials (Figure 1). Each protocol was approved by the Institutional Review Boards at each site, and written informed consent was obtained from all patients before randomization. All trials were conducted in North America. DOSE and CARRESS-HF were prospective double-blinded trials testing the efficacy and renal consequences of different decongestive strategies in hospitalized patients with acute HF.[13-16] The diagnosis of acute HF was based on the presence of ≥1 sign (rales, peripheral edema, ascites, or radiographic evidence of pulmonary congestion) and 1 symptom (dyspnea, orthopnea, or edema), regardless of ejection fraction (EF). RELAX enrolled ambulatory patients who had EFs ≥50% and objective evidence of HF.[17,18] Subjects were required to have elevated N-terminal pro-B-type natriuretic peptide (≥400 ng/L) or elevated invasively measured filling pressures and reduced exercise capacity (≤60% age-, sex-, and body size–specific predicted Vo_2). In all trials patients with advanced chronic kidney disease were excluded. A left ventricular (LV) EF of >50% as measured by echocardiogram was used as cutoff for HFpEF across all studies. Patients provided informed consent as part of the respective HFN study.

High Sensitivity Troponin Measurement

Patients were grouped on the basis of troponin levels (below and above median for initially hospitalized and ambulatory patients, separately). In initially hospitalized patients hs-TnI was measured at baseline, after 3 to 4 days, on day 7, and on day 60. In ambulatory patients hs-TnI was measured at baseline and at week 24. All hs-TnI testing was processed at a central core laboratory using Access hs-TnI (Beckman Coulter Inc, Brea, CA), a fully automated chemiluminescent 2-site ("sandwich") immunoassay. Beckman AccuTnI measurements were performed using an Access 2 (Beckman-Coulter) instrument. The detection limit of the instrument is 10 ng/L; the upper limit is 100 000 ng/L. The 99th percentile of the upper

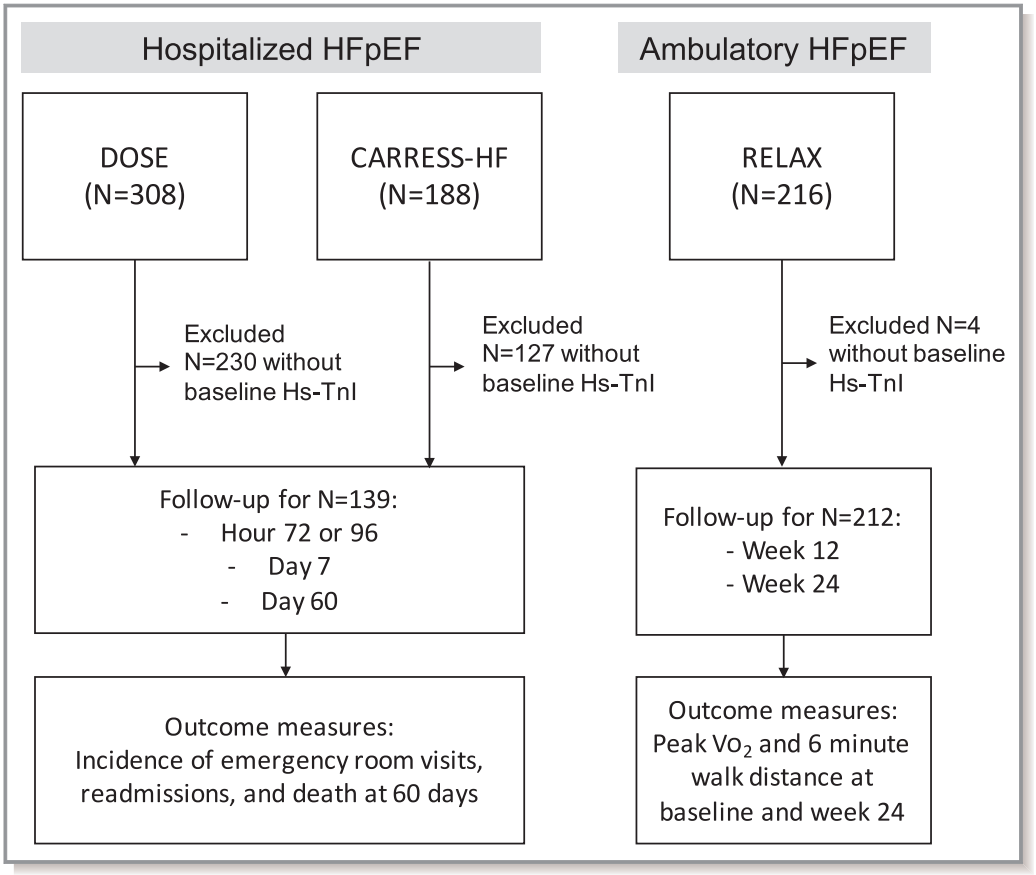

Figure 1. CONSORT diagram. CARRESS-HF indicates Cardiorenal Rescue Study in Acute Decompensated Heart Failure; DOSE, Diuretic Optimization Strategies Evaluation; HFrEF, heart failure with reduced ejection fraction; Hs-TnI, high-sensitivity troponin I; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction; VO_2, oxygen ventilation.

reference limit was 8.6 ng/L, and the lowest concentration with a coefficient of variation ≤10% was 2.1 ng/L. The analytical performance including linearity, imprecision, analytical and functional specificity, and sample handling have been previously reported.[19,20]

Imaging Assessment

Patients in the RELAX trial had baseline cardiac imaging assessments per study protocol. Limited 2-dimensional, M-mode, and Doppler echocardiograms were performed on each subject. Measurements and derived values were obtained in triplicate and evaluated at a core echocardiographic laboratory. Measurements and derived values included: LV dimensions, LV mass, LVEF, diastolic parameters such as the ratio of peak velocity blood flow from gravity in early diastole to peak velocity flow in late diastole, e′, left atrial volume, and pulmonary artery systolic pressures.

Patients in normal sinus rhythm underwent baseline cardiac MRI. MRI-based measurement of the LV volumes, LV dimensions, LV mass, LVEF, and aortic distensibility were performed. Cardiac cycle–dependent changes in the aortic lumen were assessed as previously described[21] with interleaved, velocity-encoded, phase-contrast, gradient-echo images acquired perpendicular to the course of the proximal ascending thoracic aorta ≈4 cm above the aortic valve. Images were analyzed at a core MRI laboratory.

Study End Points

Study end points used for the primary and the present post hoc analysis are the following. For ambulatory patients with HFpEF (RELAX), study end points included exercise capacity (peak Vo_2 and 6-minute walk distance) at 24 weeks after randomization. For patients initially hospitalized with HFpEF (DOSE and CARRESS-HF), the end point was the composite of emergency room visits, readmissions, and mortality at day 60.

Statistical Analysis

To evaluate associations between baseline hs-TnI and the composite end point at 60 days in the initially hospitalized

HFpEF cohort, univariable and multivariable Cox proportional hazards models were used. Similar analyses were performed evaluating the association with peak and peak change hs-TnI and clinical end points in initially hospitalized HFpEF. Peak change in hs-TnI was the largest change from log_2-transformed baseline hs-TnI value and the log_2-transformed peak hs-TnI value. Prespecified adjustment variables included covariates previously found to be prognostic of each end point: age, sex, New York Heart Association functional class, heart rate, systolic blood pressure, serum creatinine, N-terminal pro-B-type natriuretic peptide levels, and selected trial (DOSE versus CARRESS-HF). Among ambulatory HFpEF patients, to evaluate associations between baseline hs-TnI (per doubling value) and functional end points, general linear models including baseline hs-TnI with or without adjustment were used. The covariate set for adjustment was the same as for the initially hospitalized HF cohort. Two-sided $P<0.05$ was considered statistically significant. Statistical analyses were completed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC). The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Results

Prevalence of hs-TnI in the Study Population

Overall, this analysis included 351 patients (139 patients initially hospitalized with HFpEF [25% of patients enrolled in DOSE and 32% in CARRESS-HF]; 212 patients with ambulatory HFpEF [98% of patients enrolled in RELAX]) with measured hs-TnI at baseline (see CONSORT diagram in Figure 1). The median (25th, 75th percentile) troponin was 17.6 (11.1, 41.0) ng/L in initially hospitalized patients and 9.5 (5.3, 19.7) ng/L) in ambulatory patients ($P<0.001$). The prevalence of hs-TnI above the 99% percentile of the upper reference limit was 86% in hospitalized patients and 53% among ambulatory patients (Figure 2). There was no change in hs-TnI in initially hospitalized patients during the course of decongestion (median [25th, 75th percentile] 18 [11, 41] ng/L) to 72/96 hours (19 [11, 38] ng/L; $P=0.709$) and after 7 days (21 [13, 50] ng/L; $P=0.484$) (Figure S1), but hs-TnI decreased from baseline to 60 days in initially hospitalized HFpEF (18 [11, 41] ng/L versus 15 [10, 24] ng/L; $P=0.022$), whereas in ambulatory HFpEF, hs-TnI remained stable from baseline to 24 weeks (10 [5, 20] ng/L versus 9 [5, 21] ng/L; $P=0.346$) (Figure 3).

Correlates of Elevated hs-TnI

Initially hospitalized HFpEF patients with hs-TnI above the median had a lower body mass index (32.8 kg/m^2 versus 37.5 kg/m^2; $P=0.021$) and markedly higher N-terminal pro-B-type natriuretic peptide levels (4235 ng/L versus 2577 ng/L; $P<0.001$) (Table 1). Age, LVEF, renal function, and atrial fibrillation status were numerically worse among patients with above-the-median hs-TnI, without meeting statistical significance. However, we found a modest correlation between these baseline variables and hs-TnI (age $r=0.23$, LVEF=−0.14, GFR=−0.34).

Most ambulatory HFpEF patients (64.2%) did not have a prior hospitalization for HF within the last year (Table 2). Among ambulatory HFpEF patients, hs-TnI above the median was associated with older age, worse renal function, and

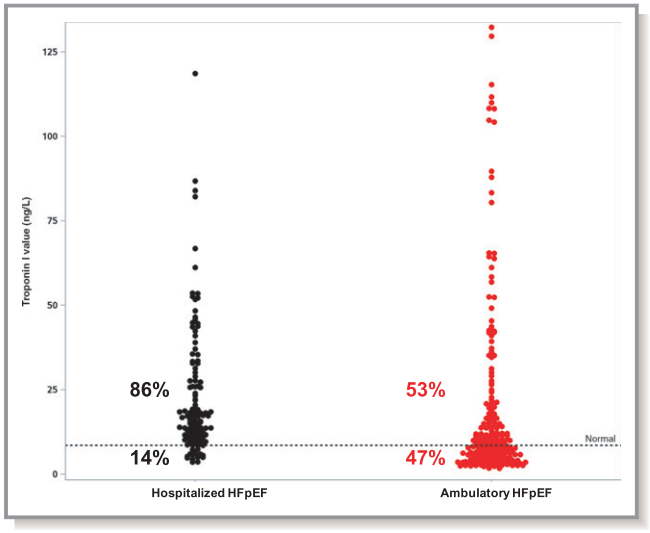

Figure 2. The prevalence of elevated hs-TnI levels at baseline in ambulatory and hospitalized HFpEF patients (for 95% data; some extreme values were not included here). HFpEF indicates heart failure with preserved ejection fraction.

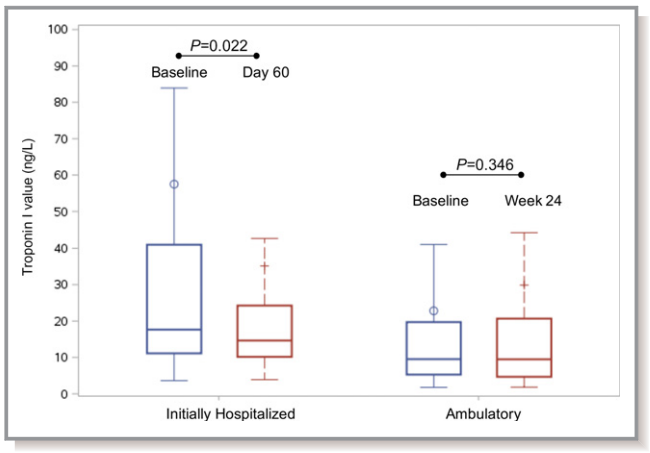

Figure 3. Boxplots of hs-TnI levels at baseline and day 60/week 24 in ambulatory and initially hospitalized HFpEF patients (hs-TnI values were truncated to the 95th percentiles). Hospitalized patients had significantly higher hs-TnI levels at baseline and follow-up ($P<0.001$) than ambulatory HFpEF patients. HFpEF indicates heart failure with preserved ejection fraction.

Table 1. Clinical Characteristics for Hospitalized HFpEF Patients by Baseline hs-TnI Level

Characteristic	Troponin I < Median 17.6 ng/L (N=69)	Troponin I ≥ Median 17.6 ng/L (N=70)	*P* Value
Demographics			
Age, y, median (25th-75th)	71 (62-78)	76 (65-81)	0.150
Men	41/69 (59.4%)	48/70 (68.6%)	0.261
White	57/69 (82.6%)	55/70 (78.6%)	0.547
Body mass index, median (25th-75th)	37.5 (28.9-45.8)	32.8 (27.3-37.5)	0.021
Ejection fraction, median (25th-75th)	60.0 (55.0-64.0)	55.0 (55.0-63.0)	0.095
Comorbidities			
Hospitalization for heart failure in past year	48/69 (69.6%)	45/67 (67.2%)	0.763
Ischemia as cause of HF	20/40 (50.0%)	51/99 (51.5%)	0.871
Hypertension	61/69 (88.4%)	60/70 (85.7%)	0.637
Atrial fibrillation/flutter	38/69 (55.1%)	46/70 (65.7%)	0.200
Diabetes mellitus	41/69 (59.4%)	39/70 (55.7%)	0.658
Chronic obstructive lung disease	23/69 (33.3%)	21/70 (30.0%)	0.673
NYHA Class			0.243
III	35/60 (58.3%)	41/63 (65.1%)	
IV	25/60 (41.7%)	20/63 (31.7%)	
Medications at enrolment			
ACE inhibitor or ARB	29/69 (42.0%)	26/70 (37.1%)	0.556
β-Blockers	52/69 (75.4%)	52/70 (74.3%)	0.884
Aldosterone antagonist	9/69 (13.0%)	16/70 (22.9%)	0.132
Any diuretic	64/69 (92.8%)	67/70 (95.7%)	0.493
Laboratory values			
Sodium, mg/L, median (25th-75th)	139 (137-141)	139 (136-142)	0.936
Blood urea nitrogen, mg/dL, median (25th-75th)	37.0 (26.0-55.0)	46.0 (35.0-70.0)	0.012
GFR, mL/(min·1.73 m^2), median (25th-75th)	41.3 (28.6-53.4)	33.9 (28.0-43.4)	0.082
Baseline core laboratory creatinine, mg/dL, median (25th-75th)	1.6 (1.1-2.2)	1.8 (1.4-2.2)	0.188
Baseline core laboratory NT-proBNP, ng/L, median (25th-75th)	2577 (1042-4210)	4235 (2380-11 228)	<0.001
Baseline core laboratory cystatin C value, mg/L, median (25th-75th)	1.9 (1.4-2.3)	2.0 (1.7-2.5)	0.067
Baseline core laboratory troponin I value, ng/L, median (25th-75th)	11.1 (8.5-13.9)	40.0 (25.7-83.9)	<0.001
Albumin, g/dL, median (25th-75th)	3.5 (3.2-3.8)	3.3 (3.1-3.6)	0.087
Physical examination			
Systolic blood pressure, mm Hg, median (25th-75th)	120 (110-136)	120 (106-129)	0.405
Heart rate, beats/min, median (25th-75th)	74 (66-81)	72 (63-78)	0.256
Jugular venous pressure ≥8 cm	62/65 (95.4%)	65/68 (95.6%)	1.000
Edema ≥2	62/69 (89.9%)	60/70 (85.7%)	0.456
Orthopnea	60/64 (93.8%)	62/67 (92.5%)	1.000

All values reported as N (%) unless otherwise noted; 25th-75th refers to percentiles. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; HF, heart failure; HFpEF, HF with preserved ejection fraction; hs-TnI, high-sensitivity troponin I; NT-proBNP, brain-type natriuretic peptide; NYHA, New York Heart Association.

increased prevalence of atrial fibrillation. An hs-TnI above the median was associated with worse cardiac structure (higher LV mass index and higher LA volume index), worse echocardiographic longitudinal strain, and higher estimated filling pressures by echocardiography and cardiac MRI, with higher E/A, E/e′, pulmonary arterial systolic pressure, and LV mass index/hypertrophy, and a lower septal e′ velocity (Table 3). N-terminal pro-B-type natriuretic peptide (moderate correlation

Table 2. Clinical Characteristics for Ambulatory HFpEF Patients by Baseline hs-TnI Level

Characteristic	Troponin I < Median 9.5 ng/L (N=106)	Troponin I ≥ Median 9.5 ng/L (N=106)	*P* Value
Demographics			
Baseline core laboratory troponin I value, ng/L, median (25th-75th)	5.3 (3.5-7.2)	19.7 (12.0-43.7)	<0.001
Age, y, median (25th-75th)	67 (61-75)	71 (63-78)	0.036
Male sex	42/106 (39.6%)	68/106 (64.2%)	<0.001
White	99/106 (93.4%)	95/106 (89.6%)	0.324
Body mass index, median (25th-75th)	32.8 (28.3-38.8)	33.0 (28.2-39.0)	0.703
Ejection fraction, median (25th-75th)	60.0 (55.0-65.0)	60.0 (55.0-66.0)	0.594
Comorbidities			
Hospitalization for heart failure in past year	36/106 (34.0%)	40/106 (37.7%)	0.567
Ischemia as cause of heart failure	47/135 (34.8%)	33/77 (42.9%)	0.245
Hypertension	88/106 (83.0%)	91/106 (85.8%)	0.570
Atrial fibrillation/flutter	44/106 (41.5%)	64/106 (60.4%)	0.006
Diabetes mellitus	40/106 (37.7%)	50/106 (47.2%)	0.165
Chronic obstructive lung disease	18/106 (17.0%)	24/106 (22.6%)	0.301
NYHA Class			0.169
II	55/106 (51.9%)	45/106 (42.5%)	
III	51/106 (48.1%)	61/106 (57.5%)	
Medications at enrollment			
ACE inhibitor or ARB	76/106 (71.7%)	73/106 (68.9%)	0.652
β-Blockers	79/106 (74.5%)	81/106 (76.4%)	0.750
Aldosterone antagonist	11/106 (10.4%)	11/106 (10.4%)	1.000
Any diuretic	82/106 (77.4%)	100/106 (94.3%)	<0.001
Laboratory values			
Sodium, mg/L, median (25th-75th)	140 (138-141)	140 (138-142)	0.632
Blood urea nitrogen, mg/dL, median (25th-75th)	23.0 (16.0-28.0)	28.0 (19.3-40.0)	<0.001
GFR, mL/(min·1.73 m^2) median (25th-75th)	61.5 (46.5-82.0)	54.7 (40.9-68.4)	0.008
Baseline core laboratory creatinine, mg/dL, median (25th-75th)	1.0 (0.8-1.2)	1.2 (1.0-1.5)	<0.001
Baseline core laboratory NT-proBNP, ng/L, median (25th-75th)	464.2 (108.2-955.2)	1075 (550.3-2123)	<0.001
Baseline core laboratory cystatin C value, mg/L, median (25th-75th)	1.2 (1.0-1.6)	1.5 (1.2-1.8)	<0.001
Baseline core laboratory troponin I value, ng/L, median (25th-75th)	5.3 (3.5-7.2)	19.7 (12.0-43.7)	<0.001
Baseline core laboratory aldosterone, ng/L, median (25th-75th)	181 (113-285)	207 (122-279)	0.256
Baseline core laboratory endothelin-1, ng/L, median (25th-75th)	2.2 (1.8-2.7)	2.6 (2.1-3.4)	<0.001
Baseline core laboratory procollagen III NTP, μg/L, median (25th-75th)	7.1 (5.3-9.0)	8.1 (6.5-10.7)	0.005
Baseline core laboratory uric acid, mg/dL, median (25th-75th)	6.8 (5.5-8.1)	7.8 (6.0-9.1)	0.015
Albumin, g/dL, median (25th-75th)	4.1 (3.8-4.4)	4.0 (3.6-4.3)	0.024
Physical examination			
Systolic blood pressure, mm Hg, median (25th-75th)	127 (112-140)	126 (116-137)	0.952
Heart rate, beats/min, median (25th-75th)	70 (61-80)	68 (61-77)	0.518

Continued

Table 2. Continued

Characteristic	Troponin I < Median 9.5 ng/L (N=106)	Troponin I ≥ Median 9.5 ng/L (N=106)	*P* Value
Jugular venous pressure ≥8 cm	36/104 (34.6%)	57/101 (56.4%)	0.002
Edema ≥2	19/106 (17.9%)	25/106 (23.6%)	0.310
Orthopnea	59/98 (60.2%)	67/100 (67.0%)	0.320

All values reported as N (%) unless otherwise noted; 25th-75th refers to percentiles. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; GFR, glomerular filtration rate; HFpEF, HF with preserved ejection fraction; hs-TnI, high-sensitivity troponin I; NT-proBNP, brain-type natriuretic peptide; NTP, N terminal aminopeptide; NYHA, New York Heart Association.

with hs-TnI of r=0.49) and biomarkers of inflammation (endothelin-1, uric acid) were higher in those with hs-TnI above the median, but there was no difference in neurohormonal activation of aldosterone or procollagen III N terminal aminopeptide (NTP) (marker of fibrosis).

Outcomes in Ambulatory HFpEF

Exercise capacity was similar across patients with increasing levels of hs-TnI, as assessed by peak Vo_2 and 6-minute walk distance at baseline and week 24 (Table S1).

Outcomes in Initially Hospitalized HFpEF

Patients with increased levels of hs-TnI had increased incidence of emergency room visits, readmissions, and death at day 60 (Table 4). Using hs-TnI as a continuous variable, baseline hs-TnI (per doubling), peak hs-TnI (per doubling), and change of hs-TnI (per 10 ng/L) were consistently associated with increased risk of the composite outcomes. The relationship remained statistically significant after adjusting (Table 4).

Discussion

Our study systematically describes the natural history and prognostic value of cardiac troponins using a highly sensitive assay validated at a core laboratory in ambulatory and hospitalized HFpEF patients with baseline imaging (ie, echocardiography and cardiac MRI) and longitudinal evaluations of functional capacity (ie, the 6-minute walk test and cardiopulmonary exercise testing). In well-characterized HFN study cohorts of ambulatory and hospitalized patients with HFpEF, we found that the majority of patients had cardiac hs-TnI elevated above the 99th percentile of the upper reference limit (86% in hospitalized patients and 53% among ambulatory patients). In initially hospitalized patients, levels of hs-TnI remained elevated over the course of the first days up to a week, with a statistically significant drop at day 60. Meanwhile, in ambulatory HFpEF patients the concentrations of hs-TnI remained unchanged over the study follow-up. Concentrations of hs-TnI above the median were associated with worse cardiac remodeling and diastolic dysfunction in ambulatory HFpEF. In initially hospitalized HFpEF patients, elevated hs-TnI levels predicted increased risk for adverse 60-day clinical outcomes.

Cardiac troponin I and T have gained increasing attention due to their prognostic utility for risk stratification in patients hospitalized with HF. Several studies have recognized a consistent association between elevated troponin levels (using regular or high-sensitivity assays) and the risk of adverse clinical outcomes among patients with heart failure and reduced EF, even in the absence of intercurrent acute coronary events.[3,5,22,23] Furthermore, the most recent HF guidelines recommend early assessment of troponin levels among patients with acute HF for risk stratification.[10] However, there are limited data in HFpEF,[24-27] with no data on high-sensitivity troponin in hospitalized HFpEF, with the largest study in hospitalized patients using less-sensitive troponin assays.[27] In addition, no prior study has stratified troponin elevation in HFpEF by ambulatory or hospitalized status.

Mechanistic Drivers of Troponin Release in HFpEF

The underlying mechanistic drivers of HFpEF remain incompletely understood. Currently, systemic inflammation and comorbidity-driven microvascular dysfunction are believed to drive the cardiac remodeling that underpins the HFpEF syndrome.[28-31] Furthermore, elevated filling pressures and abnormal transmural stress are also central to the pathophysiology of this syndrome.[32] Importantly, levels of hs-TnI were found to be elevated in the absence of suspicion for acute coronary syndrome and were found not to be associated with a prior history of coronary artery disease, suggesting that epicardial coronary artery disease is not the driver of hs-TnI release in HFpEF. The introduction of high-sensitivity assays with strong correlation between high-sensitivity troponin I and T essays[24] has allowed the accurate detection

Table 3. Biomarker, Cardiopulmonary Exercise Testing, Echocardiogram, and MRI Data for Ambulatory Heart Failure With Preserved Ejection Fraction Patients by Baseline hs-TnI Level

Characteristic	Troponin I < Median 9.5 ng/L (N=106)	Troponin I ≥ Median 9.5 ng/L (N=106)	*P* Value
Core laboratory cardiopulmonary exercise data			
Baseline peak Vo_2, mL/(min·kg), median (25th-75th)	11.7 (10.3-15.3)	11.6 (10.2-13.8)	0.261
Baseline age and sex predicted peak Vo_2, mL/(min·kg), median (25th-75th)	29.0 (27.0-33.0)	29.0 (27.0-33.0)	0.125
Baseline peak respiratory exchange ratio (RER=Vco_2/Vo_2 ratio), median (25th-75th)	1.09 (1.03-1.16)	1.10 (1.02-1.15)	0.612
Baseline peak SBP, mm Hg, median (25th-75th)	158 (138-180)	154 (129-168)	0.153
Baseline clinically significant chronotropic incompetence (Brawner formula)	45/104 (43.3%)	50/105 (47.6%)	0.528
Baseline 6-min walk distance, m, median (25th-75th)	335 (253-396)	299 (202-367)	0.022
Baseline percentage of predicted 6-min walk distance, median (25th-75th)	72.7 (54.9-86.8)	65.4 (47.7-79.6)	0.025
Core laboratory echocardiography data			
Baseline LVEF (composite of all EF variables measured, %), median (25th-75th)	60.0 (56.0-66.0)	60.0 (55.0-65.0)	0.075
Baseline global longitudinal strain, median (25th-75th)	−15.8 (−17.9 to −13.2)	−13.7 (−16.0 to −11.2)	<0.001
Baseline cardiac index, mL, median (25th-75th)	2484 (2092-3014)	2482 (2073-2843)	0.432
Baseline 2D PLAX: LV diastolic dimension, cm, median (25th-75th)	4.6 (4.3-5.2)	4.6 (4.2-5.1)	0.677
Baseline LV mass index, n, g/m^2, median (25th-75th)	68.0 (59.7-80.3)	77, 85.6 (67.3-113.0)	<0.001
Baseline ECHO left ventricular hypertrophy (Chirinos formula)	33/78 (42.3%)	41/77 (53.2%)	0.173
Baseline RWT ≥0.42	31/78 (39.7%)	44/77 (57.1%)	0.030
Baseline E/A ratio, median (25th-75th)	1.3 (0.9-2.0)	1.6 (1.0-3.0)	0.098
Baseline MV inflow (deceleration time at leaf tip), ms, median (25th-75th)	194.0 (156.0-223.5)	179.5 (153.0-212.0)	0.190
Baseline LV relaxation septal (medial), e, median (25th-75th)	0.06 (0.05-0.08)	0.06 (0.04-0.07)	0.018
Baseline filling pressure septal (medial), E/e, median (25th-75th)	14.0 (11.3-20.0)	18.0 (13.3-25.0)	0.004
Baseline LA volume index, mL/m^2, median (25th-75th)	40.7 (31.6-51.0)	54.2 (39.7-62.2)	<0.001
Baseline pulmonary artery systolic pressure, mm Hg, median (25th-75th)	39.2 (32.0-48.6)	45.5 (35.0-52.5)	0.045
Core laboratory cardiac MRI data			
Baseline LVEF (%), median (25th-75th)	65.9 (61.0-70.5)	63.6 (50.8-70.5)	0.124
Baseline cardiac index, L/min/m^2, median (25th-75th)	2.3 (1.9-2.7)	2.4 (2.1-2.9)	0.354
Baseline EDV, mL, median (25th-75th)	110 (93-134)	130 (102-160)	0.011
Baseline LV mass index, mg/m^2, median (25th-75th)	59.3 (51.7-68.4)	76.5 (61.7-95.6)	<0.001
Baseline MRI left ventricular hypertrophy (Chirinos formula)	11/72 (15.3%)	19/44 (43.2%)	<0.001
Baseline aortic distensibility, $(mm\ Hg)^{-1}$, median (25th-75th)	1.2 (0.7-2.4)	1.1 (0.7-1.6)	0.386

25th-75th refers to percentiles. 2D indicates 2-dimensional; ECHO, echocardiogram; EDV, end-diastolic volume; EF, ejection fraction; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MV, mitral valve; PLAX, parasternal long-axis; RER, respiratory exchange ration; RWT, relative wall thickness; SBP, systolic blood pressure; Vo_2, oxygen ventilation.

of very low levels of circulating cardiac troponins in acute, but also stable ambulatory HF patients. Notably high-sensitivity troponin assays are no longer restricted to clinical trials but are now available and approved for use in clinical practice.[33]

Unlike in acute HF, where troponin elevation may be related to an acute precipitant such as volume overload with increased ventricular wall stress, the finding of elevated hs-TnI in stable ambulatory HFpEF is suggestive of ongoing subclinical myocardial stress.[34,35] Potential contributing mechanisms include subendocardial ischemia, neurohormonal activation, and altered myocyte calcium handling.[1] Elevated hs-TnI may also reflect cardiac cell loss secondary to chronic inflammation, supported by a higher prevalence of inflammatory markers such as endothelin-1 and uric acid as well as greater renal dysfunction in ambulatory HFpEF with high levels of hs-TnI. The association between renal dysfunction and elevated troponin levels can be the result of impaired biomarker clearance and a greater burden of myocardial disease, such as higher left ventricular mass and worse diastolic dysfunction in patients with chronic kidney disease.[36] Given that high-

Table 4. Risk of Emergency Room Visits, Readmissions, and Mortality at Day 60 Among Patients Hospitalized for Heart Failure With Preserved Ejection Fraction

Variable	Event Numbers	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)*	*P* Value
Baseline hs-TnI†	61/123	1.24 (1.06-1.44)	0.006	1.20 (1.00-1.43)	0.042
Peak hs-TnI†	56/112	1.11 (1.00-1.23)	0.040	1.18 (1.05-1.33)	0.007
Peak change hs-TnI per 10 ng/L	30/54	1.02 (1.01-1.03)	<0.001	1.02 (1.00-1.03)	0.008

Adjusted for age, sex, New York Heart Association functional class, heart rate, systolic blood pressure, serum creatinine, natriuretic peptide levels, trial (DOSE vs CARRESS-HF). CARRESS-HF indicates Cardiorenal Rescue Study in Acute Decompensated Heart Failure; CI, confidence interval; DOSE, Diuretic Optimization Strategies Evaluation; HR, hazard ratio; hs-TnI, high-sensitivity tropoinin I.

*Models adjusted for age, sex, New York Heart Association functional class, heart rate, systolic blood pressure, serum creatinine, and natriuretic peptide levels.

†Expressed per doubling of hs-TnI.

sensitivity troponin elevations have been detected in asymptomatic subjects with adverse cardiac remodeling,[37] and changes in troponin predict incident HF,[38] the myocardial process leading up to troponin release may be important to the progression and transition to clinical HFpEF and merits further study.

Although elevation in resting troponins has been previously reported and closely linked to worse systolic and diastolic function at rest, we found a lack of an association between resting hs-TnI and exercise function parameters in ambulatory HFpEF patients. Interestingly, in a smaller prospective study in patients with HFpEF, troponin levels were inversely associated with cardiac oxygen supply, and troponin elevation during exercise was associated with limitations in LV systolic and diastolic reserve.[39] Although our study is the largest to investigate the relationship between hs-TnI and exercise function in HFpEF, our study is likely underpowered to detect a significant association.

Temporal Profile of Cardiac Troponin in HFpEF

We uniquely define the temporal profile of cardiac troponin in hospitalized and ambulatory patients with HFpEF. We found hs-TnI to be elevated in a majority of hospitalized and ambulatory patients, with persistent elevation in initially hospitalized patients (median 18 ng/L at baseline and 21 ng/L on day 7) and only a small but statistically significant drop-off at 60 days (median of 15 ng/L). Longer-term postdischarge follow-up may have shown continued declines in biomarker release to levels similar to that observed in ambulatory HFpEF patients (9 ng/L). The prevalence of elevated high-sensitivity troponin confirms and extends findings from the RELAX-AHF trial (hospitalized HF with reduced EF and HFpEF, 90% with elevated baseline high-sensitivity troponin T),[5] and an analysis of the PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of Heart Failure With Preserved Ejection Fraction) Trial (ambulatory HFpEF patients, 55% with elevated high-sensitivity troponin T).[25] A previous study by Pandey et al, which assessed 34 233 patients hospitalized for HFpEF in the Get With The Guidelines-Heart Failure registry, found that a standard assay detected troponin elevation at baseline in 23% of patients.[27] In contrast, we used a high-sensitivity assay to detect troponin I elevation not only in hospitalized patients but also in ambulatory HFpEF patients.

Clinical Implications

Our data support hs-TnI as a marker of disease severity and prognosis regardless of ambulatory or hospitalized status in patients with HFpEF, providing potentially incremental prognostic information to standard clinical assessment and other laboratory variables. Because hs-TnI/troponin appears to provide unique mechanistic insight into the physiology of patients with chronic or acute HFpEF state,[34,35,39] it remains to be determined whether hs-TnI can provide incremental prognostic value beyond established biomarkers (B-type natriuretic peptide) and novel biomarkers (such as ST2, growth differentiation factor-15, and galectin 3), which have been shown to correlate with cardiopulmonary exercise function and a change in the exercise function over time.[40] Further, preliminary studies indicate that cardiac troponin may help assess response to HF therapy.[25,41,42] Taken together, the data suggest a potential role of measuring high-sensitivity troponin for risk stratification, independent of concerns for acute coronary syndrome, although its value for routine serial monitoring and high-risk patient management remains to be explored. The findings of persistent elevation suggest that therapies administered over the longer term (ie, not short-term therapies confined to a hospitalization) may be most promising.

Limitations

This is a post hoc analysis of a pooled cohort from 3 randomized controlled, double-blinded trials, which were not powered to detect clinical end points according to baseline, peak, or change in hs-TnI levels. Yet, all short-term and

postdischarge clinical end points were reviewed within the limits of a clinical trial, supporting the validity of these findings. These results may not be generalizable to all ambulatory and hospitalized HFpEF phenotypes, especially because trials were skewed toward white participants.

Conclusions

In this study of a well-characterized cohort of ambulatory and hospitalized HFpEF patients, hs-TnI was elevated in a large majority of hospitalized patients and more than half of outpatients with HFpEF, raising the hypothesis of ongoing myocardial injury. In initially hospitalized HFpEF patients the level of hs-TnI was unchanged in the short term and in ambulatory patients over a long term. HFpEF patients with elevated hs-TnI levels have an advanced clinical phenotype characterized by elevated filling pressures, abnormalities in systolic and diastolic function, as well as high rates of cardiovascular morbidity and mortality in the initially hospitalized HFpEF. Future work needs to further define the diagnostic and prognostic value of prospective single-time-point and serial measurement of high-sensitivity troponin in routine practice and the role of high-sensitivity troponin as a surrogate efficacy end point in clinical trials.

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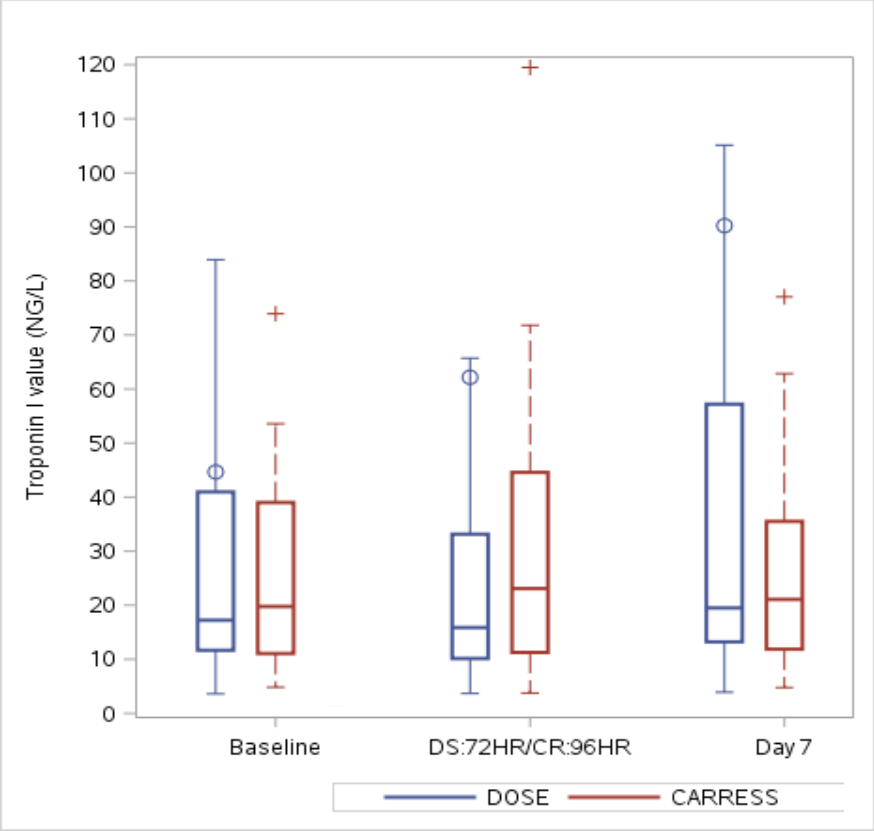
Supplemental Material

Table S1. Estimate: per doubling in Troponin I (treatment was included in the adjusted model).

Outcomes	Models	Estimate	Standard Error	P Value	Number of Observations Used
Baseline Peak VO2 in ml/min	**Unadjusted**	-22.45	20.00	0.263	210
	Adjusted	9.17	16.47	0.578	
Baseline walk distance (meters)	**Unadjusted**	-8.67	4.94	0.081	211
	Adjusted	-5.02	5.65	0.376	
Week 24 Peak VO2 in ml/min	**Unadjusted**	-19.96	22.52	0.376	181
	Adjusted	2.90	19.68	0.883	
Week 24 walk distance (meters)	**Unadjusted**	-4.87	5.48	0.374	182
	Adjusted	-2.69	6.29	0.670	
Week 24 walk distance (meters)	**Unadjusted: up to 4 NG/L**	-98.31	43.69	0.026	182
	Unadjusted: above 4 NG/L	1.83	6.25	0.770	
	Adjusted: up to 4 NG/L	-73.87	48.69	0.131	
	Adjusted: above 4 NG/L	0.82	6.70	0.903	

Figure S1. Box-plot for high sensitivity troponin I over the short-term for hospitalized patients only.



Troponin I values were truncated to 95 percentile. DS = Dose trial; CR = CARRESS-HF trial. Follow up high sensitivity troponin I was not significantly different from baseline value at all times ($p>0.05$)