

# Use of High-Sensitivity Troponin T to Identify Patients With Acute Heart Failure at Lower Risk for Adverse Outcomes



## An Exploratory Analysis From the RELAX-AHF Trial

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**CME Objective for This Article:** After reading this article, the reader should be able to discuss: 1) the prevalence of troponin elevation in clinical trials of acute heart failure patients; 2) the potential role of a negative troponin to identify lower risk patients; and 3) the implications of these data related to clinical practice and future research.

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### ABSTRACT

**OBJECTIVES** The aim of this study was to determine if a baseline high-sensitivity troponin T (hsTnT) value  $\leq$ 99th percentile upper reference limit (0.014  $\mu$ g/l ["low hsTnT"]) identifies patients at low risk for adverse outcomes.

**BACKGROUND** Approximately 85% of patients who present to emergency departments with acute heart failure are admitted. Identification of patients at low risk might decrease unnecessary admissions.

**METHODS** A post-hoc analysis was conducted from the RELAX-AHF (Serelaxin, Recombinant Human Relaxin-2, for Treatment of Acute Heart Failure) trial, which randomized patients within 16 h of presentation who had systolic blood pressure  $>$ 125 mm Hg, mild to moderate renal impairment, and N-terminal pro-brain natriuretic peptide  $\geq$ 1,600 ng/l to serelaxin versus placebo. Linear regression models for continuous endpoints and Cox models for time-to-event endpoints were used.

**RESULTS** Of the 1,076 patients with available baseline hsTnT values, 107 (9.9%) had low hsTnT. No cardiovascular (CV) deaths through day 180 were observed in the low-hsTnT group compared with 79 CV deaths (7.3%) in patients with higher hsTnT. By univariate analyses, low hsTnT was associated with lower risk for all 5 primary outcomes: 1) days alive and out of the hospital by day 60; 2) CV death or rehospitalization for heart failure or renal failure by day 60; 3) length of stay; 4) worsening heart failure through day 5; and 5) CV death through day 180. After multivariate adjustment, only 180-day CV mortality remained significant (hazard ratio: 0.0; 95% confidence interval: 0.0 to 0.736;  $p = 0.0234$ ; C-index = 0.838 [95% confidence interval: 0.798 to 0.878]).

**CONCLUSIONS** No CV deaths through day 180 were observed in patients with hsTnT levels  $\leq$ 0.014  $\mu$ g/l despite high N-terminal pro-brain natriuretic peptide levels. Low baseline hsTnT may identify patients with acute heart failure at very low risk for CV mortality. (J Am Coll Cardiol HF 2016;4:591-9) © 2016 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**T**he primary goal of hospital-based risk stratification in acute heart failure (AHF) is the identification of patients at highest risk for adverse events (1-4). Targeting high-risk patients aligns limited resources with the greatest needs. In the emergency department (ED) setting, however, AHF risk stratification has an opposing aim: the identification of low risk. Because nearly all ED patients

provided the kits for measurements of hs-TnT. Drs. Pang, Teerlink, Voors, Ponikowski, Greenberg, Filippatos, Felker, and Metra are members of the RELAX AHF Executive Committee. Dr. Pang is or has been over the past year a consultant for or received honoraria from Intersection Medical, Janssen, Medtronic, Relpysa, Trevena, scPharmaceuticals, CardioXyl, Roche, and Palatin Technologies. Dr. Teerlink receives research/consulting fees from Amgen, Madeleine, Mast Therapeutics, Novartis, Relpysa, and Trevena. Drs. Voors and Filippatos are consultants for Novartis. Dr. Ponikowski is a consultant for Novartis, Cardioentis, and Bayer; and receives research grants from Singulex. Dr. Greenberg is a consultant for Novartis and Janssen. Dr. Felker receives grant funding from the NIH, Roche Diagnostics, Amgen, Otsuka, and Novartis; and consulting fees from Novartis, Amgen, Trevena, Merck, Celladon, Singulex, Stealth Biotherapeutics, BMS, and Medtronic. Drs. Cotter and Davison are employees of Momentum Research Inc., which received remuneration for conducting clinical studies from Novartis, Amgen, Cardio3, Trevena, Chan RX, Laguna Pharmaceuticals, and Singulex. Drs. Prescott, Hua, and Severin are employees of Novartis. Dr. Metra has received honoraria as a consultant for Novartis and Bayer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Roche kindly provided the kits for measurements of hs-TnT. Anthony DeMaria, MD, served as Guest Editor for this paper.

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with AHF are admitted, the costliest resource in health care is already overconsumed: hospitalization (5). Identifying patients safe for discharge is the unmet need of ED AHF risk stratification (6). With nearly 800,000 annual AHF admissions originating from EDs, safe discharge, or observation status, for even a small fraction of patients would yield tremendous health care cost savings (7).

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Unfortunately, no prospectively validated, facile, accepted AHF risk instruments for use in the ED setting exist (8-12). Risk scores derived from administrative data show promise, but their lack of external prospective validation or difficulty of use has limited their uptake (13-16). Even the creation of risk instruments in the ED setting is difficult. Because most patients are admitted, separating the influence of hospitalization on the prognostic trajectory of patients is difficult (12). This limits the applicability of hospital-based AHF risk scores to the ED setting. Emergency physicians' low tolerance of risk compounds the problem: survey work suggests that significant adverse events cannot exceed 1% (17). Thus, identification of low-risk patients with AHF in the ED setting is a major unmet clinical need.

Myocardial injury, as measured by troponin release, is a marker of higher risk (18-21). A previous RELAX-AHF (Serelaxin, Recombinant Human Relaxin-2, for Treatment of Acute Heart Failure) analysis demonstrated that baseline, peak, and peak change in high-sensitivity troponin T (hsTnT) was associated with worse outcomes (22). Similar to acute coronary syndrome (ACS), higher levels of troponin are associated with worse outcomes in AHF (18-20,23). Unlike ACS, the potential value of negative troponin values in AHF is less well known. The value of troponin may be greater in discriminating low from high risk.

The increasing sensitivity of troponin assays had led to increased detection of myocardial injury in AHF: 6.2% in ADHERE (Acute Decompensated Heart Failure National Registry; published in 2008), approximately 50% in the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial (published in 2011), and more than 90% in the RELAX-AHF trial (published in 2013). Although trials enroll higher risk patients at baseline compared with registries, the trend is informative. Perhaps myocardial injury is a key pathophysiologic marker in the majority of patients with AHF; prior to higher sensitivity assays, it was more difficult to detect (21). Thus, we tested whether the absence of myocardial injury identifies a subgroup of

patients with signs and symptoms of AHF at very low risk for adverse events.

## METHODS

**OBJECTIVE.** The objective of this study was to determine the association between a low baseline hsTnT level ( $\leq$ 99th percentile upper reference limit) and outcomes.

**STUDY DESIGN.** The design, rationale, and results of the RELAX-AHF trial have been previously reported (19,24,25). Briefly, this was an international, multicenter, randomized, placebo-controlled trial of serelaxin versus placebo, infused over 48 h, both in addition to usual care. To be included, patients had to have signs and symptoms of heart failure (HF), radiographic evidence of pulmonary congestion, systolic blood pressure  $>125$  mm Hg, brain natriuretic peptide or N-terminal pro-brain natriuretic peptide (NT-proBNP)  $>350$  ng/ml or  $>1,400$  ng/ml, respectively, mild to moderate renal dysfunction, treatment with intravenous loop diuretic agents, and randomization within 16 h of presentation. All clinical trial sites were Institutional Review Board or ethics committee approved to participate in RELAX-AHF. The trial was registered at [ClinicalTrials.gov](http://ClinicalTrials.gov) (NCT00520806).

**OUTCOMES AND STATISTICAL ANALYSIS.** Pre-specified endpoints from the RELAX-AHF trial were used. These included days alive and out of the hospital through day 60, cardiovascular (CV) death or HF or renal failure (RF) hospitalization through day 60, length of initial hospital stay, worsening HF through day 5, and CV mortality through day 180. Mode of death and rehospitalization were adjudicated by an independent, blinded committee. Because this was an exploratory study, additional analyses were performed for the following outcomes: 180-day all-cause mortality; worsening HF by day 14; dyspnea visual analogue scale area under the curve through day 5; marked or moderate improvement in dyspnea by Likert-type scale at 6, 12, and 24 h; and CV death or HF or RF hospitalization through 30 days. Of these, 180-day all-cause mortality was a pre-specified safety endpoint in the main trial. Both dyspnea endpoints were the original coprimary efficacy outcomes, and worsening HF was a pre-specified exploratory efficacy endpoint. Only CV death or HF or RF hospitalization by 30 days was a new endpoint constructed for this analysis. Correction for multiple comparison testing was not performed.

Patients were divided into 2 groups on the basis of baseline hsTnT  $\leq 0.014$   $\mu$ g/l. Patient characteristics are presented as frequencies and percentages for

## ABBREVIATIONS AND ACRONYMS

**ACS** = acute coronary syndrome  
**AHF** = acute heart failure  
**CI** = confidence interval  
**CV** = cardiovascular  
**ED** = emergency department  
**HF** = heart failure  
**hsTnT** = high-sensitivity troponin T  
**NT-proBNP** = N-terminal pro-brain natriuretic peptide  
**RF** = renal failure

categorical variables, mean  $\pm$  SD, or geometric mean (95% confidence interval [CI]) if log transformed, as appropriate. Comparisons between groups were done using chi-square or Fisher exact tests as indicated or Student *t* tests or Wilcoxon rank sum tests if not normally distributed.

Results from both univariate and multivariate analyses are presented, using predictor variables of clinical importance and consistent with past RELAX-AHF analyses (24,26). See [Online Table 1](#) for a list of the covariates, which included, among other variables, age, sex, blood pressure, treatment, NT-proBNP, creatinine, and blood urea nitrogen. [Online Table 1](#)

presents the adjustment variables included in the multivariate models. Of note, NT-proBNP was modeled as a continuous variable. Linear regression models were created for noncategorical endpoints, and Cox models for time-to-event endpoints. (Proportional hazards assumptions were checked and satisfied.) These models are conservative, as all clinical variables of interest were included. However, given the concern for overspecification, additional models with greater efficiency were created using backward elimination ([Online Table 3](#)). Cross validated C-indexes were calculated to allow model comparison. Statistical significance was set at the 0.05 level. When no events were observed in a patient subgroup of interest, score test methods were used to report *p* values and CIs. In all other cases, Wald procedures were used.

**BIOMARKERS.** Plasma hsTnT (Roche Elecsys Assay; Roche Diagnostics GmbH, Mannheim, Germany) was measured, per protocol, at baseline (a median of 8.7 h after initial presentation). The 99th percentile upper reference limit was 0.014  $\mu\text{g/l}$ , and the lowest concentration with a coefficient of variation  $\leq 10\%$  was 0.013  $\mu\text{g/l}$ . Patients with low hsTnT levels were defined by values  $\leq 0.014 \mu\text{g/l}$  (14 ng/l). All samples were analyzed in a central laboratory in a blinded manner.

## RESULTS

**BASELINE CHARACTERISTICS.** Of the 1,161 patients enrolled in the RELAX-AHF trial, 1,076 had hsTnT measured at baseline. Of these, 107 (9.9%) did not have evidence of myocardial injury (baseline value  $\leq 0.014 \mu\text{g/l}$ ). [Table 1](#) shows baseline characteristics stratified by hsTnT  $\leq 0.014 \mu\text{g/l}$ . Age was similar between the groups, with an average age of 71 years in the low-hsTnT group. Fewer patients in the low-hsTnT group were male or had reduced ejection fractions. There were no differences in baseline vital signs, with the exception of heart rate being 3 beats/min faster in the low-hsTnT group. Of note, there were no differences in history of ischemic heart disease, New York Heart Association class, HF hospitalization in the past year, or signs and symptoms of HF. With the exception of oral loop diuretic agents and beta-blockers, there were no other differences in terms of baseline medications. Fewer patients had histories of diabetes, but no other significant differences in comorbidities were observed. In terms of laboratory values, low-hsTnT patients had better renal function and lower NT-proBNP levels (median 3,422 vs. 5,313 ng/l in the elevated-hsTnT group) ([Online Table 2](#) lists a comprehensive comparison of baseline characteristics).

**TABLE 1** Baseline Characteristics by Baseline Troponin Above or Below the 99th Percentile Upper Reference Limit of 0.014  $\mu\text{g/l}$

	Elevated Troponin (n = 969)	Low Troponin (n = 107)	p Value*
<b>Demographics and heart failure characteristics</b>			
Age, (yrs)	72.5 $\pm$ 10.7	71.0 $\pm$ 11.1	0.1560
Male	623 (64.3)	42 (39.3)	<0.0001
White/Caucasian	926 (95.6)	101 (94.4)	0.6219 [F]
Left ventricular EF (%)	38.4 $\pm$ 14.5	42.8 $\pm$ 13.8	0.0036
EF <40%	509 (55.9)	41 (40.6)	0.0033
Ischemic heart disease	516 (53.3)	47 (43.9)	0.0668
Time from presentation to randomization (h)	8.0 $\pm$ 4.7	7.0 $\pm$ 4.4	0.0286
<b>NYHA functional class 30 days before admission</b>			
I	280 (29.2)	27 (25.2)	0.0609
II	237 (24.7)	39 (36.4)	
III	322 (33.6)	32 (29.9)	
IV	120 (12.5)	9 (8.4)	
<b>Clinical signs</b>			
Systolic blood pressure (mm Hg)	142.4 $\pm$ 16.5	141.7 $\pm$ 15.4	0.6813
Diastolic blood pressure (mm Hg)	78.7 $\pm$ 14.1	80.8 $\pm$ 14.2	0.1406
Heart rate (beats/min)	79.2 $\pm$ 14.7	82.2 $\pm$ 15.3	0.0477
HF hospitalization in past year	327 (33.7)	29 (27.1)	0.1658
Serelaxin administration	477 (49.2)	58 (54.2)	0.3283
<b>Congestion at baseline</b>			
Edema	762 (78.7)	88 (82.2)	0.3952
Orthopnea	929 (96.0)	99 (92.5)	0.1278 [F]
JVP	714 (75.5)	76 (72.4)	0.4862
Dyspnea on exertion	954 (99.6)	106 (100.0)	1.0000 [F]
Rales	923 (95.3)	99 (92.5)	0.2197
<b>Comorbidities</b>			
Hypertension	836 (86.3)	94 (87.9)	0.6515
Hyperlipidemia	521 (53.8)	53 (49.5)	0.4048
Diabetes mellitus	493 (50.9)	30 (28.0)	<0.0001
Stroke or other cerebrovascular event	134 (13.8)	11 (10.3)	0.3077
Asthma, bronchitis, or COPD	158 (16.3)	10 (9.3)	0.0598
History of atrial fibrillation or flutter	496 (51.2)	64 (59.8)	0.0901
History of CRT or ICD procedures	253 (26.1)	21 (19.6)	0.1441
Myocardial infarction	342 (35.3)	29 (27.1)	0.0907

Continued on the next page

**Table 2** presents the 5 primary outcomes by univariate and multivariate analyses, including troponin level by treatment interaction. Covariates used for the multivariate model are listed in **Online Table 1**. By univariate analysis, low hsTnT ( $\leq 99\%$  upper reference limit) was significantly associated with more favorable outcomes for all 5 primary outcomes. However, by multivariate analysis, only CV mortality at day 180 remained significant: no patients with low hsTnT experienced CV death through 180 days (hazard ratio: 0.0; 95% CI: 0.0 to 0.736;  $p = 0.0234$ ; C-index = 0.838 [95% CI: 0.798 to 0.878]). Of the 85 patients without baseline hsTnT values, 9 died of CV causes through day 180. Of the 969 patients with elevated hsTnT, 79 died of CV causes through day 180. Given the potential concern for overfitting the model, **Online Table 3** shows the results of a more efficient backward elimination multivariate model, demonstrating similar significance for 180-day CV mortality (hazard ratio: 0.0; 95% CI: 0.0 to 0.737;  $p = 0.0225$ ; C-index = 0.812 [95% CI: 0.770 to 0.855]).

**Table 3** shows the association between hsTnT status and the 6 secondary outcomes by univariate analysis only. With the exception of dyspnea improvement by Likert-type scale and CV death or HF or RF rehospitalization by day 30, the 4 remaining outcomes demonstrated statistically significant associations with lower risk.

Given the absence of 180-day CV events in the low-hsTnT group, a multivariate analysis of 180-day all-cause mortality was performed and did not show statistical significance ( $p = 0.0788$ ) (**Online Table 3**). Only 1 patient with low hsTnT died of a non-CV cause.

## DISCUSSION

In this post hoc analysis of the RELAX-AHF trial, patients with baseline hsTnT values below the 99th percentile (low hsTnT) were at significantly lower risk for CV death through day 180. In fact, there were no CV deaths in this group. Importantly, patients with low hsTnT were more likely to be female and to have higher ejection fractions. However, there were more similarities than differences between the groups. Furthermore, low hsTnT remained significant after adjustment for known markers of risk, such as NT-proBNP, renal function, serum sodium, blood pressure, hemoglobin, and baseline historical features and medications. This suggests that patients with signs and symptoms of AHF, without evidence of myocardial injury as measured by hsTnT assay, are at very low risk for CV death. Given that only 1 non-CV death occurred, hsTnT may be a powerful marker of low risk.

Past studies have demonstrated that lower values of troponin are associated with lower risk (22). However, it is not clear what threshold value of troponin defines low risk, specifically, to inform early decision making. Unique to this analysis is the potential value of the absence of hsTnT in patients with AHF, specifically, hsTnT  $\leq 99\%$ th percentile of the reference upper limit. Further strengths of this analysis include the use of a contemporary high-sensitivity assay, central laboratory processing, independent adjudication of events, and the largest published cohort of hsTnT from a contemporary AHF trial. In a previous analysis of the RELAX-AHF dataset, the lowest quartile of hsTnT was associated with lower risk for CV outcomes (22). However, this group included patients above and below the 99th percentile;

**TABLE 1 Continued**

	Elevated Troponin (n = 969)	Low Troponin (n = 107)	p Value*
<b>Baseline laboratory values†</b>			
Sodium (mmol/l)	140.81 ± 3.65	140.94 ± 3.18	0.7179
Hemoglobin (g/dl)	12.76 ± 1.85	12.97 ± 1.88	0.2869
Potassium (mmol/l)	4.28 ± 0.64	4.25 ± 0.63	0.6296
Creatinine (μmol/l)	118.7 ± 33.5	98.1 ± 25.7	<0.0001 [S]
Uric acid (μmol/l)	480.8 ± 136.7	425.0 ± 120.0	<0.0001
BUN (mmol/l)	10.01 ± 4.11	8.00 ± 2.73	<0.0001 [S]
Cystatin C (mg/l)	1.48 (1.46-1.51)	1.23 (1.18-1.29)	<0.0001 [S]
NT-proBNP (ng/l)	5,313 (5,029-5,613)	3,422 (2,893-4,047)	<0.0001
eGFR (ml/min/1.73 m <sup>2</sup> )	52.78 ± 12.85	58.39 ± 12.91	<0.0001
Total cholesterol (mmol/l)	4.09 ± 1.18	4.10 ± 1.08	0.9789
Glucose (mmol/l)	7.85 ± 3.72	7.09 ± 2.67	0.0090 [S]
<b>Devices</b>			
Pacemaker	106 (10.9)	7 (6.5)	0.1592
Implantable cardiac defibrillator	131 (13.5)	12 (11.2)	0.5052
Biventricular pacing	98 (10.1)	7 (6.5)	0.2374
<b>Medication (day 0, except nitrates)</b>			
ACE inhibitors	526 (54.3)	65 (60.7)	0.2022
ACE inhibitors or ARBs	659 (68.0)	78 (72.9)	0.3016
ARBs	158 (16.3)	17 (15.9)	0.9115
Beta-blockers	648 (66.9)	86 (80.4)	0.0044
Allosterone antagonists	317 (32.7)	28 (26.2)	0.1686
Oral loop diuretic agents 30 days prior	46.5 (67.3)	34.0 (57.5)	0.0373 [S]
Digoxin	200 (20.6)	14 (13.1)	0.0632
Nitrates at randomization	74 (7.6)	4 (3.7)	0.1400

Values are mean ± SD or geometric mean (95% confidence interval) if log transformed, presented for continuous variables, and n (%) for categorical variables (percentage based on total number of patients with nonmissing values for the endpoint). \*For continuous variables, p values are based on Student t tests. For categorical variables, p values are based on chi-square tests if the count in each cell is >1 and the count is  $\geq 5$  for at least 80% of the cells. Otherwise, Fisher exact test was used. "[F]" indicates that the Fisher exact test was used to calculate the p value. "[S]" indicates that the Satterthwaite method was used to calculate the p value because of unequal variance in comparison groups. †The following variable was log transformed: NT-proBNP.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; JVP = jugular venous pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.



**TABLE 2 Effect (95% Confidence Interval) of Low Versus Elevated Troponin at Baseline in Univariate and Multivariate Models for Primary Outcomes and p Values for Models Including Treatment by Troponin Interactions**

Outcome	Elevated Troponin <sup>‡‡</sup> (n = 969)	Low Troponin <sup>‡‡</sup> (n = 107)	Univariate Model* (n = 1,076)		Multivariate Model <sup>†</sup> (n = 1,076)		Multivariate Model With Interaction <sup>‡</sup> (n = 1,076)
			Effect	p Value	Effect	p Value	Interaction p Value
Days alive and out of hospital by day 60 <sup>§</sup>	47.71 (46.95 to 48.47)	51.38 (50.32 to 52.44)	3.67 (1.36 to 5.98)	0.0018	1.88 (−0.44 to 4.19)	0.1128	0.1758
CV death or rehospitalization for HF or renal failure by day 60 <sup>  </sup>	132 (13.62%)	7 (6.54%)	0.46 (0.22 to 0.99)	0.0472	0.76 (0.34 to 1.71)	0.5053	0.6751
Length of initial hospital stay <sup>§</sup>	10.24 (9.64 to 10.84)	7.81 (7.09 to 8.54)	−2.43 (−4.23 to −0.62)	0.0085	−1.54 (−3.35 to 0.26)	0.0944	0.2129
Worsening heart failure by day 5 <sup>  </sup>	100 (10.32%)	3 (2.80%)	0.26 (0.08 to 0.82)	0.0217	0.30 (0.09 to 1.03)	0.0566	0.2102**
CV death through day 180 <sup>  </sup>	79 (8.15%)	0 (0.00%)	0 (0 to 0.42 <sup>¶</sup> )	0.0025	0 (0 to 0.74 <sup>¶</sup> )	0.0234	−††

Values are hazard ratio (95% confidence interval). \*Independent variable is dichotomized (low vs. elevated) troponin. †Adjustment variables are as listed in [Online Table 1](#) and treatment. ‡Troponin level by treatment interaction term is added to multivariate model. §Continuous endpoint: mean difference (95% CI) reported as effect. ||Time-to-event endpoint: HR (95% CI) reported as effect. ¶There were no cardiovascular death events in the low-troponin group. This caused the Wald chi-square test to be unreliable, so much so that SAS could not produce an upper confidence limit. Upper confidence limits and p values were produced using score-test methods instead. #No patient scored 0 on BMDEX (BMDEX = baseline dyspnea on exertion-imputed) at level 0 had a CVDT180 event (CVDT 180 = CV death through day 180). BMDEX = 0 and BMDEX = 1 are grouped together as the reference level. \*\*Interaction p value was calculated using the score-test chi-square statistic with 1 degree of freedom. ††There was insufficient information in the data to estimate the interaction p value. ‡‡Mean (95% CI) is presented for continuous outcomes, and n (%) is presented for time-to-event outcomes.

CV = cardiovascular; HF = heart failure.

thus, the threshold value of hsTnT to define low risk is unknown. A less sensitive assay was used in ASCEND-HF (27). Unlike the RELAX-AHF trial, patients were enrolled up to 24 h after presentation. Furthermore, only 50% of patients had troponin values above the 99th percentile. In ASCEND-HF, an elevated troponin value at baseline was not associated with 30- or 180-day post-discharge outcomes. Although elevated troponin did predict length of hospital stay and in-hospital worsening HF, the prognostic value of troponin values below the 99th percentile were not reported (27).

By itself, focusing on the absence of a marker of injury in CV disease is not novel; it is a common approach in ACS and remains an area of active study,

despite decades of work to identify lower risk patients with chest pain. In ACS, lower values of troponin are associated with better outcomes. Identifying the threshold value for low risk remains an active area of study (28). Similar to ACS, future AHF work involving hsTnT assays will require careful scrutiny of patient selection, serial testing, and peak values. Unlike ACS, biomarker research to identify patients with signs and symptoms of HF who are at low risk in the ED setting is in its infancy. Well-established AHF risk scores for use in the ED setting are lacking, though several show promise (13). Although observation unit pathways exist, they are underused and lack the supportive evidence from a robust randomized controlled trial (11). In fact, American Heart Association and American

**TABLE 3 Effect (95% Confidence Interval) of Low Versus Elevated Troponin at Baseline in Univariate Models for Secondary Outcomes**

Outcome	Elevated Troponin <sup>  </sup> (n = 969)	Low Troponin <sup>  </sup> (n = 107)	Univariate Model* (n = 1,076)	
			Effect	p Value
All-cause mortality by day 180 <sup>‡</sup>	92 (9.49%)	1 (0.93%)	0.09 (0.01 to 0.68)	0.0187
WHF by day 14 <sup>‡</sup>	141 (14.55%)	7 (6.54%)	0.42 (0.2 to 0.91)	0.0275
Total dose of IV loop diuretic agents through day 5 <sup>†</sup>	189.50 (169.35 to 209.66)	122.29 (85.71 to 158.87)	−67.21 (−129.11 to −5.32)	0.0333
Dyspnea VAS AUC to day 5 <sup>†</sup>	2,502.39 (2,318.63 to 2,686.15)	3,270.76 (2,814.25 to 3,727.27)	768.37 (196.53 to 1,340.21)	0.0084
Moderate or marked improvement by Likert-type scale at 6, 12, 24 h <sup>§</sup>	263 (27.14%)	28 (26.17%)	0.95 (0.6 to 1.5)	0.8313
CV death or rehospitalization for HF or renal failure by day 30 <sup>‡</sup>	72 (7.43%)	4 (3.74%)	0.491 (0.18 to 1.34)	0.1659

Values are hazard ratio (95% confidence interval). \*Independent variable is dichotomized (low vs. elevated) troponin. †Continuous endpoint: mean difference (95% CI) reported as effect. ‡Time-to-event endpoint: HR (95% CI) reported as effect. §Categorical endpoint: OR (95% CI) reported as effect. ||Mean (95% CI) is presented for continuous outcome, and n (%) is presented for binary and time-to-event outcomes.

AUC = area under the curve; IV = intravenous; OR = odds ratio; VAS = visual analogue scale; WHF = worsening heart failure; other abbreviations as in [Table 2](#).

College of Cardiology HF guidelines focus on management once hospitalized, highlighting the paucity of ED-based evidence (29).

In the setting of low-risk identification, these findings from a clinical trial support its potential role in the real-world setting. Clinical trials generally enroll higher risk patients. For example, if patients with low hsTnT values did not have AHF at all—despite a median NT-proBNP level >3,400 pg/ml, signs and symptoms, admission for AHF, and inclusion in a clinical trial the value of low hsTnT in an ED population of patients with signs and symptoms of HF still holds. Patients may only appear to be higher risk at the time of presentation. Another hypothesis is that cardiac injury may define AHF. With increasingly sensitive troponin assays, patients without hsTnT release may: 1) not have AHF; 2) have less severe AHF; or 3) represent a unique phenotype. More than 90% of patients in RELAX-AHF had hsTnT release, supporting this injury-defining theory; however, it remains a preliminary hypothesis.

This study, however, did not show adjusted differences in rehospitalization. Whether preventing a first hospitalization leads to a return ED visit is not well known. More important, whether safe prevention of an initial admission alters outcomes for patients is also unknown. Factors that contribute to early mortality, however, may differ from those that contribute to rehospitalization (30). Non-CV comorbidities play a key role, as well as socioeconomic and psychosocial issues. Focusing solely on myocardial injury or CV comorbidities will be insufficient to dramatically improve outcomes. Although hospitalization independently predicts a worse outcome (31,32), whether the prevention of unnecessary hospitalization for patients with AHF worsens the prognosis of patients, improves it, or makes no difference requires further study. Regardless, any successful discharge strategy must ensure symptom alleviation as well as robust transitions of care. Given that many hospitals already use transitional care strategies for hospitalized patients, leveraging such resources to the ED or observation unit setting would facilitate uptake of a strategy of low risk to discharge with close follow-up.

Future studies using hsTnT to stratify risk should target lower risk ED patients with AHF. Current clinical decision making already leads to admission for most patients (33,34). Focusing on high risk is of relatively less value in the ED setting. Identifying even a small fraction of patients safe for discharge, coupled with robust transitions of care, would result in a significant decrease in the absolute number of

hospitalized patients. Whether troponin release at baseline reflects the severity of underlying structural heart disease, decompensation, or both is not well known. Serial values that demonstrate rising, falling, or peak values would better inform the mechanisms of myocardial injury in patients with AHF.

**STUDY LIMITATIONS.** A major limitation of this study is the absence of patients discharged from the ED. Risk stratification schemata derived from already hospitalized patients may not identify ED patients safe for discharge (13-15,35,36). Multimarker approaches were also not considered because a recent study demonstrated the potential value of such an approach in hospitalized patients (36). However, we did adjust for known prognostic markers, and in the ED setting, troponins are routinely ordered as part of clinical care. Importantly, the results are hypothesis generating only. Another major limitation is the small number of patients with low hsTnT ( $n = 107$ ). However, the RELAX-AHF trial enrolled a higher risk group of patients with AHF compared with real-world patients. A larger proportion of patients may actually have low hsTnT. Whether these findings apply to patients who do not meet the trial inclusion and exclusion criteria was not examined. There is the possibility that not all patients had AHF, as it remains a clinical diagnosis without an established gold standard. Although the strict inclusion and exclusion criteria suggest that this is unlikely, this would not rule out the potential value of low hsTnT in patients with AHF signs and symptoms; it may prompt the search for alternative diagnoses. Other strategies to leverage hsTnT in AHF were not tested: 1) different thresholds of hsTnT, such as the limit of detection; 2) more rapid serial testing (i.e., 0 and 3 h); and 3) as part of a risk score.

## CONCLUSIONS

In the RELAX-AHF trial, no patient with an hsTnT value below the 99th percentile upper reference limit died through 180 days. Future studies are needed to confirm whether absence of myocardial injury identifies ED patients with AHF safe for discharge or brief observation.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** The absence of validated, facile risk instruments for EDs caring for patients with AHF contributes to the very high proportion of admissions. Troponin, as a marker of myocardial injury in AHF, is a known prognostic marker. However, it has been studied primarily as a marker of high risk; whether absence of troponin release is associated with low risk has not been previously well studied. In this post hoc study, baseline hsTnT  $\leq$ 99th percentile identified patients at very low risk for 180-day CV mortality.

**TRANSLATIONAL OUTLOOK:** Because this was a post hoc analysis, further work is needed to verify the potential clinical value of hsTnT in AHF patients in the ED setting. In the United States however, studying discharged patients with AHF is difficult because most patients are admitted. Thus, separating the impact of hospitalization from baseline risk is difficult. Nevertheless, given the high proportion of admissions, this hypothesis-generating study should lead to future work exploring the role of hsTnT as a marker of low risk in patients with AHF. We suggest studying hsTnT in patients with lower risk features in the ED setting, as higher risk patients will likely be admitted regardless.

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**KEY WORDS** acute heart failure, emergency department, risk stratification, serelaxin

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**APPENDIX** For supplemental tables, please see the online version of this article.

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