



# Troponin I in acute decompensated heart failure: insights from the ASCEND-HF study

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## Aims

We examined the prognostic importance of cardiac troponin I (cTnI) in a cohort of patients enrolled in the ASCEND-HF study of nesiritide in acute decompensated heart failure (ADHF). Circulating troponins are a prognostic marker in patients with ADHF. Contemporary assays with greater sensitivity require reassessment of the significance of troponin elevation in HF.

## Methods and results

Cardiac troponin I was measured in a core laboratory in 808 ADHF patients enrolled in the ASCEND-HF biomarkers substudy using a sensitive assay (VITROS Trop I ES, Ortho Clinical Diagnostics) with a lower limit of detection of 0.012 ng/mL and a 99th percentile upper reference limit (URL) of 0.034 ng/mL. Patients with clinical evidence of acute coronary syndrome or troponin  $>5 \times$  the URL were excluded. Multivariable modelling was used to assess the relationship between log(cTnI) and in-hospital and post-discharge outcomes. Baseline cTnI was undetectable in 22% and elevated above the 99th percentile URL in 50% of subjects. cTnI levels did not differ based on HF aetiology. After multivariable adjustment, higher cTnI was associated with worsened in-hospital outcomes such as length of stay ( $P = 0.01$ ) and worsening HF during the index hospitalization ( $P = 0.01$ ), but was not associated with worsened post-discharge outcomes at 30 or 180 days. The relationship between cTnI and outcomes was generally linear and there was no evidence of a threshold effect at any particular level of cTnI.

## Conclusion

cTnI is elevated above the 99th percentile URL in 50% of ADHF patients and predicts in-hospital outcome, but is not an independent predictor of long-term outcomes.

## Keywords

Troponin • Biomarkers • Heart failure

## Introduction

Cardiac troponins are sensitive biomarkers of myocardial injury, and play a fundamental role in the diagnosis and risk stratification of patients with acute coronary syndromes (ACS). Data from multiple studies have demonstrated that circulating cardiac troponins are detectable in patients with heart failure (HF) even in the

absence of clinically apparent myocardial ischaemia, and that cardiac troponins may be useful prognostic markers in patients with acute and chronic HF.<sup>1</sup> Although the exact mechanisms of myocardial injury in HF are uncertain, ischaemia, haemodynamic stress, oxidative stress, inflammation, altered calcium handling, and impaired renal clearance have all been proposed as mechanisms of troponin elevation in HF.<sup>1,2</sup>

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Recent improvements in the sensitivity of troponin assays have complicated the interpretation of these biomarkers in HF. The increasing sensitivity of more contemporary assays has resulted in the detection of circulating troponin in a progressively greater proportion of HF patients, including many patients with troponin levels greater than the diagnostic myocardial infarction threshold [the 99th percentile upper reference limit (URL)]. This phenomenon has led to increasing uncertainty about the clinical interpretation of troponin data from contemporary assays, particularly in patients with acute decompensated HF (ADHF). A substantial proportion of ADHF patients have elevations of circulating troponin,<sup>3–5</sup> and both the symptoms and the aetiology of ADHF may overlap significantly with those of ACS. Using a contemporary troponin assay, we analysed data from a pre-specified biomarker substudy of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) study in order to assess (i) the prevalence and clinical correlates of troponin elevation in ADHF; (ii) the association between troponin elevation and in-hospital and post-discharge clinical outcomes; (iii) the prognostic implications of changes in troponin levels during initial ADHF therapy; and (iv) the relationship between nesiritide treatment and troponin status.

## Methods

The methods and primary results of the ASCEND-HF study (NCT00475852, clinicaltrials.gov) have been published previously.<sup>6,7</sup> Briefly, ASCEND-HF was a multicentre, randomized, double-blind, placebo-controlled trial of nesiritide compared with placebo in 7141 patients hospitalized with ADHF. Co-primary endpoints were improvement in dyspnoea at 6 or 24 h as measured by a 7-point Likert scale and HF hospitalization or death at 30 days. Patients with clinical evidence of ACS or baseline troponin level  $>5 \times$  the URL at the local clinical laboratory were excluded from the trial. A subgroup of patients from the ASCEND-HF study were enrolled in a biomarker substudy ( $n = 808$ ). Blood samples were obtained in serum and EDTA plasma at baseline, 48–72 h, and 30 days, and were immediately centrifuged and stored at  $-80^{\circ}\text{C}$  for subsequent analysis. At a central core laboratory blinded to all clinical data, cardiac troponin I (cTnI) was measured in serum samples using a contemporary 'guideline-acceptable'<sup>8</sup> sensitive assay (VITROS Trop I ES, Ortho Clinical Diagnostics, Raritan, NJ, USA) with a lower limit of detection of 0.012 ng/mL, a 99th percentile URL of 0.034 ng/mL, and a coefficient of variation of 10% at the 99th percentile URL. N-terminal pro brain natriuretic peptide (NT-proBNP) was measured on serum samples at the same core laboratory using a clinically available assay (VITROS NTproBNP, Ortho Clinical Diagnostics).

## Statistical analysis

Categorical variables were described as counts and percentages, and continuous variables were summarized as medians (25th, 75th percentiles). Differences in binary variables were calculated using the  $\chi^2$  test. Continuous and ordinal variables were compared using the Wilcoxon rank-sum test. Because cTnI was not normally distributed, this variable was log transformed in all analyses using log base 2, such that reported hazard ratios (HRs) and odds ratios (ORs) represented the risk associated with a doubling of cTnI. All ORs and HRs are reported as point estimates with 95% confidence intervals (CIs). For the purposes of analysis, levels below the lower limit of detection ( $<0.012$  ng/mL) were imputed as 0.006 ng/mL, since this provided the best statistical

fit for the observed distribution of troponin data. We used multivariable linear regression to identify clinical predictors of elevated cTnI at baseline. The association between cTnI and outcomes was determined using both univariable and multivariable logistic regression analysis or Cox proportional hazards analysis (for length of stay and 180-day mortality). The clinical endpoints of interest were (i) 30-day mortality; (ii) the composite of 30-day mortality and rehospitalization for HF; (iii) 180-day mortality; (iv) dyspnoea improvement at 6 and 24 h; (v) worsening HF or death up to day 7; and (vi) length of stay for the index hospitalization. For multivariable analysis, adjusted models for each endpoint of interest ('final adjusted models') were constructed in the overall ASCEND-HF population (see Appendix for the final list of covariates for each endpoint). These covariates were then used to perform multivariable adjustment in the biomarker substudy subset reported herein. Models were tested with and without the inclusion of NT-proBNP. We also examined the interaction between randomized treatment (nesiritide or placebo) and troponin status with regard to each outcome using an interaction term (treatment  $\times$  cTnI) in the multivariable model for each endpoint.

To evaluate the relationship between change in cTnI during the acute hospitalization (between baseline and 48–72 h) and subsequent outcomes, we evaluated both the absolute change in troponin values and a 20% change in troponin from baseline. Both these analyses excluded patients with undetectable troponin at baseline. Finally, we examined the significance of a rise or fall in troponin that crossed the 99th percentile URL, consistent with the universal definition of myocardial infarction.<sup>9</sup>

## Results

### Patient population

The biomarker substudy population ( $n = 808$ ) was broadly similar to the overall ASCEND-HF population ( $n = 7141$ ), with the exception that 85% of patients in the biomarker substudy were enrolled in North America (compared with 43% in the main trial). The median cTnI level was 0.034 ng/mL (0.012, 0.058). Baseline cTnI was below the lower limit of detection ( $<0.012$  ng/mL) in 22% and elevated above the 99th percentile URL in 50%. The proportion of patients with cTnI levels above the 99th percentile URL decreased at each time point, but remained substantial (31%) even at day 30 (Figure 1). Baseline characteristics for the study population stratified by cTnI above or below the 99th percentile URL (which was also the median cTnI level) are shown in Table 1. Patients with higher cTnI levels had other characteristics associated with higher risk, including being older, more often male, and having higher NT-proBNP and worse renal function ( $P < 0.05$  for all). Notably, cTnI levels did not differ based on whether patients had HF of ischaemic vs. non-ischaemic aetiology (median cTnI = 0.034 ng/mL for ischaemic vs. 0.035 ng/mL for non-ischaemic;  $P = 0.77$ ). Patients with HF and preserved ejection fraction ( $\geq 40\%$ ) had significantly lower cTnI levels (median = 0.026 ng/mL) than those with systolic dysfunction (median = 0.037;  $P = 0.03$ ) (Figure 2).

### Correlates of elevated baseline troponin

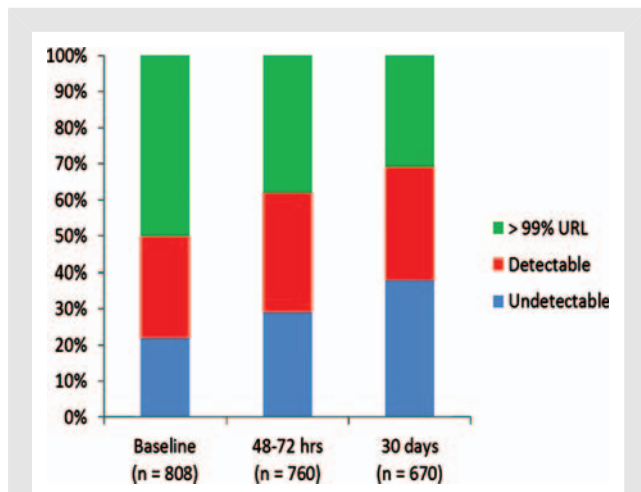
Variables that were significantly associated with elevated cTnI at baseline are shown in Table 2. The factor with by far the strongest association with elevated cTnI was elevated NT-proBNP ( $P < 0.0001$ ). Region was also a significant predictor of elevated cTnI, with patients enrolled in North America or Latin America

having lower cTnI levels than those enrolled in other regions (Western Europe, Central Europe, or Asia).

## Association of baseline troponin and outcomes

### In-hospital outcomes

For analysis of the relationship between cTnI and dyspnoea response, dyspnoea was dichotomized as moderately or markedly improved (based on the Likert scale) at 6 and 24 h relative to the



**Figure 1** Proportion of patients at each time point with troponin I values below the lower limit of detection ( $<0.012$  ng/mL), between the lower limit of detection and the 99th percentile URL ( $\geq 0.012$  ng/mL to  $\leq 0.034$  ng/mL), and greater than the 99th percentile URL ( $>0.034$  ng/mL). URL, upper reference limit.

time of randomization. Baseline cTnI was not a significant predictor of dyspnoea relief at 6 h (adjusted OR 1.04, 95% CI 0.92–1.18) per doubling of cTnI;  $P = 0.502$ ), but troponin elevation was modestly associated with lower odds of dyspnoea relief at 24 h (adjusted OR 0.85, 95% CI 0.72–0.99 per doubling of cTnI;  $P = 0.035$ ) (Table 3).

Baseline troponin status was a strong predictor of other clinical outcomes during the index hospitalization. Specifically, increased baseline cTnI was associated with a higher risk of the endpoint of death or worsening HF prior to discharge in both univariate (OR 1.31, 95% CI 1.12–1.54 per doubling of cTnI;  $P = 0.001$ ) and multivariable analysis (OR 1.34, 95% CI 1.10–1.62 per doubling of cTnI;  $P = 0.013$ ) (Figure 3A). Increases in baseline cTnI were also associated with a higher risk for increased length of stay in both univariate analysis (HR 0.93, 95% CI 0.89–0.97;  $P = 0.001$ ) and after adjustment for other known predictors (HR 0.95, 95% CI 0.91–0.99;  $P = 0.013$ ).

### Long-term outcomes

Event rates were 3.1% ( $n = 25$ ) for 30-day mortality, 12.1% ( $n = 98$ ) for the composite of death or rehospitalization at 30 days, and 11.5% ( $n = 93$ ) for 180-day mortality. The univariable and adjusted relationships between baseline cTnI and 30- and 180-day outcomes are shown in Table 3. Higher baseline cTnI was associated with a higher 30-day mortality rate in univariate analysis (OR 1.23, 95% CI 1.01–1.50 per doubling of cTnI;  $P = 0.035$ ). However, after adjustment for other predictors, cTnI was no longer associated with 30-day mortality (adjusted OR 1.11, 95% CI 0.89–1.38 per doubling of cTnI;  $P = 0.37$ ) (Figure 3B). For the composite endpoint of death or HF rehospitalization at 30 days, elevated cTnI was not significantly associated with outcome in either univariable (OR 1.09, 95% CI 0.97–1.22;

**Table 1** Baseline characteristics stratified by troponin I above or below the 99th percentile upper reference limit

	Total (n = 808)	cTnI $\leq 0.034$ ng/L (n = 404)	cTnI $> 0.034$ ng/mL (n = 404)	P-value
Age (years)	67	65	69	0.022
Sex (male, %)	70.1	64.6	75.5	0.0007
Race (White, %)	68.2	68.8	67.6	0.84
Systolic BP (mmHg)	124.0	124.0	124.5	0.52
Heart rate (b.p.m.)	79.0	79.0	79.0	0.82
Atrial fibrillation (%)	41.3	40.6	42.1	0.67
Hypertension (%)	77.7	80.2	75.3	0.091
NT-proBNP (pg/mL)	3700	2980	4554	0.0008
Serum creatinine ( $\mu$ mol/L)	114.9	106.1	123.8	$<0.0001$
BUN (mg/dL)	8.6	8.2	9.6	0.0001
Sodium (mmol/L)	139	139	139	0.038
EF (%)	25	30	25	0.052
Time from presentation to randomization (h)	18.1	18.8	17.3	0.094
Ischaemic aetiology (%)	60.6	61.1	60.2	0.77
On beta-blocker (%)	75.5	78.0	73.0	0.10
On ACE inhibitor or ARB (%)	64.2	65.4	63.1	0.51
On aldosterone antagonist (%)	24.6	27.5	21.8	0.060

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; BUN, blood urea nitrogen; cTnI, cardiac troponin I; EF, ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide.

$P = 0.15$ ) or multivariable (OR 1.04, 95% CI 0.92–1.18;  $P = 0.51$ ) analyses. For 180-day mortality, elevations of baseline cTnI were associated with higher mortality in univariable analysis (HR 1.25, 95% CI 1.13–1.38 per doubling of cTnI;  $P < 0.0001$ ), but were no longer significant after adjustment for other predictors (adjusted HR 1.11, 95% CI 0.99–1.25 per doubling of cTnI;  $P = 0.086$ ).

### Change in troponin status and outcomes

A total of 685 patients had paired samples from both the baseline and 48–72 h time point available for analysis. Event rates in patients with paired samples were generally similar to those in patients without paired samples available (data not shown). In general, cTnI levels from baseline to the 48–72 h time point were highly correlated ( $r = 0.77$ ;  $P < 0.001$ ). There was no significant association between the absolute change in troponin from baseline to 48–72 h and either 30-day mortality ( $P = 0.063$ ) or the composite of 30-day death or heart failure hospitalization ( $P = 0.14$ ). When troponin change was dichotomized at a 20% increase, 30-day event rates were higher for those with a troponin increase (Table 4), and a 20% increase in troponin was a significant predictor of 30-day death ( $P = 0.012$ ) but not 30-day death or HF hospitalization ( $P = 0.304$ ). Finally, we assessed the clinical significance of a rise or fall in troponin that crossed the 99th percentile

URL (consistent with the universal definition for myocardial infarction). Event rates for 30-day endpoints (death and death or HF rehospitalization) based on changes in troponin status are shown in Figure 4. Although crude event rates were numerically highest for patients with persistently elevated cTnI, there was no clear and consistent relationship between change in troponin category and 30-day outcome for either mortality or the composite of mortality and rehospitalization. Notably, patients whose cTnI went from low to high during the course of treatment (presumably suggestive of ongoing or worsening myocardial injury) actually had the lowest event rate for the composite of death or HF hospitalization at 30 days.

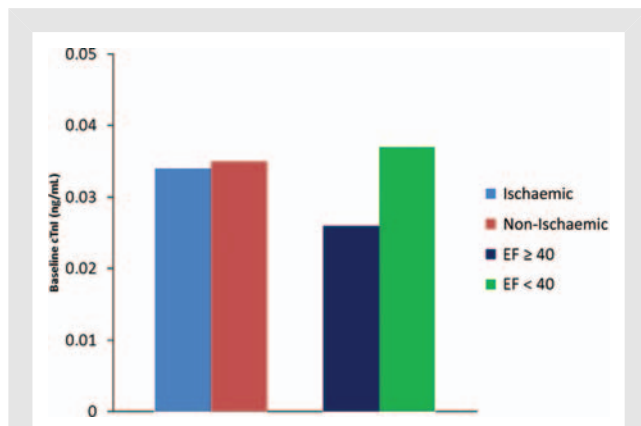
When both baseline and 48–72 h log(cTnI) were entered together into a logistic regression model for 30-day mortality, the 48–72 h cTnI level remained a significant predictor ( $P = 0.04$ ), whereas the baseline cTnI level did not ( $P = 0.81$ ), suggesting that the most recent value provided the most prognostic information. In a similar analysis examining change from baseline to 30- and 180-day outcomes, the 30-day cTnI level remained a significant predictor ( $P = 0.0001$ ) whereas baseline cTnI did not ( $P = 0.434$ ).

### Interaction between troponin status and treatment

Given that ASCEND-HF was a randomized controlled study of nesiritide, we evaluated the association between treatment assignment (nesiritide or placebo) and troponin status using interaction terms in the relevant multivariable model for each endpoint. There was no evidence of a differential effect of nesiritide treatment based on troponin status for either dyspnoea at 24 h ( $P = 0.56$  for treatment  $\times$  cTnI interaction) or for the 30-day composite of death or HF rehospitalization ( $P = 0.42$  for treatment  $\times$  cTnI interaction). Additionally, we investigated whether the changes in cTnI during initial ADHF treatment differed by treatment assignment (nesiritide or placebo). There was no significant difference between 72 h cTnI (while controlling for baseline troponin) based on treatment assignment ( $P = 0.56$ ), suggesting that nesiritide treatment did not affect changes in cTnI over time.

### Discussion

The ongoing development of more sensitive assays for troponin has led to uncertainty about the clinical significance of detectable



**Figure 2** Relationship between heart failure aetiology, ejection fraction (EF), and baseline cardiac troponin I (cTnI).

**Table 2** Predictors of higher baseline troponin I levels by linear regression

Variable	Coefficient	95% CI	F-value	P-value
Log(NT-proBNP)	0.212	0.140–0.284	33.38	<0.0001
Region <sup>a</sup>	NA		5.21	0.0004
Log(BUN)	0.171	0.015–0.327	4.66	0.0313
Potassium	0.122	0.007–0.237	4.30	0.0385
No diabetes	–0.150	–0.294 to –0.022	4.13	0.0424
No atrial fibrillation	–0.141	–0.286 to 0.004	3.62	0.0576

BUN, blood urea nitrogen; CI, confidence interval; NT-proBNP, N-terminal pro brain natriuretic peptide.

<sup>a</sup>North America, Latin America, Central Europe, Western Europe, or Asia.

**Table 3** Baseline troponin I levels and outcomes

Endpoint	Unadjusted				Adjusted <sup>a</sup>			
	OR <sup>b</sup> or HR <sup>b</sup>	95% CI	$\chi^2$	P-value	OR <sup>b</sup> or HR <sup>b</sup>	95% CI	$\chi^2$	P-value
Death at 30 days	1.234	1.014–1.501	4.42	0.035	1.106	0.887–1.379	0.80	0.37
Death/rehospitalization at 30 days	1.090	0.970–1.224	2.08	0.15	1.043	0.919–1.184	0.43	0.51
Death at 180 days	1.246	1.126–1.377	18.3	<0.0001	1.108	0.985–1.247	2.95	0.086
Improved dyspnoea at 6 h	1.008	0.930–1.093	0.04	0.84	1.037	0.933–1.153	0.45	0.502
Improved dyspnoea at 24 h	0.886	0.788–0.991	4.02	0.045	0.845	0.724–0.988	4.47	0.035
Death or worsening HF prior to discharge	1.310	1.115–1.538	10.8	0.001	1.336	1.101–1.620	8.65	0.013
Length of stay <sup>c</sup>	0.931	0.894–0.970	11.7	0.001	0.946	0.905–0.988	6.14	0.013

CI, confidence interval; HF, heart failure; HR, hazard ratio; OR, odds ratio.

<sup>a</sup>Adjusted models using the covariates listed in Appendix for each endpoint.

<sup>b</sup>Per doubling of cardiac troponin I.

<sup>c</sup>For length of stay, a numerically lower hazard ratio equates to high risk for increased length of stay.

or elevated troponin levels in patients with HF. Specifically, improvements in analytical sensitivity have transformed circulating troponin from a biomarker that was only detectable in a minority of patients to one that is detectable in the vast majority of patients with HF and elevated (above the 99th percentile URL) in a substantial minority.

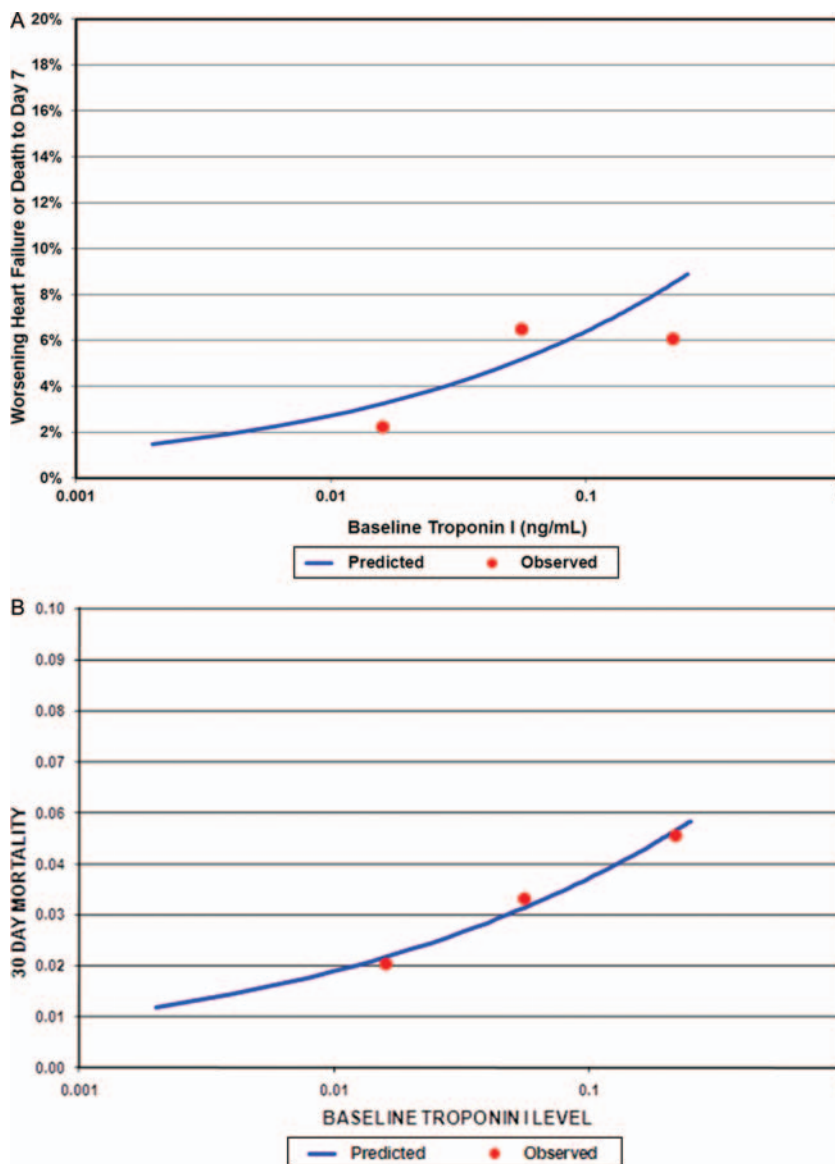
In the current analysis of a substudy from the ASCEND-HF trial, we found a high prevalence of baseline cTnI levels that were detectable (78%) or elevated above the 99th percentile URL (50%) using a contemporary sensitive troponin assay. The prevalence of cTnI elevation in our study was generally higher than in previously published reports in ADHF, where the prevalence of troponin elevation above the 99th percentile URL has ranged from 6% to 83%.<sup>4,5,10–13</sup> Previous studies of troponin prevalence have been either small single-centre studies<sup>5,14–16</sup> or pooled data from large registries such as ADHERE and EFFECT<sup>4,11</sup> and have generally used older assays or pooled clinical data from multiple sites using a variety of assays. Thus, the current analysis from ASCEND-HF is the largest study to date reporting troponin data in ADHF patients using a centralized core laboratory and a contemporary sensitive assay. Additionally, our study utilized carefully adjudicated clinical events using a blinded endpoints committee, further adding to the validity of our findings.

The ongoing evolution of troponin assays has resulted in assays of markedly greater sensitivity (at least 10-fold); not surprisingly, this led to substantial increases in the proportion of HF patients with detectable (i.e. above the lower limit of detection) and elevated (i.e. above the 99th percentile URL) troponin. Consistent with this trend, a recent single-centre study by Xue *et al.* demonstrated, using an experimental ultrasensitive nanoparticle assay, that the median troponin value in an ADHF population was 29.5 ng/L (> 4-fold greater than the 99th percentile URL for that assay) and all ADHF patients studied had detectable troponin.<sup>14</sup> These progressive improvements in analytical sensitivity have resulted in the commonly used distinction of troponin as 'positive' or 'negative' becoming increasingly meaningless in the context of ADHF, where the vast majority of patients have detectable troponin using contemporary sensitive assays.

In our analysis, elevations in baseline cTnI were independent predictors of events during the acute index hospitalization (worsening or persistent HF or death as well as increased length of stay) and modestly predicted lack of dyspnoea improvement at 24 h. In this analysis, cTnI levels, while predictive of in-hospital outcomes, were not independent predictors of post-discharge outcomes at 30 or 180 days after adjustment for other known predictors. These results are generally consistent with previous results from ADHERE examining in-hospital events,<sup>4</sup> but are in contrast to previous published studies that have consistently shown troponin elevation to be an independent predictor of post-discharge outcomes in ADHF.<sup>5,10,11,16–18</sup> The reasons underlying the difference between our results and previous data in ADHF are speculative. Our study is several fold larger than any previous study (excluding the two large registry studies), suggesting that limited statistical power (i.e. type II error) is an unlikely explanation for our results. Our study included relatively robust adjustment for other covariates, which may have served to attenuate the prognostic significance of troponin in the face of other strong predictors of outcome. The ASCEND-HF study excluded patients with troponin > 5-fold the URL, and so the exclusion of patients with very elevated troponin levels may have limited our ability to detect associations between troponin and outcomes. Finally, publication bias may contribute to the lack of other reports in the literature showing no association between troponin and post-discharge outcomes.

Changes in troponin status during initial treatment for ADHF have been proposed as potentially important signals in drug development.<sup>19</sup> Previous studies in both chronic and acute HF have suggested that changes in troponin over time are associated with greater risk.<sup>18,20</sup> In the current analysis, troponin values were relatively stable over the initial 48–72 h of ADHF therapy. Substantial increases in troponin (> 20%) were associated with risk for 30-day mortality but not for the composite of death or HF rehospitalization. The most recent value available provided the most important prognostic information in predicting outcomes, consistent with recent data on the natriuretic peptides.<sup>21</sup> Of particular interest in our analysis were patients whose troponin either rose above the 99th percentile URL (5%;  $n = 33$ ) or fell below the 99th



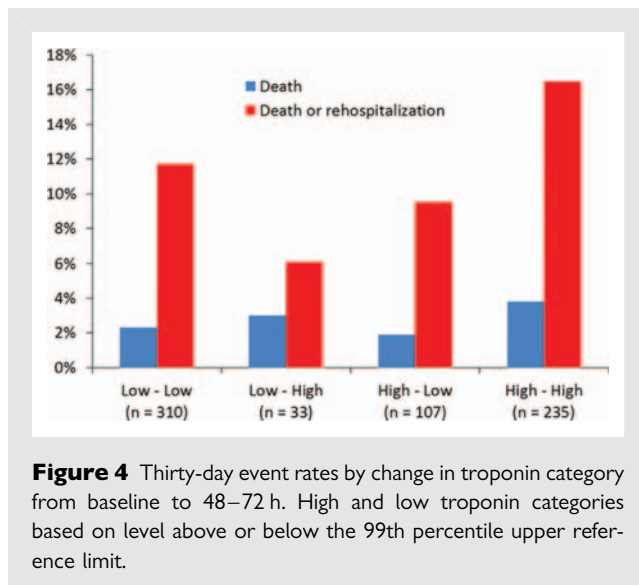


**Figure 3** Continuous relationship between baseline troponin I and (A) in-hospital worsening heart failure or death to day 7, and (B) 30-day mortality.

**Table 4** Change in troponin from baseline to 48–72 h and 30-day outcomes

Endpoint, % (n/N)	Event rates based on 20% increase in troponin			
	No 20% increase	20% increase	P-value	
30-day death	2.3% (10/441)	7.7% (7/91)	0.012	
30-day death/HF rehospitalization	12.5% (55/441)	16.5% (15/91)	0.304	
Endpoint	Absolute change in troponin and 30-day endpoints			
	OR	95% CI	Wald $\chi^2$	P-value
30-day death	0.762	0.572–1.015	3.46	0.063
30-day death/HF rehospitalization	0.856	0.696–1.054	2.14	0.144

CI, confidence interval; HF, heart failure; OR, odds ratio.



**Figure 4** Thirty-day event rates by change in troponin category from baseline to 48–72 h. High and low troponin categories based on level above or below the 99th percentile upper reference limit.

percentile URL (16%;  $n = 107$ ) between baseline and 48–72 h measurements. Given that the clinical presentation of acute HF and ACS substantially overlaps, this subgroup of patients satisfies many of the diagnostic criteria for acute myocardial infarction using the current universal definition, which requires a rise and/or fall in cardiac troponin with at least one value above the 99th percentile URL in the setting of appropriate clinical symptoms.<sup>9</sup> Absolute changes in troponin in these groups were modest, with a median rise of 0.031 ng/mL in the low–high group and a median fall of 0.025 ng/mL in the high–low group. Despite these changes in troponin status during acute therapy, there was no clear or consistent pattern in event rates based on these categories, as shown in *Figure 4*. These data call into question the clinical significance of modest changes in troponin in the context of acute HF, a finding that may have potential implications for the use of troponin monitoring to identify cardiotoxicity in drug development.<sup>22</sup> Larger increases in troponin during acute treatment may have prognostic implications for post-discharge events.

Given the importance of the 99th percentile URL in current guidelines for diagnosing myocardial infarction,<sup>9</sup> we evaluated whether there was any evidence for a threshold effect (a change in the slope of the risk curve) at this level of cTnI values. Graphical evaluation of the continuous relationship between cTnI and risk of in-hospital worsening HF/death to day 7 (*Figure 3A*) or 30-day mortality (*Figure 3B*) did not suggest a threshold effect at any particular level of cTnI. Combined with our data showing little significance of the changes in troponin categories based on troponin levels above or below this threshold, the data from ASCEND-HF generally raise questions regarding the relevance of the 99th percentile URL in the evaluation and management of patients with ADHF.

Important limitations of our study include the selection bias inherent in clinical trial populations, as well as the fact that patients with clinical evidence of ACS and elevations of troponin  $>5\times$  the URL were excluded from the ASCEND-HF trial. If anything, these exclusion criteria would bias our data towards an underestimate of the prevalence of elevated troponin levels in less selected ADHF

populations. However, this limitation may also have led us to underestimate the prognostic importance of troponin elevations in ADHF patients with a broader range of troponin values. The majority of our substudy population was from North America, potentially limiting the generalizability of our results. Patients in ASCEND-HF could be randomized as long as 24 h after initiation of intravenous therapy, and thus baseline cTnI levels in our study may have differed from those that would have been obtained at initial presentation. The relatively long time window between baseline and follow-up sampling (48–72 h) may have obscured shorter term changes in troponin levels. Although our study was relatively large compared with other similar studies in the literature, the total number of events was still small, which may have limited our statistical power. Finally, our study was a retrospective analysis of data from a clinical trial, and thus cannot establish cause and effect.

The ongoing development of troponin assays of progressively greater sensitivity necessitates a change in thinking about troponin as a dichotomous variable (with associated ‘cut-off points’) to a continuous prognostic variable (similar to the natriuretic peptides), a change that has resulted in substantial uncertainty in the clinical community.<sup>23</sup> In this analysis of a large clinical trial population, cTnI levels were associated with in-hospital outcomes but not post-discharge outcomes in a large cohort of patients with ADHF. Given that these results differ from those of other recent analyses,<sup>24,25</sup> they will require confirmation in other data sets. Further research with contemporary assays is needed to define the appropriate role of troponin as a biomarker in the clinical care of patients with HF.

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## Appendix

Final covariates for multivariable adjustment for each endpoint were based on multivariable modelling from the overall ASCEND-HF cohort, and then applied to models for each endpoint in the troponin subset. Final adjustment covariates for each endpoint are shown below.

### Death at 30 days

Age, log(BUN), serum sodium, hypotension (baseline), dyspnoea at rest (baseline).

## Death or HF rehospitalization at 30 days

Hypotension (baseline), serum sodium, age, log(BUN), history of cerebrovascular disease (baseline), log(creatinine), history of depression, dyspnoea at rest (baseline), elevated jugular venous pressure (JVP), history of chronic respiratory disease.

## Length of stay

Hypotension (baseline), serum sodium, age, log(BUN), history of cerebrovascular disease (baseline), log(creatinine), history of depression, dyspnoea at rest (baseline), elevated JVP, history of chronic respiratory disease.

## Dyspnoea at 6 h

Age, serum sodium, respiratory rate (baseline), congestion on chest X-ray, race, hypotension (baseline), haemoglobin, log(BUN), New York Heart Association (NYHA) class prior to decompensation.

## Dyspnoea at 24 h

Age, serum sodium, respiratory rate (baseline), congestion on chest X-ray, race, hypotension (baseline), haemoglobin, NYHA class prior to decompensation.

## Death at 180 days

Age, log(BUN), serum sodium, hypotension (baseline), dyspnoea at rest (baseline).

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