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Circulating Cardiac Troponin I Levels Measured by a Novel Highly Sensitive Assay in

Acute Decompensated Heart Failure: Insights from the ASCEND-HF Trial

Short title: High-Sensitivity Troponin I in ADHF

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ABSTRACT

BACKGROUND. Circulating cardiac troponin levels (cTn), representative of myocardial injury, are commonly elevated in heart failure (HF) and related to adverse clinical events. However, whether cTn represents a spectrum of risk in HF is unclear.

METHODS. Baseline, 48–72 hour, and 30 day plasma cTnI was measured by a novel highly-sensitive assay in 900 subjects with acute decompensated HF (ADHF) in ASCEND-HF. Multivariable models determined the relationship between cTnI and outcomes.

RESULTS. The median(interquartile range) cTnI was 16.4 (9.3-31.6) ng/L at baseline, 14.1 (7.8-29.7) ng/L at 48-72 hours, and 11.6 (6.8-22.5) ng/L at 30 days. After additional adjustment for amino terminal pro-B-type natriuretic peptide (NT-proBNP) to established risk predictors, both baseline and 48-72 hour cTnI were associated with higher risk for death or worsening HF prior to discharge (OR 1.25, P=0.03 and OR 1.43, P=0.001, respectively). However, only cTnI at 30 days was associated 180-day death (HR 1.25, P=0.007). There were no curvilinear associations between changing cTnI and clinical outcomes.

CONCLUSIONS. Circulating cTnI level was associated with clinical outcomes in ADHF, but these observations diminished with additional adjustment for NT-proBNP. Although they likely represent a spectrum of risk in ADHF, these findings question the implications of changing cTnI levels during treatment.

KEY WORDS. Troponin, nesiritide, acute decompensated heart failure

LIST OF ABBREVIATIONS:

cTnI – Cardiac troponin I

ADHF – Acute decompensated heart failure

cTn – Cardiac troponin

cTnT – Cardiac troponin T

URL – upper reference limit

ASCEND-HF - Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure

NRI - net reclassification improvement

IDI - integrated discrimination improvement

NT-proBNP – amino terminal pro-B-type natriuretic peptide

BUN – blood urea nitrogen

LVEF – left ventricular ejection fraction

INTRODUCTION

Circulating cardiac troponin levels are commonly elevated in patients with heart failure. These elevations likely represent a diversity of adverse myocardial responses to hemodynamic stress and abnormalities in cardiomyocyte pathobiology.[1] It is therefore no surprise that there is an increasing interest in the clinical usage of circulating cTn in patients with heart failure. Over the past decade, multiple epidemiologic studies have investigated both the prognostic role and clinical implications of static or changing cTn levels in heart failure.[2-12] Even though cTn levels were measured in these studies by assays with widely varying sensitivities and cTn subtypes (cTnT and cTnI), there is general agreement that higher circulating cTn is associated with worse outcomes across the spectrum of HF patients. Unlike cTn in acute coronary syndromes where cTn levels >99% URL, determined by each assay, have a high clinical sensitivity for detecting a myocardial infarction,[13] there is uncertainty as to whether there is an appropriate cTn cut-off for risk in heart failure. Although, circulating cTn levels below the 99% URL in patients with acute HF may be of low, long-term risk.[14] Yet, there remains a prognostic role for very low levels of circulating cTn[2], especially when only detectable by increasingly sensitive assays,[15] and whether there is a prognostic advantage apart from lower cTn detection is not clear. Unlike myocardial infarction with a clearer link to pathology and cTn level, changes in cTn levels in HF are not well understood.

The ASCEND-HF biomarker substudy provides a unique opportunity to answer these questions.[16] We aim to characterize the relationship of cTnI levels measured by a novel highly sensitive assay with short-term, intermediate, and long-term endpoints and make a comparison to cTnI levels measured by a concomitant standard sensitivity assay.[11] Also, we aim to determine

the impact of nesiritide on serial cTnI levels and provide a better understanding of changing cTnI levels in ADHF.

MATERIALS AND METHODS

STUDY POPULATION. The ASCEND-HF trial was a multicenter, randomized, double-blind placebo-controlled trial that sought to determine the effects of nesiritide, a recombinant B-type natriuretic peptide with vasodilating properties, in patients hospitalized with ADHF. Participants with clinical evidence for an acute coronary syndrome or baseline cardiac troponin >5x the upper reference limit, as measured by the local clinical laboratory, were excluded. The design and primary results of ASCEND-HF have been previously reported [16,17]. Of the 7,411 patients randomly assigned, 904 were enrolled in the biomarker sub-study. This is not a validation cohort, and overall the sub-study population is comparable to that of the ASCEND-HF study population (Supplemental Table 1). These subjects had serial venous blood sampling at baseline, 48–72 hours after therapy initiation, and at a 30-day follow-up visit [11,18]. Blood samples were collected in ethylenediaminetetraacetic acid–plasma, immediately centrifuged and stored at -80ºF for subsequent analysis at a core laboratory.

CARDIAC TROPONIN I MEASUREMENT. Circulating plasma cardiac troponin I levels were determined in 900 of these individuals with a novel highly sensitive Single Molecule Counting immunoassay technology which has been previously described[19]. Briefly, cTnI levels in 50 µl plasma samples were quantified using a plate-based sandwich immunoassay. At the completion of the assay, single molecules of detection antibody were counted on the Erenna® System (Singulex). The reporting range spanned 0.4–600 ng/nL, with inter-assay coefficient of variation ranging from 0–20% with a 99th percentile URL of 7.1 ng/L. Samples reporting results

>600 ng/L, were diluted 1:10 and retested to obtain a result within the assay reporting range. Circulating plasma cTnI was also measured with a contemporary 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.

CLINICAL ENDPOINTS. The co-primary endpoints from the ASCEND-HF trial were dyspnea improvement (via 7-point Likert scale) at 6 to 24 hours and the composite endpoint of death or recurrent heart failure hospitalization within 30 days of randomization. Death and worsening heart failure were assessed together as a composite secondary endpoint and all events were adjudicated through 180 days.

STATISTICAL ANALYSES. Baseline characteristics and clinical endpoints (for both placebo and nesiritide arms) were presented as mean ± standard deviation or median (interquartile range), where appropriate, for continuous variables and as count (percentage) for categorical variables. Right-skewed variables were transformed via log base 2 so that an increase in one unit represented adoubling of the variable values. The Jonckheere-Terpstra and Cochran-Armitage trend tests were used to assess the significance of a trend across increasing tertiles of cTnI for continuous and categorical variables, respectively. Two-sided p-values <0.05 were considered statistically significant. Circulating cTnI levels were compared between patients randomly assigned to placebo or nesiritide via the Wilcoxon rank sum test. In a hypothesis-generating analysis, multivariable predictors of baseline and percent change in cTnI levels (modeled as a spline functions for either an increase or decrease in cTnI from baseline) were determined via backwards elimination linear regression modelling from candidate variables collected which included demographic, clinical, and metabolic characteristics (Supplemental Table 1). In this

analysis, variables with P>0.1 were excluded from the model and P-values were bias-corrected from 500 bootstrapped samples. Kaplan-Meier failure estimates according to baseline cTnI tertile were compared by the Log-rank test. The association between cTnI and intermediate-term outcomes was performed via logistic regression analyses for death or worsening heart failure in the hospital, and 30-day death or hospitalization for worsening heart failure. The association of cTnI and the long-term outcome 180-day death was performed via Cox-proportional hazards models. The proportional hazards assumption was verified by determining if there were trends with time for the Schoenfeld residuals. Fractional polynomial curves were generated to demonstrate the continuous multivariable risk-adjusted probability of clinical outcomes across cTnI levels. For multivariable analyses, we adjusted for covariates that have been identified for the overall ASCEND-HF study population, as previously described [11,18]. Differences in 180-day death curves determined by the log-rank test. The discrimination (C-statistic) of the impact of cTnI levels on 180-day death was determined as previously described.[20] Category-free NRI and IDI were calculated for the addition of cTnI to the ASCEND-HF model.[21] All statistical analyses were performed using Stata software, version 13.1 (StataCorp LP, College Station, TX).

RESULTS

STUDY POPULATION. Of the 900 patients with baseline cTnI levels, 723 had cTnI levels drawn at 48-72 hours, and 599 had cTnI levels drawn at 30 days. The median circulating cTnI level at baseline was 16.4 (9.3, 31.6) ng/L. The median cTnI level at 48-72 hours was 14.1 (7.8, 29.7) ng/L and at 30 days was 11.6 (6.8, 22.5) ng/L. There were no patients below the lower limit of quantification at baseline or at 30-days, and except one patient (0.14%); no others at 48-72 hours were below the lower limit of quantification. Figure 1 illustrates the relationship of

measured cTnI by both the highly sensitive and standard sensitivity assays. Baseline characteristics stratified by baseline circulating cTnI levels of this substudy cohort are shown in Table 1. Higher circulating cTnI levels were associated with male sex, less prevalent white race, lower left ventricular ejection fraction (LVEF), and less prevalent diabetes mellitus. It was also associated with higher N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels, higher blood urea nitrogen (BUN) levels, and lower estimated glomerular filtration rate (eGFR).

SERIAL cTnI LEVELS. Table 2 demonstrates that there were no associations between nesiritide randomization and change in troponin level from either baseline to 48-72 hours or 30 days.

DEMOGRAPHIC, CLINICAL, AND METABOLIC PREDICTORS OF cTnI LEVELS. The complete results from backwards selection are shown in the table within Supplemental Table 1. Significant predictors of baseline cTnI included hs-CRP (P=0.049) and the LVEF above ≥40% (P=0.047), with the strongest associations with African American race (P=0.008), BUN (P=0.004), and NT-proBNP (P<0.001). Interestingly, there was a strong inverse association with diabetes (P=0.008). Significant predictors of increasing cTnI from baseline to 48-72 hours were age below 55 years (P=0.007), potassium (P=0.019), and body mass index >30 kg/m^2 (P=0.038). On the other hand, significant predictors of decreasing cTnI from baseline to 48-72 hours were baseline cTnI level (P<0.001), per 250 pg/mL NT-proBNP change from baseline to 48-72 hours (P<0.001), ischemic heart failure (P=0.004); cerebrovascular disease (P=0.006); NT-proBNP (P=0.015); and hs-CRP (P=0.015).

ASSOCIATION OF BASELINE AND FOLLOW-UP cTnI AND OUTCOMES. There were 42 (4.7%) deaths or worsening heart failure events by discharge. ,105 deaths or recurrent heart failure hospitalizations and by 30 days, and 106 deaths (11.9%) by 180 days. Cumulative event

rates for these two outcomes according to baseline cTnI are shown in Figure 2. All univariable and multivariable models for clinical outcomes are shown in Table 3. In univariable analyses, higher baseline, 48-72 hour, and 30-day log base 2-transformed cTnI was associated with all adverse clinical outcomes (P<0.01 for all) but not baseline log base 2-transformed cTnI and death/rehospitalization at 30 days (P=0.06). Baseline log base 2-transformed cTnI was associated with death or worsening heart failure prior to discharge (P=0.02) and with 180-day death (P=0.02) after multivariable adjustment for the variables in Model 1. However, baseline log base 2-transformed cTnI only remained associated with death or worsening heart failure prior to discharge after additional adjustment for NTproBNP (P=0.03). Log base 2-transformed cTnI at 48-72 hours and at 30-days was associated with all outcomes after multivariable adjustment for the variables in Model 1 (P<0.05 for all). However, with additional adjustment for NTproBNP, 48-72 hours log base 2-transformed cTnI only remained associated with death or worsening heart failure prior to discharge (P=0.001). The continuous, risk-adjusted (Model 2) curvilinear associations between log base 2-transformed cTnI at baseline and 48-72 hours and % change in cTnI from baseline to 48-72 hours with clinical outcomes is shown in Figure 3. While these curves depict an increase in risk with increasing log base 2-transformed cTnI when measured statically at baseline and 48-72 hours, the relative difference between the two values did not appear to have a relationship with any of the clinical outcomes.

In a separate analysis (Supplemental Table 3) in subjects in whom cTnI was measured by both the highly sensitive and standard sensitivity assays, the performance of the ASCEND-HF models with cTnI added was mildly improved. Both assays measured at the 3 time points performed comparably in terms of improvement in model fit, yet there was no added model discrimination (C-statistics) or integrated discrimination improvement. Only the highly sensitive

assay had significant net reclassification for death or rehospitalization by 30 days (NRI 36.3%, P=0.007) and death or worsening heart failure prior to discharge (NRI 45.6%, P=0.02). The prognostic relevance of the standard sensitivity cTnI assay in this biomarker substudy of ASCEND-HF has been previously published.[11]

DISCUSSION

This analysis from ASCEND-HF highlights several new insights regarding the utility of circulating cTnI levels in patients with ADHF. First, cTnI was detectable in all but one subject at all three time points, with the majority having levels >99% URL. Second, compared with placebo, nesiritide was not associated with changing cTnI levels. Third, only neurohormonal biomarkers (NTproBNP and BUN) and few demographic variables (African American Race and Diabetes) were significant predictors of cTnI level. Fourth, circulating cTnI levels were highly predictive of both short-term and long-term adverse events, but might not be incremental to more traditional ADHF markers of risk or hemodynamic stress. Interestingly, there appeared to be a time-dependency with the time-point of cTnI measurement (baseline, 48-72 hours, and 30 days) and the outcomes for which it was associated. In aggregate, these findings highlight that cTnI levels represent a spectrum of risk in heart failure with the possibility of risk-stratification at different time points. In particular, follow-up cTnI levels were more useful than baseline to establish prognosis – findings which oppose the current heart failure treatment guideline's emphasis on admission cTnI.[22]

Circulating cardiac troponin levels are rarely detectable in the general population, [23-26] but when in the measureable range they are associated with cardiac abnormalities and adverse outcomes. In patients with heart failure, however, circulating cardiac troponin levels are higher

and more frequently detectable. There is a litany of studies showing an increased risk for adverse outcomes with higher circulating cardiac troponin levels (measured by both standard and highly sensitive assays) in both acute and chronic heart failure.[2-10] While the precise reasons for this are unclear, higher cardiac troponin may indicative of progressive myocardial dysfunction with its release likely triggered by acute or chronic myocardial stress, sub-endocardial ischemia, or direct cardiomyocyte injury.[27]

In a marked contrast to a comparable analysis detecting cTnI by a contemporary, but less sensitive assay (LOD 0.012 ng/ml, which is 30x less sensitive) in the same ASCEND-HF population where cTnI was detectable in 78% of the population with 50% having cTnI levels above the 99% URL,[11] we found cTnI was detectable in virtually all patients by this more highly sensitive assay at all three time points (100%, 99.9%, and 100%, respectively) with the majority above the 99% URL (83%, 78%, and 73%, respectively) and the relationship between these two assays when measured together is shown in Figure 1. This striking difference is no doubt a result of a more highly sensitive cTnI assay and is relatively consistent with a prior analysis from RELAX-AHF, which suggested showed that cTnT measured by a highly sensitive assay was above the 99% URL in 90% of patients with acute heart failure.[12] Interestingly, neither cTnI assay improved risk stratification when added to other strong risk factors in the ASCEND-HF population. The implications of this in HF are twofold: 1) calling into question the clinical utility of measuring cTnI changes; and 2) that, if in the measurable range, cTn may have little interassay prognostic difference.

Regardless, this near-total prevalence of detectable circulating cTnI serves as a sobering reminder that hemodynamic stress from ADHF is associated alterations in cardiomyocyte homeostasis, even on the "ultra-small" scale; and that subtle differences in circulating cTnI, in

contrast to "positive" or "negative", may represent a spectrum of processes within the myocardium during decompensation or hemodynamic stress resulting in troponin release or turnover. In addition, the lack of association between cTnI levels and nesiritide supports the hypothesis that cTnI levels may change may be additionally mediated by non-hemodynamic variables and questions its utility as a surrogate for safety or efficacy for other therapies that do not directly impact cardiomyocytes.

Cardiac troponin release may be a result of the impact of several adverse pathological processes on the myocardium, but its changes during the treatment of ADHF are less well understood. Interestingly, our finding that both NT-proBNP and BUN are strong independent predictors of circulating cTnI levels suggests that both myocardial wall stress and neurohormonal activation may be related to troponin release. Natriuretic peptide elevation is a compensatory response to the direct effects of hemodynamic stress the myocardium and is a biochemical surrogate for elevated cardiac filling pressures;[28,29] and blood urea nitrogen is commonly recognized as surrogate for both glomerular and renal tubular function, but is closely correlated to neurohormonal activation such as the heightened renin-angiotensin-aldosterone-system activity in heart failure.[30] Decreasing cTnI during treatment is most closely associated impacted by baseline troponin release and is halted by a history of ischemic heart failure. However, the opposite directionality of NT-proBNP and decreasing cTnI suggests that cTnI levels are impacted from other non-hemodynamic factors.

There is a growing body of literature regarding the prognostic of circulating cTn levels in heart failure populations. With the transition from earlier studies analyzing cTn by standard sensitivity assays to the current more modern highly-sensitive assays in which cTn is nearly ubiquitously detectable, circulating cTn likely represents a spectrum or risk for heart failure

populations. This relationship is well represented in Figure 3, as there is a graded increase in adjusted risk for all outcomes for increasing cTnI levels. Unlike prior analyses that have shown higher risk for increasing troponin levels in patients with ADHF, [12,31,32] we found no consistent association with changing cTnI levels and outcomes. Although, the shape of curves suggests higher risk for both a decrease in cTnI or increase in cTnI for 30-day adverse outcomes, perhaps identifying a risk in intermediate events with cTnI level lability. While there was no association with changing cTnI levels and nesiritide usage, cTn levels may be mediated by other therapies such as seralaxin.[32]

STUDY LIMITATIONS. The results of this study must be interpreted in light of various limitations inherent to its design. First, this analysis was *post-hoc,* which renders these findings hypothesis generating. Second, w*e* cannot exclude selection bias for patients whom agreed to participate in the ASCEND-HF trial. Although, the baseline clinical characteristics (Table 1) of this cohort are representative of contemporary populations hospitalized with ADHF with the majority on guideline directed medical therapies and presenting with marked NT-proBNP elevation. Third, even though nesiritide use was not associated with changes in circulating cTnI levels, the impact of other therapies on cTnI or whether they modified the prognostic effect of cTnI on clinical outcomes remains unclear. Regardless, with carefully adjudicated outcomes and cTnI measured in a core laboratory, our analysis suggests that circulating cTnI levels are independently prognostic in ADHF and, even when detected at low levels by this highly sensitive assay, are associated with a spectrum of risk. We also acknowledge that prospective studies in both ADHF and chronic heart failure (and by LVEF), within a multi-marker setting, are necessary to establish the clinical importance of cTn measured by highly sensitive assays.

CONCLUSIONS

In our study cohort, circulating cTnI measured at baseline, during hospitalization, and at 30-days was associated with adverse clinical outcomes in ADHF, but may not be incremental to more traditional predictors of risk. Interestingly, after additional adjustment for NT-proBNP, higher circulating cTnI was more closely associated with death or worsening heart failure prior to discharge in comparison to outcomes occurring more remotely from discharge. Unlike prior reports, these findings question the implications of changing cTnI levels in ADHF.

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Table 1. Baseline characteristics

	cTnI [ng/L]				
	Total	**Tertile 1, < 11.3**	**Tertile 2, 11.3 - 24.0**	**Tertile 3, > 24.0**	***P-value**
	(N=900)	**(N=300)**	**(N=300)**	**(N=300)**	
Age [years]	65.6 +/- 15.1	64.8 +/- 15.6	66.4 +/- 14.3	65.7 +/- 15.4	0.53
Sex (female, %)	284 (31.6)	125 (41.7)	85 (28.3)	74 (24.7)	<.001
Race (white, %)	610 (67.8)	212 (70.7)	209 (69.7)	189 (63.0)	0.045
BMI [kg/m²]	32.0 +/- 8.8	32.8 +/- 9.0	31.0 +/- 7.6	32.1 +/- 9.7	0.31
LVEF [%]	30.7 +/- 15.4	33.6 +/- 17.0	28.6 +/- 14.4	29.9 +/- 14.4	0.006
NYHA Classification					
I	33 (5.0)	10 (4.5)	13 (6.2)	10 (4.4)	
II	147 (22.3)	47 (21.1)	45 (21.4)	55 (24.4)	
III	318 (48.3)	113 (50.7)	97 (46.2)	108 (48.0)	
IV	160 (24.3)	53 (23.8)	55 (26.2)	52 (23.1)	
Diabetes Mellitus	414 (46.0)	143 (47.7)	156 (52.0)	115 (38.3)	0.022
Hypertension	704 (78.2)	234 (78.0)	241 (80.3)	229 (76.3)	0.62
Ischemic Heart Failure	540 (60.0)	172 (57.3)	190 (63.3)	178 (59.3)	0.62
Beta-Blockers	676 (75.1)	228 (76.0)	233 (77.7)	215 (71.7)	0.22
ACEI or ARB	579 (64.3)	193 (64.3)	193 (64.3)	193 (64.3)	1
MRA	219 (24.3)	77 (25.7)	76 (25.3)	66 (22.0)	0.30
Time-to-randomization [hours]	16.4 +/- 9.4	16.9 +/- 9.2	16.2 +/- 10.3	16.0 +/-8.6	0.29
NT-proBNP [pg/mL]	5791 (2986-11579)	4073 (2144-7444)	7499 (3498-12920)	7582 (3583-12984)	<.001
BUN [mmol/L]	10.3 +/- 6.1	8.8 +/- 5.0	10.6 +/- 6.0	11.4 +/- 6.9	<.001
eGFR [mL/min/1.73m²]	59.8 +/- 24.5	64.8 +/- 24.9	56.5 +/- 23.2	58.0 +/- 24.8	0.001
Hemoglobin [g/dL]	12.6 +/- 4.9	12.9 +/- 1.8	12.5 +/- 2.0	12.6 +/- 1.9	0.45
Sodium [mmol/L]	138.5 +/- 3.9	138.1 +/- 4.1	138.6 +/- 3.8	138.9 +/- 3.9	0.011
*p-value for trend					

Table 2. Effect of Nesiritide Therapy on Serial Changes in cTnI Levels*

cTnI Levels [ng/L]	Placebo (N=450)	Nesiritide (N=450)	P-value
Baseline	15.9 (8.7, 29.2)	16.9 (9.5, 34.1)	0.39
Actual change from baseline to 48–72 hours	-2.1 (-7.1, 1.1)	-1.7 (-6.9, 1.0)	0.78
Actual change from baseline to 30 days	-2.3 (-11.1, 1.9)	-2.2 (-10.0, 1.6)	0.65
Relative change from baseline to 48–72 hours [%]	-18.4 (-40.2, 11.3)	-15.2 (-34.9, 8.9)	0.60
Relative change from baseline to 30 days [%]	-22.2 (-52.2, 16.0)	-18.2 (-49.6, 19.2)	0.46
*Variables expressed as median (Q1-Q3)			

Table 3. cTnI Levels and in-hospital-, intermediate-, and long-term outcomes

Endpoint	*Unadjusted			*Adjusted Model 1			*Adjusted Model 2		
	†OR/HR	95% CI	P-Value	†OR/HR	95% CI	P-value	†OR/HR	95% CI	P-value
Baseline cTnI Level									
Death or worsening heart failure prior to discharge	1.28	1.09-1.50	0.003	1.26	1.04-1.52	0.02	1.25	1.02-1.55	0.03
Death or HF hospitalization at 30 Days	1.12	0.997-1.27	0.06	1.07	0.94-1.22	0.30	1.07	0.93-1.22	0.37
Death at 180 days	1.18	1.06-1.31	0.002	1.14	1.02-1.26	0.02	1.09	0.97-1.22	0.16
48-72 Hour cTnI Level									
Death or worsening heart failure prior to discharge	1.42	1.20-1.67	<.001	1.42	1.17-1.73	0.001	1.43	1.17-1.75	0.001
Death or HF hospitalization at 30 Days	1.20	1.06-1.35	0.003	1.14	1.004-1.30	0.04	1.12	0.98-1.28	0.08
Death at 180 days	1.17	1.05-1.31	0.006	1.16	1.03-1.31	0.02	1.11	0.97-1.26	0.14
30 day cTnI Level									
Death at 180 days	1.23	1.08-1.40	0.001	1.29	1.11-1.50	0.001	1.25	1.06-1.47	0.007
*Unadjusted: only natural log base 2-transformed cTnI; Adjusted Model 1 = log base 2-transformed cTnI adjusted with covariates derived from the original ASCEND-HF population; andAdjusted Model 2 = log base 2 -transformed cTnI adjusted with covariates derived from the original ASCEND-HF population including natural log base 2-transformed NT-proBNP. †Cox proportional hazards models (HRs) determined the association between log base 2-transformed cTnI and death at 180 days while logistic regression									

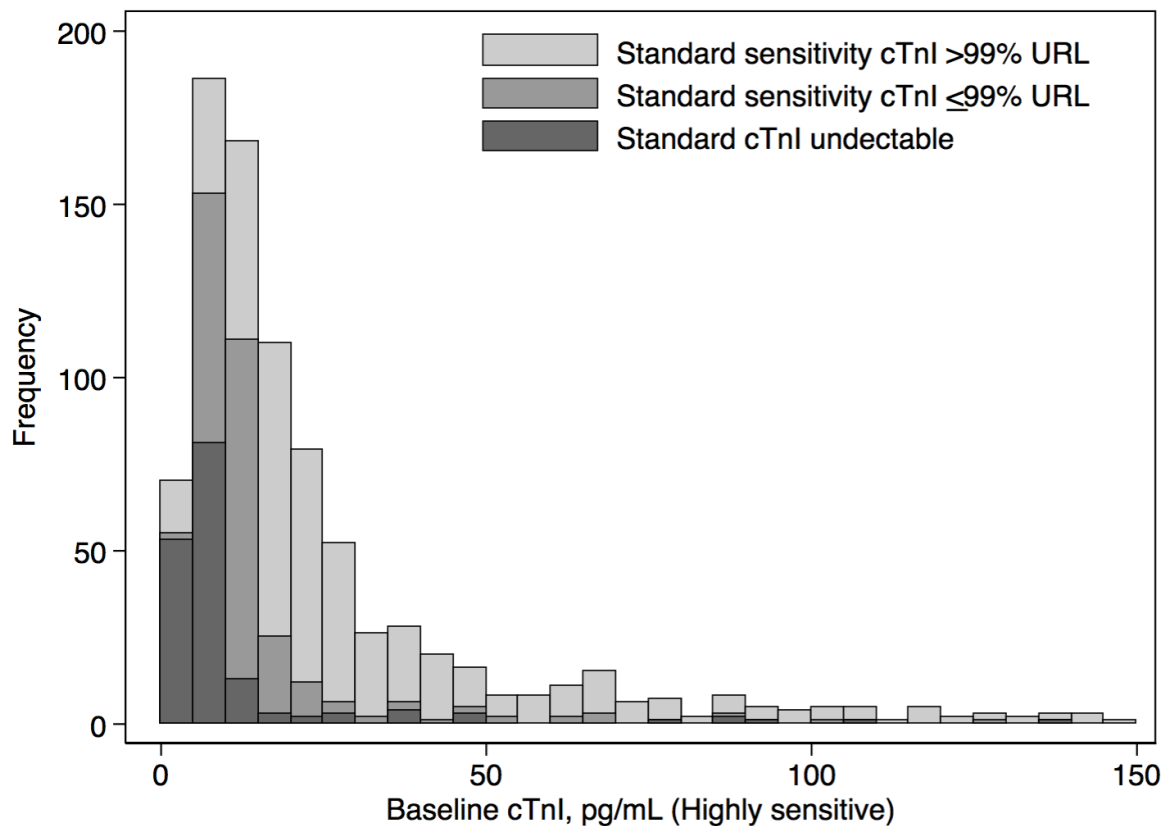models (ORs) were used for all other outcomes.

Figure 1.

Title: Distribution of cardiac troponin I levels measured by the highly sensitive assay.

Caption: All values are > the lower limit of quantification (<0.04 ng/L) for the highly sensitive cardiac troponin I assay. For the cardiac troponin I levels measured by the standard assay; 170 (21.5%) subjects were undetectable (<0.012 ng/mL); 225 (28.1%) subjects were detectable, but below the 99th percentile URL (≥0.012 ng/mL to ≤0.034 ng/mL); and 396 (50.1%) subjects were above the 99th percentile URL (>0.034 ng/mL). URL, upper reference limit.
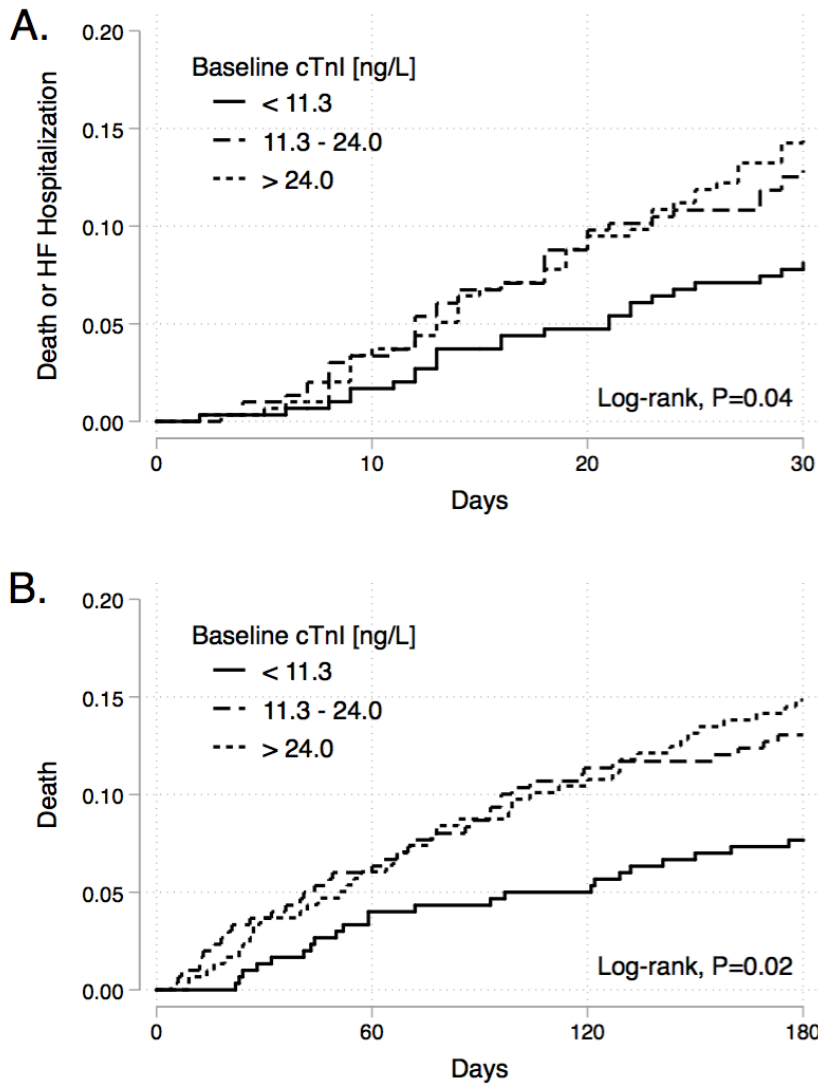
Figure 2.

Title: Kaplan-Meier estimates of intermediate- and long-term outcomes according to baseline

cTnI tertile

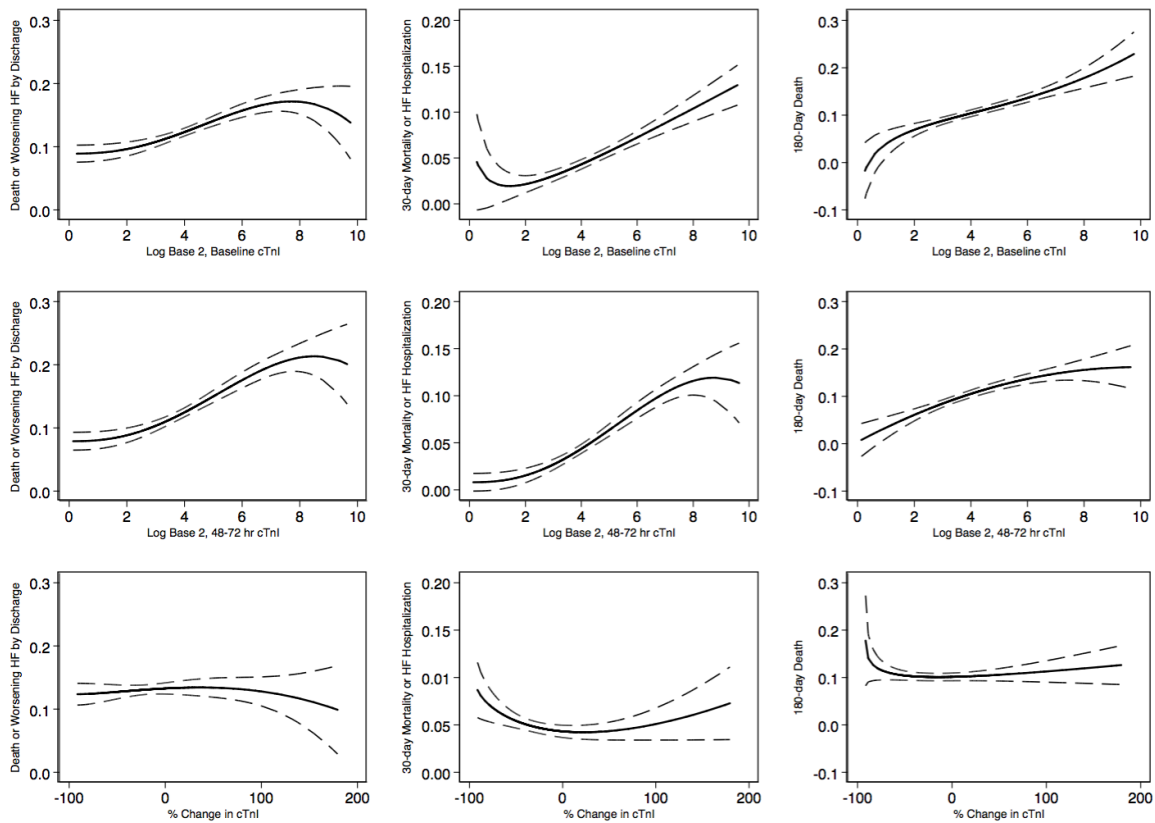Caption: A) 30-day death or HF hospitalization and B) 180-day death.

Figure 3.

Title: The risk-adjusted, continuous probability of death or worsening HF by discharge, 30-day death or HF hospitalization, and 180-day death for baseline cTnI, 48-72 hour cTnI, and percent change in cTnI from baseline to 48-72 hours.

Caption: All models are risk-adjusted with covariates derived from the original ASCEND-HF population with the addition of NT-proBNP. The vertical axes represent predicted probabilities. For the baseline and 48-72 hour cTnI, the horizontal axes represent log base 2-transformed values (every doubling).