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ORIGINAL RESEARCH

Significance of an Early Repeat Troponin Measurement Upon Presentation to the Hospital for Acute Heart Failure

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BACKGROUND: Higher cardiac troponin is associated with worse outcomes in patients with acute heart failure. The significance of repeat measurements over hours remains unclear. We assessed whether a repeat measurement and the Δ between measurements of high-sensitivity cardiac troponin I (hs-cTnI) were associated with outcomes in hypervolemic patients with acute heart failure without acute coronary syndrome.

METHODS AND RESULTS: We analyzed 582 individuals from AKINESIS (Acute Kidney Injury Neutrophil Gelatinase-Associated Lipocalin Evaluation of Symptomatic Heart Failure Study) with hs-cTnI measured ≤12 hours from admission and repeated ≤6 hours thereafter. Associations between hs-cTnI levels and their Δ with short-term (death, intensive care unit admission, receipt of inotropes, or positive pressure ventilation during hospitalization) and long-term (death or heart failure readmission within 1 year) outcomes were assessed. The average age was 69±13 years, 62% were men, 65% were White, 46% had coronary artery disease, and 22% had chest pain. Median hs-cTnI levels were 27 (interquartile range [IQR], 13–62) ng/L initially and 28 (IQR, 14–68) ng/L subsequently, with a Δ of 0 [IQR, −2 to 4] ng/L over 3.4±1 hours. Only the second measurement was associated with short-term outcomes (odds ratio, 1.14 per 2-fold higher [95% CI, 1.02–1.28]). Both individual measurements and the Δ were associated with long-term outcomes (hazard ratios, 1.09, 1.12, and 1.16 for first, second, and Δ, respectively). Associated risk for the first and second measurements were not constant over the year but highest early after being measured and decreased over 1 year.

CONCLUSIONS: Repeat measurements of hs-cTnI over hours can identify individuals with acute heart failure without acute coronary syndrome at risk for short- and long-term outcomes.

Key Words: acute heart failure ■ myocardial injury ■ prognosis ■ troponin

Repeated measurements of cardiac troponin (cTn) are often performed in individuals presenting to the hospital with acute heart failure (AHF) to evaluate for an acute coronary syndrome (ACS) provoking AHF.[1–4] However, cTn levels are frequently elevated in individuals with hypervolemic AHF without ACS due to diverse pathologic mechanisms such as supply–demand mismatch, stress, inflammation, and neurohormonal activation, all contributing to myocardial injury.[4–6] Unlike ACS, where cTn levels have a typical rise and fall, cTn levels may vary in hypervolemic AHF without ACS based on the mechanism of injury, the severity

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CLINICAL PERSPECTIVE

What Is New?

- Repeat measurements of cardiac troponin are frequently elevated within the first hours of a presentation for hypervolemic acute heart failure without acute coronary syndrome. However, the prognostic value of each repeat measurement and their Δ for outcomes is uncertain.
- We found higher levels of both measurements of high-sensitivity cardiac troponin I and their Δ were associated with risk of in-hospital events and death or heart failure readmission at 1 year, with the second measurement and Δ more prognostic for outcomes compared with the initial measurement.

What Are the Clinical Implications?

- Clinicians should consider the prognostic implications of cardiac troponin levels and their Δ in patients presenting with hypervolemic acute heart failure without acute coronary syndrome.

Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
AKINESIS	Acute Kidney Injury Neutrophil Gelatinase-Associated Lipocalin Evaluation of Symptomatic Heart Failure Study
cTn	cardiac troponin

of decompensation, or the response to therapeutic interventions. Higher isolated cTn measurements upon presentation for AHF are associated with a greater risk for adverse outcomes including longer length of stay, higher odds of worsening heart failure (HF), higher risk of HF readmission, and greater risk of death, but a single measurement of cTn may incompletely capture AHF severity.[7–10]

Studies have shown serial measurements of cTn are associated with risk of death and HF readmission, although measurements were performed over several days of hospitalization.[11,12] Waiting for days to measure cTn may delay the identification of high-risk patients who are rapidly deteriorating, missing an opportunity for early intervention to mitigate risk. Repeating measurements of cTn within the initial hours of presentation for AHF, as routinely done for ACS, may identify individuals with more severe AHF at greater risk for adverse outcomes during the hospitalization and postdischarge.

In this study, we aimed to determine if either of 2 consecutive measurements of high-sensitivity cardiac troponin I (hs-cTnI) and the Δ between measurements was associated with short- and long-term outcomes in patients presenting with hypervolemic AHF without ACS in AKINESIS (Acute Kidney Injury Neutrophil Gelatinase-Associated Lipocalin Evaluation of Symptomatic Heart Failure Study). We hypothesized that later measurements of hs-cTnI would have additional prognostic value beyond the initial hs-cTnI measurement.

METHODS

Study Population

The original study design of AKINESIS has been described previously.[13] Briefly, AKINESIS was an observational study designed to evaluate novel biomarkers of cardiorenal syndrome in patients hospitalized with AHF. AKINESIS enrolled 927 participants at 16 sites in the United States and Europe from January 2011 through September 2013. Patients were enrolled if they had findings consistent with AHF and had received or planned to receive intravenous diuretic therapy. Individuals with ACS were excluded. Presence of ACS was determined by the treating physician using the local institution's protocol and troponin assay. Additionally, final hospital diagnoses were collected, and none of the individuals in the analytic cohort had a diagnosis of ACS. Other exclusion criteria were dialysis dependence or planned initiation during the hospitalization, organ transplantation, enrollment in a drug treatment study within the past 30 days or prior enrollment in AKINESIS, and pregnant or vulnerable populations determined by the institutional review board. The study was approved by the institutional review boards at each site, and each participant gave consent. Data necessary for reproduction of analyses in this study will be made available upon reasonable request after review by study investigators.

The AKINESIS protocol collected 2 sequential blood specimens on the day of hospital presentation. The first specimen was collected within 2 hours of loop diuretic administration, and the second specimen was collected 2 to 6 hours after the first specimen. Of the 927 participants, 296 were missing a specimen, lacked information on collection time, or lacked follow-up data, leaving 631 participants.

We further narrowed the analytic cohort based on (1) the time between hospital presentation and the first specimen collection and (2) the time between the first and second specimen collection. Our primary analytic cohort consisted of 582 individuals who had the initial collection ≤12 hours from hospital presentation and the second collection ≤6 hours thereafter (Figure S1).

We chose this as our primary analytic cohort, because these times reflect real-world timing for evaluation of patients presenting with AHF. We performed sensitivity analyses in the complete cohort (n=631) and in individuals with the initial collection ≤6 hours from hospital presentation and second collection ≤6 hours thereafter (n=555).

Biomarker Measurements

hs-cTnI was measured from blood specimens stored at −80 °C at the core laboratory at the University of College Dublin Clinical Research Center. All specimens were consecutively measured once using the ARCHITECT platform (Abbott Laboratories, Lake Forest, IL). This assay has a lower limit of detection of 1.1 to 1.9 ng/L and <10% coefficient of variation.

Outcomes

We assessed the association between the first and second hs-cTnI measurements, and the Δ between measurements, with composite short- and long-term outcomes. The short-term outcome consisted of in-hospital events including death, admission to the intensive care unit, receipt of inotropes, or receipt of positive pressure ventilation. The long-term outcome was death or HF readmission within 1 year.

Statistical Analysis

Baseline characteristics are presented as mean±SD for normally distributed variables, median and interquartile range (IQR) for nonnormally distributed variables, and counts and percentages for categorical variables. We compared differences in baseline characteristics between individuals with and without the outcomes using the Student *t*-test or Mann-Whitney *U* test for continuous variables and χ^2 test or Fisher exact test for categorical variables, as appropriate.

The distribution of the first and second hs-cTnI measurements were right skewed and log base 2 transformed to achieve a more normal distribution. Associations of $\log_2$ hs-cTnI can be interpreted as per 2-fold change. Change in hs-cTnI was normally distributed but with fat tails, resulting in a wide SD but small Δ between the first (−2 ng/L) and third (4 ng/L) quartiles. Therefore, we analyzed the Δ hs-cTnI per SD as a continuous variable and by quartiles. We also evaluated the first and second hs-cTnI measurements by quartiles to evaluate nonlinear associations. Lastly, we modeled the hs-cTnI measurements as restricted cubic splines, selecting between 3 and 5 knots based on the model with lowest Akaike information criterion and tested the significance of the spline term.

The association of hs-cTnI with the short-term outcome was assessed with logistic regression using robust variance estimators in sequential models. In Model 1, the first and second measurements were unadjusted, whereas the Δ was adjusted for time between specimens as an offset variable. Model 2 additionally adjusted for age, sex, race, body mass index, admission systolic blood pressure, admission sodium, estimated glomerular filtration rate, and hemoglobin; presence of jugular venous distension and edema; and history of coronary artery disease (CAD), hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and loop diuretic use before admission. These variables were selected based on prior literature and their association with the outcomes (Table S1).[14–20] When 2 correlated and potentially collinear variables were both associated with the outcomes, such as diastolic blood pressure and systolic blood pressure, we only chose 1 of the variables. Model 3 additionally adjusted for admission B-type natriuretic peptide. Model assumptions were tested, and no significant deviations were found. Because some covariates were missing in up to 10% of data at random, we performed multiple imputations by chained equations with a total of 10 imputations using all of the variables from the fully adjusted model. Estimates were combined using the Rubin rule to account for variability in the imputation procedure.[21]

The association of hs-cTnI measurements with the long-term outcome were assessed with Cox regression using robust variance estimators in the same sequential models as logistic regression. Review of Schoenfeld residual plots for the first and second hs-cTnI measurements showed a violation of proportional hazards, revealing a nonconstant hazard that declined over the year of follow-up. Proportional hazards were not violated for Δ hs-cTnI. Thus, we reported the average hazard ratio (HR) over the year of follow-up and calculated time-dependent HRs over 91-day intervals for the first and second hs-cTnI measurements.

Although ACS was an exclusion criterion for AKINESIS, individuals with ACS may have still been included. To account for this, we evaluated the interaction between hs-cTnI and history of CAD (continuous hs-cTnI*CAD) and the presence of chest pain on presentation (continuous hs-cTnI*chest pain). We conducted sensitivity analyses in the whole cohort and the cohort with a more restrictive time from presentation for inclusion, as described.

Lastly, we evaluated the predictive ability of each measurement of hs-cTnI for the short- and long-term outcomes by assessing the area under the receiver operating characteristic curve (AUC). AUCs for the biomarkers alone and added to the fully adjusted model were assessed.

All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing,

Vienna, Austria). A *P* value <0.05 was considered statistically significant for all analyses.

RESULTS

Primary Cohort Baseline Characteristics

Compared with the 345 individuals excluded, the primary analytic cohort was significantly older, less often had hyperlipidemia, more often received β-blockers before presentation, less often had symptoms of chest pain, and had a lower hemoglobin on hospital presentation (Table S2). Among the 582 individuals included, the average age was 69±13 years, 62% were men, 65% were White, 46% had CAD, and 22% had chest pain (Table 1). The median value of the first hs-cTnI measurement was 27 (IQR, 13–62) ng/L and 28 (IQR, 14–68) ng/L for the second measurement. The average Δ between measurements was 35±329 ng/L with a median Δ of 0 (IQR, –2 to 4) ng/L and an average of 3.4±1 hours between measurements (Table 1, Figure S2).

Association of hs-cTnI With the Short-Term Outcome

There were 139 individuals who had the short-term outcome including 19 deaths, 85 intensive care unit admissions, 54 receiving inotropes, and 49 receiving positive pressure ventilation. Compared with individuals without the short-term outcome, those who experienced it were more frequently White, had lower admission systolic blood pressure, more likely had chronic kidney disease, less often had edema, had lower admission serum sodium and estimated glomerular filtration rate, had higher serum creatinine and B-type natriuretic peptide, and received a higher initial dose of loop diuretic (Table 1). Additionally, those with the short-term outcome had significantly higher values for both the first and second hs-cTnI measurement and a significant increase between measurements (Table 1). The second hs-cTnI was obtained 3.3 hours after the initial collection in individuals without the short-term outcome and 3.7 hours in those with the short-term outcome, a difference of 0.4 hours that was statistically significant (Table 1).

The first hs-cTnI measurement was associated with 17% higher odds of having the short-term outcome in unadjusted analysis, but this attenuated and was no longer significant in the fully adjusted model (odds ratio [OR], 1.12 [95% CI, 0.99–1.27]; Table 2). When modeled as a spline, the spline term was not significant (*P*=0.505, Figure 1A). Quartiles showed a linear increase in risk with higher quartiles of hs-cTnI (Table 2). There was no difference in the association for individuals with chest pain (*P*-interaction=0.209), but there was a significant difference for those with CAD (*P*-interaction=0.042). Individuals without CAD had 29% higher odds for the short-term outcome (OR, 1.29 [95% CI, 1.08–1.54]), whereas there was no association in individuals with CAD (OR, 1.01 [95% CI, 0.83–1.22]).

The second hs-cTnI measurement was associated with 18% higher odds of the short-term outcome in unadjusted analysis, which attenuated but remained significantly associated in the fully adjusted model (OR, 1.14 [95% CI, 1.02–1.28]; Table 2). When modeled as a spline, the spline term was not significant (*P*=0.170, Figure 1B). Quartiles showed a linear increase in risk with higher quartiles of hs-cTnI (Table 2). Associations were not different in individuals with chest pain (*P*-interaction=0.634) or CAD (*P*-interaction=0.191).

On a continuous scale, Δ hs-cTnI was not associated with the short-term outcome (Table 2). When modeled as a spline, the spline term was significant (*P*=0.013), and the spline plot showed that risk was flat but increased, with the greatest increases in hs-cTnI (Figure 1C). Similarly, quartile analysis showed that Δ hs-cTnI was not associated with the short-term outcome in the first 3 quartiles, but individuals in the fourth quartile had higher odds of the short-term outcome, although this did not reach statistical significance (OR, 1.75 [95% CI, 0.96–3.18]; Table 2). Associations were not different in individuals with chest pain (*P*-interaction=0.863) or CAD (*P*-interaction=0.893).

When biomarkers were evaluated by AUCs, Δ hs-cTnI had the highest AUC both alone (AUC, 0.63 [95% CI, 0.58–0.68]; Table 3) and when added to the clinical model (AUC, 0.72 [95% CI, 0.67–77]). This was higher than the AUC of the clinical model alone (AUC, 0.69 [95% CI, 0.64–0.74]). Findings were similar in the alternative analytic cohorts (Tables S3–S5).

Association of hs-cTnI With Death or HF Readmission Within 1 Year

There were 186 individuals who had the long-term outcome including 74 deaths alone, 88 HF readmissions alone, and 24 who had an HF readmission and subsequently died. Compared with individuals without the long-term outcome, those who had the long-term outcome were older, had lower admission body mass index, systolic blood pressure, and diastolic blood pressure; more often had CAD, coronary artery bypass grafting, chronic kidney disease, and COPD; less often had hypertension; more often had jugular venous distension; were more often on loop diuretics before admission; had lower admission hemoglobin and estimated glomerular filtration rate; and had higher admission B-type natriuretic peptide (Table 1). Those who experienced the long-term outcome had significantly higher hs-cTnI measurements at both the first and second measurement times, with a significant increase between measurements (Table 1). The second hs-cTnI

Table 1. Baseline Characteristics in the 582 Participants With hs-cTnI Measured ≤12 Hours From Presentation and Repeated ≤6 Hours Later in hs-cTnI in Individuals With and Without Short- and Long-Term Outcomes in AKINESIS

	All	In-hospital events			Death or heart failure hospitalization		
Characteristic	n=582	Without, n=443	With, n=139	*P* value	Without, n=396	With, n=186	*P* value
Age, y, mean±SD	69±13	69±14	71±12	0.076	68±13	72±13	<0.001
Men, % (n)	62% (359)	60% (265)	67% (94)	0.120	62% (245)	61% (114)	0.834
White, % (n)	65% (377)	62% (273)	74% (104)	0.009	63% (247)	70% (130)	0.124
BMI, mean±SD	31.5±8.9	31.9±9.0	30.2±8.5	0.058	32.4±9.4	29.7±7.5	0.001
SBP, mm Hg, mean±SD	131±30	143±29	134±32	0.002	146±30	131±28	<0.001
DBP, mm Hg, mean±SD	81±20	81±19	78±21	0.091	84±20	75±16	<0.001
CAD, % (n)	46% (268)	44% (197)	51% (71)	0.196	42% (165)	55% (103)	0.002
PCI, % (n)	22% (128)	21% (91)	26% (37)	0.142	21% (84)	24% (44)	0.528
CABG, % (n)	17% (98)	15% (67)	22% (31)	0.053	13% (50)	26% (48)	<0.001
Stroke, % (n)	13% (78)	15% (65)	9% (13)	0.103	13% (51)	14% (27)	0.606
PAD, % (n)	3% (20)	4% (16)	3% (4)	0.785	4% (16)	2% (4)	0.520
Hypertension, % (n)	81% (473)	83% (366)	76% (107)	0.103	84% (331)	76% (142)	0.028
Diabetes, % (n)	43% (250)	42% (186)	46% (64)	0.437	43% (170)	43% (80)	0.973
COPD, % (n)	26% (150)	26% (113)	26% (37)	0.828	22% (89)	33% (61)	0.009
Hyperlipidemia, % (n)	50% (289)	48% (218)	51% (71)	0.756	49% (193)	51% (96)	0.558
Atrial fibrillation, % (n)	28% (165)	28% (125)	29% (40)	0.935	29% (114)	27% (51)	0.705
Illicit drug use, % (n)	1% (7)	1% (6)	1% (1)	0.524	1% (5)	1% (2)	0.847
Tobacco use, % (n)	15% (87)	14% (64)	16% (23)	0.566	15% (59)	15% (28)	0.981
Anemia, % (n)	22% (130)	21% (91)	28% (39)	0.070	20% (80)	27% (50)	0.077
CKD, % (n)	24% (141)	22% (98)	31% (43)	0.038	19% (75)	35% (66)	<0.001
Chest pain on admission, % (n)	22% (128)	23% (100)	20% (28)	0.521	25% (98)	16% (30)	0.018
Orthopnea present, % (n)	65% (377)	65% (290)	62% (87)	0.473	62% (246)	70% (131)	0.061
JVD present, % (n)	26% (151)	25% (110)	29% (41)	0.294	23% (90)	33% (61)	0.011
Edema present, % (n)	74% (431)	77% (339)	67% (92)	0.011	74% (293)	74% (138)	0.961
Loop diuretics, % (n)	73% (423)	74% (330)	66% (93)	0.062	70% (276)	79% (147)	0.024
ACE-I/ARB, % (n)	62% (364)	64% (285)	56% (79)	0.092	64% (252)	60% (112)	0.388
β-Blocker, % (n)	73% (427)	74% (327)	71% (100)	0.578	72% (286)	75% (141)	0.418
Hemoglobin, g/dL, mean±SD	11.4±2.5	11.5±2.4	11.2±2.7	0.128	11.7±2.4	11.0±2.5	0.002
Serum sodium, mEq/L, mean±SD	138±7	139±4	136±13	<0.001	138±8	138±5	0.895
Serum creatinine, mg/dL, mean±SD	1.42±0.82	1.37±0.80	1.57±0.88	0.009	1.37±0.84	1.51±0.76	0.053
eGFR, mL/min per 1.73 m^2, mean±SD	60±25	61±25	55±26	0.011	63±25	54±25	<0.001
BNP, pg/mL, median [IQR]	580 [229–1118]	520 [211–1089]	712 [299–1268]	0.011	456 [203–1011]	797 [318–1334]	<0.001
First hs-cTnI, ng/L, median [IQR]	27 [13–62]	24 [13–55]	34 [18–84]	<0.001	24 [12–56]	33 [17–74]	0.002
Second hs-cTnI, ng/L, median [IQR]	28 [14–68]	26 [13–60]	35 [21–90]	<0.001	25 [13–63]	35 [18–77]	0.001
Time between hs-cTnI, h, mean±SD	3.4±1.0	3.3±1.0	3.7±0.8	<0.001	3.4±0.9	3.5±1.0	0.269
LVEF, mean±SD	40±18	41±17	38±18	0.186	41±18	38±17	0.282
Dose furosemide, mg, median [IQR]	40 [40–80]	40 [40–60]	40 [40–80]	0.031	40 [40–60]	40 [40–80]	0.557

ACE-I indicates angiotensin-converting enzyme inhibitor; AKINESIS, Acute Kidney Injury Neutrophil Gelatinase-Associated Lipocalin Evaluation of Symptomatic Heart Failure Study; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure, eGFR, estimated glomerular filtration rate; hs-cTnI, high-sensitivity cardiac troponin I; IQR, interquartile range; JVD, jugular venous distension; LVEF, left ventricular ejection fraction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; and SBP, systolic blood pressure.

Table 2. Association of Repeat hs-cTnI Measurements and the Δ Between Measurements With In-Hospital Events

hs-cTnI measurement	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
First hs-cTnI			
Per 2-fold higher	1.17 (1.05 to 1.30)	1.15 (1.01 to 1.30)	1.12 (0.99 to 1.27)
Q1 (0 to 13 ng/L)	Reference	Reference	Reference
Q2 (13 to 27 ng/L)	1.19 (0.66 to 2.16)	1.12 (0.60 to 2.09)	1.04 (0.56 to 1.96)
Q3 (27 to 62 ng/L)	1.67 (0.95 to 2.93)	1.56 (0.84 to 2.89)	1.40 (0.74 to 2.65)
Q4 (62 to 8330 ng/L)	2.16 (1.24 to 3.75)	1.98 (1.07 to 3.67)	1.72 (0.90 to 3.29)
P-trend quartiles	0.003	0.014	0.059
Second hs-cTnI			
Per 2-fold higher	1.18 (1.08 to 1.29)	1.17 (10.5 to 1.30)	1.14 (1.02 to 1.28)
Q1 (0 to 14 ng/L)	Reference	Reference	Reference
Q2 (14 to 28 ng/L)	2.33 (1.26 to 4.29)	2.43 (1.29 to 4.58)	2.27 (1.19 to 4.33)
Q3 (28 to 66 ng/L)	2.31 (1.25 to 4.27)	2.11 (1.09 to 4.09)	1.93 (0.96 to 3.84)
Q4 (66 to 6843 ng/L)	3.01 (1.65 to 5.49)	2.96 (1.54 to 5.71)	2.64 (1.31 to 5.29)
P-trend quartiles	0.001	0.003	0.015
Δ Between			
Per SD	1.08 (0.85 to 1.36)	1.04 (0.79 to 1.35)	1.03 (0.80 to 1.34)
Q1 (–1488 to –2 ng/L)	Reference	Reference	Reference
Q2 (–2 to 0 ng/L)	0.68 (0.37 to 1.23)	0.66 (0.35 to 1.24)	0.71 (0.37 to 1.36)
Q3 (0 to 4 ng/L)	1.11 (0.64 to 1.91)	1.03 (0.57 to 1.87)	1.07 (0.59 to 1.94)
Q4 (4 to 4656 ng/L)	1.78 (1.05 to 3.02)	1.75 (0.97 to 3.17)	1.75 (0.96 to 3.18)
P-trend quartiles	0.012	0.026	0.032

Model 1: unadjusted for first and second troponin measurements. Δ hs-cTnI was adjusted for time between measurements as an offset variable. Model 2: Model 1+age, sex, race, body mass index, admission systolic blood pressure, estimated glomerular filtration rate, admission hemoglobin, admission serum sodium, presence of coronary artery disease, chronic kidney disease, diabetes, hypertension, chronic obstructive pulmonary disease, presence of jugular venous distension, presence of edema, and loop diuretic use before admission. Model 3: Model 2+admission B-type natriuretic peptide. hs-cTnI indicates high-sensitivity cardiac troponin I; OR, odds ratio; and Q, quartile.

was collected at 3.4 hours after the first collection in individuals without the long-term outcome and 3.5 hours in those with the long-term outcome (Table 1).

The first hs-cTnI measurement was associated with a 12% higher risk of death or HF readmission within 1 year in unadjusted analysis, which attenuated but remained significant in the fully adjusted model (HR, 1.09 [95% CI, 1.01–1.19]; Table 4). When evaluated as time-dependent HRs, the risk for death or HF readmission was highest during the first 91 days and decreased in subsequent time periods, with no associated risk after 182 days (Table S6). When modeled as a spline, the spline term was significant (*P*=0.049), and the spline plot showed that risk increased with higher values of hs-cTnI but leveled off at the highest values (Figure 2A). Quartile analysis similarly showed this pattern, with risk increasing from the first to the third quartile but showing similar risk estimates for the third and fourth quartiles (Table 4). Associations were not different in individuals with chest pain (*P*-interaction=0.953) or CAD (*P*-interaction=0.549).

The second hs-cTnI measurement was associated with a 13% higher risk of death or HF readmission at 1 year in unadjusted analysis, which was similar in the fully adjusted model (HR, 1.12 [95% CI, 1.04–1.21]; Table 4). When evaluated as time-dependent HRs, the HR reduced over time similar to the first measurement (Table S6). When modeled as a spline, the spline term was significant (*P*=0.033, Figure 2B). The spline plot and quartile analysis showed a pattern similar to the first hs-cTnI measurement (Table 4). Associations were not different in individuals with chest pain (*P*-interaction=0.487) or CAD (*P*-interaction=0.191).

The Δ between measurements was not associated with the long-term outcome in unadjusted analysis but was associated in the fully adjusted model (HR, 1.16 [95% CI, 1.00–1.35]; Table 4). When the Δ was modeled as a spline, the spline term was not significant (*P*=0.134, Figure 2C). Quartile analysis generally showed risk increasing with higher quartiles (Figure 2C, Table 4). Associations were not different in individuals with CAD (*P*-interaction=0.125) but were different in individuals with chest pain (*P*-interaction=0.007). Individuals without chest pain had a significantly higher risk of death or HF readmission (HR, 1.29 [95% CI, 1.11–1.51]), whereas there was no association in those with chest pain (HR, 0.88 [95% CI, 0.69–1.12]).

When biomarkers were evaluated by AUC, both the first and second hs-cTnI had the highest AUCs alone (AUC, 0.59 [95% CI, 0.55–0.63]; Table 3) for predicting the long-term outcome. However, when added to the clinical model, all 3 measures of hs-cTnI had the same AUC (AUC, 0.70), which was not different than the AUC for the clinical model alone (AUC, 0.70 [95% CI, 0.66–0.73]). Findings were similar in sensitivity analyses (Tables S5, S7, and S8).

DISCUSSION

In this analysis, we assessed whether repeated hs-cTnI measurements, taken hours apart at hospital presentation, and their Δ were associated with the risk for

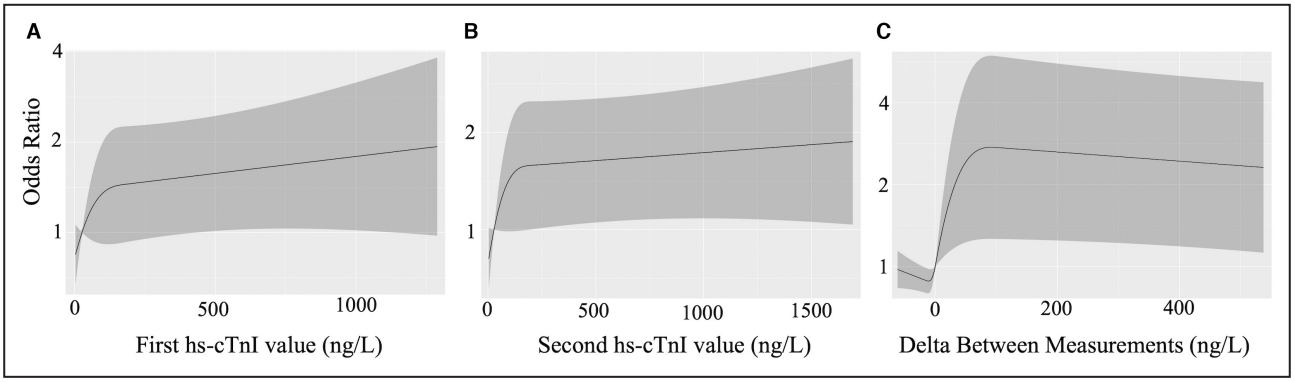

Figure 1. Association of repeat hs-cTnI measurements and the Δ between measurements modeled as restricted cubic splines with in-hospital events.
The median hs-cTnI value is set as the reference for hazard ratio estimates. Risk increased in a linear fashion with higher values of the first and second hs-cTnI measurement (**A** and **B**). Risk for the Δ between measurements was relatively flat before increasing, with higher risk in individuals with the greatest increase in hs-cTnI (**C**). hs-cTnI indicates high-sensitivity cardiac troponin I.

in-hospital events and death or HF readmission within 1 year among individuals presenting with hypervolemic AHF without ACS. We found that higher values of the second hs-cTnI measurement were significantly associated with greater odds of in-hospital events. Additionally, the Δ between measurements was not significantly associated with the short-term outcome; however, its association was nonlinear, and individuals with the greatest increase in hs-cTnI between measurements may be at higher risk for in-hospital events. We found that all 3 measurements were associated with a greater risk of death and HF readmission within 1 year. Risk was not constant for the first and second hs-cTnI measurements though, with risk highest near the time of measurement and decreasing thereafter. Lastly, the Δ between measurements was most predictive of short-term outcomes, whereas the first and second measurements were more predictive of long-term outcomes. These findings suggest that repeat measurement of hs-cTnI taken over hours upon presentation to the hospital for AHF without ACS can better identify individuals at risk for adverse outcomes compared with a single measurement of cTn.

ACS is an important provocateur of AHF, but many patients presenting with hypervolemic AHF have an elevated cTn without ACS.[3] In these patients, higher levels of cTn, reflecting greater myocardial injury and stress, are associated with worse outcomes whether measured at admission or during hospitalization for AHF.[7–12,22] However, patients with AHF can experience varying clinical trajectories, with some having a gradual decompensation and resolution of signs and symptoms, whereas others may rapidly improve or deteriorate.[23] Our findings suggest repeat hs-cTnI measurement over the initial hours of hospitalization may identify these different trajectories. In our cohort, at least 50% of individuals had a minimal change in hs-cTnI between the first and second measurements, potentially reflecting patients with a more gradual development of AHF. Conversely, as many as 50% had significant increases or decreases in hs-cTnI, suggesting these individuals had more rapid changes in clinical status.

Compared with the initial measurement of hs-cTnI, we found the repeat measurement and the Δ between measurements were associated with greater risk and were better at identifying high-risk patients with AHF, especially in individuals with rising hs-cTnI values. Studies have found that rising trajectories of cTn and peak cTn

Table 3. Area Under the Receiver Operating Characteristic Curve for Repeat hs-cTnI Measurements and the Δ Between Measurements for Short- and Long-Term Outcomes

hs-cTnI measurement	Biomarker alone AUC (95% CI)	Biomarker + model AUC (95% CI)
Short-term outcome		
First hs-cTnI	0.59 (0.54–0.64)	0.70 (0.65–0.75)
Second hs-cTnI	0.60 (0.55–0.65)	0.71 (0.66–0.75)
Δ Between	0.63 (0.58–0.68)	0.72 (0.67–0.77)
Long-term outcome		
First hs-cTnI	0.59 (0.54–0.63)	0.70 (0.66–0.74)
Second hs-cTnI	0.59 (0.55–0.63)	0.70 (0.66–0.74)
Δ Between	0.53 (0.49–0.57)	0.70 (0.66–0.73)

Model was unadjusted for first and second troponin measurements. Δ hs-cTnI was adjusted for time between measurements as an offset variable, age, sex, race, body mass index, admission systolic blood pressure, estimated glomerular filtration rate, admission hemoglobin, admission serum sodium, presence of coronary artery disease, chronic kidney disease, diabetes, hypertension, chronic obstructive pulmonary disease, presence of jugular venous distension, presence of edema, loop diuretic use before admission, and admission B-type natriuretic peptide. AUC indicates area under the receiver operating characteristic curve; and hs-cTnI, high-sensitivity cardiac troponin I.

Table 4. Association of Repeat hs-cTnI Measurements and the Δ Between Measurements With Death or Heart Failure Readmission Within 1 Year in AKINESIS

hs-cTnI measurement	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)
First hs-cTnI			
Per 2-fold higher	1.12 (1.04 to 1.21)	1.12 (1.04 to 1.22)	1.09 (1.01 to 1.19)
Q1 (0 to 13 ng/L)	Reference	Reference	Reference
Q2 (13 to 27 ng/L)	1.50 (0.96 to 2.36)	1.53 (0.96 to 2.44)	1.40 (0.88 to 2.24)
Q3 (27 to 62 ng/L)	2.02 (1.32 to 3.09)	2.06 (1.34 to 3.16)	1.81 (1.17 to 2.81)
Q4 (62 to 8330 ng/L)	2.07 (1.33 to 3.21)	2.05 (1.30 to 3.24)	1.78 (1.13 to 2.82)
Second hs-cTnI			
Per 2-fold higher	1.13 (1.05 to 1.21)	1.15 (1.07 to 1.24)	1.12 (1.04 to 1.21)
Q1 (0 to 14 ng/L)	Reference	Reference	Reference
Q2 (14 to 28 ng/L)	1.59 (1.00 to 2.52)	1.72 (1.07 to 2.75)	1.57 (0.98 to 2.53)
Q3 (28 to 66 ng/L)	2.61 (1.70 to 4.01)	2.71 (1.76 to 4.17)	2.40 (1.54 to 3.76)
Q4 (66 to 6843 ng/L)	2.18 (1.37 to 3.43)	2.40 (1.48 to 3.90)	2.12 (1.30 to 3.47)
Δ Between			
Per SD	1.10 (0.94 to 1.29)	1.15 (0.99 to 1.35)	1.16 (1.00 to 1.35)
Q1 (−1488 to −2 ng/L)	Reference	Reference	Reference
Q2 (−2 to 0 ng/L)	1.24 (0.83 to 1.87)	1.23 (0.81 to 1.86)	1.38 (0.91 to 2.10)
Q3 (0 to 4 ng/L)	1.05 (0.68 to 1.60)	1.18 (0.76 to 1.82)	1.18 (0.77 to 1.82)
Q4 (4 to 4656 ng/L)	1.35 (0.87 to 2.05)	1.49 (0.97 to 2.29)	1.45 (0.94 to 2.23)

Model 1 was unadjusted for first and second troponin measurements. Δ hs-cTnI was adjusted for time between measurements as an offset variable. Model 2: Model 1+age, sex, race, body mass index, admission systolic blood pressure, estimated glomerular filtration rate, admission hemoglobin, admission serum sodium, presence of coronary artery disease, chronic kidney disease, diabetes, hypertension, chronic obstructive pulmonary disease, presence of jugular venous distension, presence of edema, and loop diuretic use before admission. Model 3: Model 2+admission B-type natriuretic peptide. AKINESIS indicates Acute Kidney Injury Neutrophil Gelatinase-Associated Lipocalin Evaluation of Symptomatic Heart Failure Study; HR, hazard ratio; hs-cTnI, high-sensitivity cardiac troponin I; and Q, quartile.

values assessed over days of AHF hospitalization are strongly association with adverse outcomes.[11,12] Our findings show that repeating measurements over the initial hours of hospitalization, potentially until a peak value or high-risk trajectory is detected, could facilitate earlier identification of high-risk patients. Furthermore, these early changes in cTn likely reflect the severity of decompensation. The nonconstant HRs observed for the first and second measurements of hs-cTnI demonstrate that risk is greatest near the time of decompensation and decreases the further an individual is from decompensation. These findings highlight the prognostic significance of repeat cTn measurements early during admission for identifying high-risk patients with AHF.

Beyond the prognostic implications of repeat measurements, it is possible that certain pathologic processes or causes of AHF lead to different cTn trajectories. Numerous different processes can cause myocardial injury in patients with hypervolemic AHF without ACS.[4,5] We found that some hs-cTnI measurements were only associated with outcomes in individuals without CAD or chest pain, potentially from distinct causes of nonischemic injury. Unfortunately, AKINESIS did not collect detailed information on causes of AHF or mechanisms of decompensation, which could have further explored this hypothesis. Additionally, trajectories of cTn may reflect inadequate response to initial therapies. Both hs-cTnI values were collected after the first diuretic dose in AKINESIS. Potentially, the diuretic dose was inadequate, therapies that relieve myocardial stress were needed, or therapies that worsen myocardial injury, such as inotropes, were administered in patients with elevated and rising cTn. Further research is needed to determine if specific therapies can alter the trajectory of cTn levels in AHF, and if altering the trajectory of cTn correlates with outcomes.

Although our findings highlight the potential prognostic usefulness of early serial cTn measurements in AHF without ACS, they remain exploratory. Given our study only evaluated 2 sequential measurements taken hours apart, there is a possibility that these values reflect variability around a mean. Further studies evaluating multiple measurements of cTn over the initial hours of hospitalization are necessary to determine whether there is a sustained trajectory or if values regress to a mean over time. Additionally, future studies should evaluate whether specific trajectories of change or early peak cTn values can more accurately identify high-risk individuals with AHF. Lastly, understanding the processes that lead to a rising cTn early during hospitalization for AHF is necessary so that targeted therapies can be applied to mitigate this risk.

LIMITATIONS

We excluded 32% of AKINESIS participants because of missing biomarker measurements, and an additional 5% because of timing, which could bias our findings. However, our findings were consistent in the larger cohort of individuals with repeat hs-cTnI measurements available, and the differences between included and excluded participants were minimal. There may be additional confounders not adjusted for that may nullify the

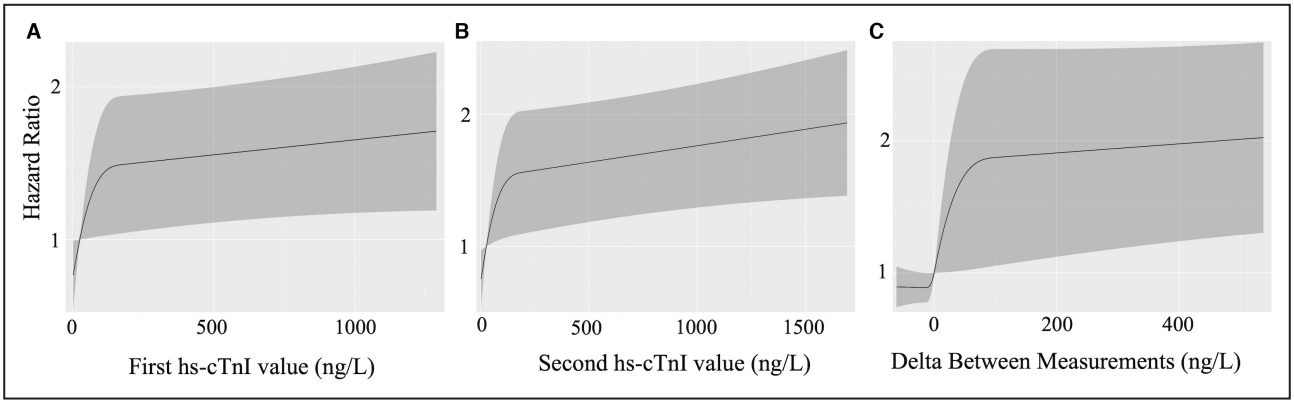

Figure 2. Association of repeat hs-cTnI measurements and the Δ between measurements modeled as restricted cubic splines with death or heart failure hospitalization at 1 year.
The median hs-cTnI value is set as the reference for hazard ratio estimates. Both the first and second hs-cTnI measurements had a sharp increase in risk from lower values to higher values until hazard ratios leveled off after the median value (**A** and **B**). Similar to the spline of odds ratio, risk for Δ hs-cTnI was relatively flat before increasing, with higher risk in individuals with the greatest increase in hs-cTnI (**C**). hs-cTnI indicates high-sensitivity cardiac troponin I.

associations found. Although ACS was an exclusion criterion in AKINESIS, it is possible some patients included had undiagnosed ACS. Although AKINESIS was a multicenter study, our findings should be validated in other populations and with other hs-cTn assays. Lastly, although detailed information on the specific causes of AHF was lacking, our findings remain relevant and important because the exact cause of AHF is often not known during initial evaluation of AHF, and our findings may help risk stratify these undifferentiated patients.

CONCLUSIONS

Repeat measurements of hs-cTnI and the Δ between measurements in the initial hours of hospitalization for hypervolemic AHF without ACS are associated with risks for short- and long-term outcomes. Repeat measurements of cTn should be considered in patients presenting with AHF, regardless of ACS status, for prognostic purposes.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S8
Figures S1–S2

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