CLINICAL RESEARCH STUDY

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# Prognostic Comparison of Different Sensitivity Cardiac Troponin Assays in Stable Heart Failure

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## ABSTRACT

**BACKGROUND:** Cardiac troponin (cTn) levels offer prognostic information for patients with heart failure. Highly sensitive assays detect levels of cTn much lower than the 99th percentile of standard cTn assays. We hypothesize that cardiac troponin levels measured by a high-sensitivity assay provide better prognostic value compared with cTn levels measured by a standard assay in patients with chronic heart failure.

**METHODS:** We measured high-sensitivity cTnT (hs-cTnT) and standard cardiac troponin I (cTnI) levels, as well as amino-terminal pro B-type natriuretic peptide (NT-proBNP) in 504 sequential stable patients with a history of heart failure who underwent elective coronary angiography, without acute coronary syndrome, and with 5-year follow-up of all-cause mortality.

**RESULTS:** The median hs-cTnT level was 21.2 (interquartile range 12.3-40.9) ng/L and 170 subjects died over 5 years. In a head-to-head overall comparison, hs-cTnT provided increased prognostic utility compared with cTnI (area under the curve [AUC] 66.1% and AUC 69.4%, respectively, $P = .03$; 9.0% integrated discrimination improvement, $P < .001$; and 13.6% event-specific reclassification, $P < .001$), and was independent of NT-proBNP and renal function. Even within the subset of patients where cTn levels by both assays were above the limit of quantification, higher hs-cTnT is associated with a 2-fold increase in 5-year mortality risk after adjusting for traditional risk factors (tertile 1 vs 3: hazard ratio [95% confidence interval] 2.0 [1.3-3.2]; $P = .0002$).

**CONCLUSION:** Cardiac troponin can be detected by the high-sensitivity assay in more patients with chronic heart failure than the standard assay, and may yield independent and better prognostic accuracy for mortality prediction than standard assay.

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**KEYWORDS:** Cardiac troponin; Heart failure; High-sensitivity cardiac troponin; Prognosis

Increasing levels of circulating cardiac troponin (cTn) are highly specific for ongoing myocardial damage and are utilized traditionally as markers for defining myocardial infarction.[1] Circulating cTn levels also can be elevated in other cardiac conditions such as acute and advanced chronic heart failure,[2,3] where they may be related to acute or chronic supply and demand mismatch[4] and may signify increased cardiomyocyte turnover in the setting of progressive myocardial dysfunction.[5]

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**Conflicts of Interest**: SLH is named as co-inventor on pending patents held by the Cleveland Clinic relating to cardiovascular diagnostics. SLH reports having been paid as a consultant for the following companies: Abbott Diagnostics, Cleveland Heart Lab, Esperion, Lilly, Liposcience Inc., Merck & Co., Inc., P&G, and Pfizer Inc. SLH reports receiving research funds from Abbott, Cleveland Heart Lab, Liposcience Inc., P&G, and Pfizer Inc. SLH reports having the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics or therapeutics from the companies shown below: Abbott Laboratories, Inc., Cleveland Heart Lab., Esperion, Frantz Biomarkers, LLC, Liposcience Inc., and Siemens. All other authors (JLG, SN, and WHWT) have no relationships to disclose.

**Authorship:** All authors had access to the data and a role in writing the manuscript.

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With technological advances, cTn levels measured by high-sensitivity assays have been developed recently, and can detect levels nearly one-tenth that of standard assays.[6] High-sensitivity cTn (hs-cTn) assays are well suited for detecting sub-clinical cardiac structural abnormalities and detect them in patients with chronic heart failure more frequently than standard assays.[7] In patients with heart failure, circulating hs-cTn is associated with adverse cardiovascular events and with both cardiac and all-cause mortality.[7-11] High-sensitivity assays expand the range of cTn detection, and there is likely significant overlap with standard assays in patients with heart failure. Yet, there are few head-to-head comparisons of the prognostic utility of these 2 assays. As such, we hypothesize that circulating high-sensitivity cTn will be associated with mortality and have increased prognostic accuracy compared with circulating cTn measured by a standard assay in patients with chronic stable heart failure.

**CLINICAL SIGNIFICANCE**

- Circulating cardiac troponin (cTn) was detectable in more stable heart failure patients via the high-sensitivity assay, compared with the standard assay.
- Heart failure with reduced ejection fraction was associated with higher cTn levels than heart failure with preserved ejection fraction.
- Although high-sensitivity cTn levels can risk-stratify lower-risk heart failure patients, there is no added prognostic value when circulating cTn is detectable by a standard assay.

## METHODS

### Study Population

We enrolled 504 consecutive subjects with a medical history of chronic heart failure who were undergoing elective diagnostic coronary angiography at the Cleveland Clinic between 2001 and 2007. We excluded patients who had an acute coronary syndrome, recent (<30 days) coronary revascularization, or history of heart transplantation. All participants gave their written informed consent and the study was approved by the Cleveland Clinic Institutional Review Board.

### Study Design

Arterial blood samples were collected at the time of coronary angiography, after an overnight fast, after arterial sheath placement, but before the catheterization procedure or any therapies that were administered (including anticoagulation medications). Estimated glomerular filtration rate (eGFR) was calculated via the Modification of Diet in Renal Disease equation.[12] Left ventricle ejection fraction was determined via transthoracic echocardiography via biplane Simpson's method by the Cleveland Clinic echocardiography laboratory, and the results were collected via chart review of the electronic medical record, EPIC (EPIC, Verona, WI). Heart failure with preserved or reduced ejection was defined as left ventricular ejection fraction ≥40% or <40%, respectively. Adjudicated outcomes including mortality, death, myocardial infarction, and stroke were collected prospectively over the 5 years by dedicated research personnel and by Social Security Death Index after enrollment for all cohort subjects.

### Cardiac Biomarkers Measurement

All biomarkers were measured at a central core laboratory; hs-cTnT was measured by a high-sensitivity (5th generation) assay on a Roche Cobas e411 platform (Roche Diagnostics, Basel, Switzerland). The limit of detection (LOD) was 3 ng/L and there were no values measured below this level in this cohort. The 99$^{th}$ percentile cutoff was 14 ng/L with an average coefficient of variation <10% at 13 ng/L. Amino-terminal pro B-type natriuretic peptide (NT-proBNP) was measured on the same Roche platform. Cardiac troponin I (cTnI) was measured by a standard sensitivity assay on the Abbott Architect platform (*STAT* Troponin I, Abbott Laboratories, Abbott Park, IL) with analytical sensitivity at 0.01 ng/mL. Troponin I values below the LOD were considered "undetectable." Creatinine and fasting lipid profiles were measured on the same Abbott platform.

### Statistical Analysis

Statistical analyses were performed using JMP Pro version 10 (SAS Institute, Inc, Cary, NC) and R software, version 3.0.2. Continuous variables were expressed as either mean ± standard deviation or median (interquartile range) and analyzed by the Student's unpaired *t* test or the Wilcoxon or Kruskal-Wallis tests where appropriate. Categorical variables were expressed as percentage (%) and analyzed by Fisher's exact test. Spearman's correlations were performed to assess relationship between hs-cTnT and clinical characteristics characterized by continuous variables. This cohort was split into 2 groups, split by the LOD of cTnI in a normal reference population: subjects with cTnI <0.01 ng/mL ("undetectable cTnI") or with cTnI ≥0.01 ng/mL ("detectable cTnI"). The subgroups above and below the cTnI LOD were each split into tertiles of hs-cTnT levels. Independent variables were cTnI ≥ or <0.01 ng/mL (n = 302 and n = 202, respectively), hs-cTnT tertiles overall, and hs-cTnT tertiles in each cTnI subgroup. Dependent variables were mortality at 5 years. Two-sided *P*-values of ≤ .05 were considered significant to reject the null hypothesis that there are no differences in mortality at 5 years of follow-up between cTn levels. Survival analyses were completed via the Kaplan-Meier method and log-rank analysis to compare survival curves between cTnI and hs-cTnT groups. Cox proportional hazards models