Prognostic Value of Very Low Plasma Concentrations of Troponin T in Patients With Stable Chronic Heart Failure

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Background—Circulating cardiac troponin T, a marker of cardiomyocyte injury, predicts adverse outcome in patients with heart failure (HF) but is detectable in only a small fraction of those with chronic stable HF. We assessed the prognostic value of circulating cardiac troponin T in patients with stable chronic HF with a traditional (cTnT) and a new precommercial highly sensitive assay (hsTnT).

Methods and Results—Plasma troponin T was measured in 4053 patients with chronic HF enrolled in the Valsartan Heart Failure Trial (Val-HeFT). Troponin T was detectable in 10.4% of the population with the cTnT assay (detection limit ≤0.01 ng/mL) compared with 92.0% with the new hsTnT assay (≤0.001 ng/mL). Patients with cTnT elevation or with hsTnT above the median (0.012 ng/mL) had more severe HF and worse outcome. In Cox proportional hazards models adjusting for clinical risk factors, cTnT was associated with death (780 events; hazard ratio=2.08; 95% confidence interval, 1.72 to 2.52; P<0.0001) and first hospitalization for HF (655 events; hazard ratio=1.55; 95% confidence interval, 1.25 to 1.93; P<0.0001). HsTnT was associated with the risk of death in unadjusted analysis for deciles of concentrations and in multivariable models (hazard ratio=1.05; 95% confidence interval, 1.04 to 1.07 for increments of 0.01 ng/mL; P<0.0001). Addition of hsTnT to well-calibrated models adjusted for clinical risk factors, with or without brain natriuretic peptide, significantly improved prognostic discrimination (C-index, P<0.0001 for both outcomes).

Conclusions—In this large population of patients with HF, detectable cTnT predicts adverse outcomes in chronic HF. By the highly sensitive assay, troponin T retains a prognostic value at previously undetectable concentrations. (Circulation. 2007;116:1242-1249.)

Key Words: heart failure ▪ natriuretic peptides ▪ prognosis ▪ troponin

Cardiac troponins I and T (cTnT) are sensitive and specific markers of myocardial injury used routinely for the diagnosis of acute coronary syndromes.1-5 Elevated troponin blood levels have been reported in several cohorts of patients with heart failure (HF), and the magnitude of elevation has been correlated with the severity of the disease and with adverse outcomes.6-15 Because of their high cardiac specificity, elevated troponins in patients with HF may suggest ongoing myocardial damage and may serve as a marker for the progression of HF. Measurement of troponin has been proposed since 1997 to monitor patients with HF.17,18 The prevalence of elevated troponin T in the general population is <1% and is associated with underlying cardiovascular disease or high-risk phenotypes.19

The levels of cardiac troponins in HF are generally lower than those in patients with acute coronary syndromes and lack the characteristic rise and fall pattern.4 Few reports exist on cTnT elevations in chronic stable HF.6,8,16,20 Previous studies included more frequently patients with severe HF (New York Heart Association [NYHA] class III and IV) and/or with decompensated HF, recruited in a single center.6,8,10,11,15,16 As expected, lesser severity of HF is associated with a larger fraction of patients with undetectable troponin. The commercial assays for troponins have sufficient sensitivity (0.01 ng/mL) for screening patients with suspected myocardial infarction21 but may be inadequate for risk stratification of patients with stable chronic HF who may have levels below...
the current detection limits. A highly sensitive assay for cTnT, currently under development, now makes it possible to measure concentrations >10-fold lower than the lower limit of the traditional assay. This provides the opportunity for a more comprehensive assessment of the relationship between cTnT and adverse outcomes in HF. We report here on the prognostic value of cardiac troponin T measured by the standard assay (cTnT) and by a precommercial new-generation highly sensitive assay (hsTnT) in 4053 patients with stable chronic HF enrolled in the ValHeFT trial (Val-HeFT) to confirm and extend previous observations obtained with cTnT in smaller samples of patients and to explore the additional clinical value of measuring previously undetectable cTnT concentrations.

Methods

Study Design and Patients

Val-HeFT was a randomized, placebo-controlled, double-blind, parallel-arm multicenter trial of 5010 patients with stable, symptomatic HF, who were on prescribed HF therapy. The patients had a left ventricular ejection fraction (LVEF) <40% and a left ventricular diameter in diastole adjusted for body surface area (LVIDD/BSA) ≥2.9 cm². Results of the main trial have been published.

Measurement of cTnT and hsTnT

Blood samples for the determination of troponin were collected at randomization in 4053 patients enrolled in Val-HeFT. Cardiac troponin was measured on the same EDTA-plasma sample as cTnT (third-generation reagents) and hsTnT (precommercial assay) by electrochemiluminescence method (ECLA; Elecsys 2010 analyzer, Roche Diagnostics, Germany). Assays were performed by personnel unaware of the patient’s identity and outcome. The lower detection limit for cTnT was 0.01 ng/mL. The interassay coefficient of variation was 10% at 0.03 ng/mL and 3% at 0.10 ng/mL. The intra-assay coefficient of variation was 8% at 0.03 ng/mL and 2% at 0.10 ng/mL. The reference value in age-matched healthy volunteers was <0.01 ng/mL. The lower detection limit of the highly sensitive precommercial hsTnT assay was 0.001 ng/mL. The interassay coefficient of variation was 8% at 0.01 ng/mL and 2.5% at 0.10 ng/mL. The intra-assay coefficient of variation was 5% at 0.01 ng/mL and 1% at 0.10 ng/mL. In a separate population of 1061 apparently healthy blood donors (amino-terminal probrain natriuretic peptide <125 pg/mL), the 99th percentile of hsTnT was 0.012 ng/mL, and the maximum value was 0.030 ng/mL (Roche Diagnostics, data on file). Brain natriuretic peptide (BNP) (IRMA Shionogi) and other circulating neurohormonal markers were measured as previously described.

Statistical Analysis

Baseline characteristics between categories of cTnT and hsTnT were compared by means of the χ² test for categorical variables; continuous variables were compared by a Student t test or by nonparametric Wilcoxon rank sum test in nonnormally distributed data. hsTnT concentrations were compared at baseline and after 4 months in patients allocated to the placebo arm of the trial and considered clinically stable on the basis of unchanged NYHA class over 4 months and 4-month variations in body weight ≤±2 kg and in LVEF ≤±5%. The average difference between hsTnT or BNP measurements at the 2 time points was evaluated in patients stratified by NYHA class II or III.

The 2 centrally validated clinical end points, all-cause mortality (780 events) and first hospitalization for HF (655 events), were also calculated.26 To evaluate the prognostic value of hsTnT concentration over time, multivariable Cox models for both outcomes were performed in patients with hsTnT value available at baseline and 4-month follow-up (n=3474). The models included all the variables statistically significant in the univariate analysis and hsTnT concentrations at both baseline and 4-month follow-up (continuous variable).

All probability values are 2-tailed, and 95% confidence intervals (CIs) were calculated. Analyses were performed with the use of SAS software, version 9.1 (SAS Institute) and the libraries Hmisc and survivalROC of the R Language.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Clinical Characteristics by Troponin T Concentrations

Of the 4053 patients, 420 (10.4%) had detectable values of cTnT (≥0.01 ng/mL) at study entry, with a median of 0.027 (quartile 1 to quartile 3, 0.016 to 0.052) ng/mL. In contrast, hsTnT was detectable (≥0.001 ng/mL) in 92% of the patients, with a median of 0.012 (0.016 to 0.052) ng/mL (mean±SD=0.018±0.025 ng/mL). A significant correlation was present between cTnT and hsTnT in the 420 patients with detectable cTnT (Spearman r=0.84, P<0.0001). Patients with cTnT elevation or those with hsTnT above the median had more severe HF than those with cTnT <0.01 ng/mL or hsTnT below the median (Table 1). These patients were older and more likely to be male and diabetic. They had a higher incidence of atrial fibrillation, had higher serum creatinine...
and bilirubin levels, were more frequently in NYHA classes III to IV, had lower LVEF, and were more likely to be treated with diuretics and digoxin but less likely to be receiving a β-blocker at study entry. All neurohormonal markers associated with poor outcome in HF were significantly higher in patients with detectable cTnT or with hsTnT above the median (Table 1).

In the 670 patients meeting the defined criteria of clinical stability, the average difference for hsTnT measurements repeated over 4 months was 0.00025 (mean±SD) and -0.0015±0.032 ng/mL for stable patients in NYHA class II (n=453) or III (n=217), respectively (Figure 1). Corresponding values for BNP were 8±101 and 12±182 pg/mL.

### TABLE 1. Characteristics of Patients at Randomization by Baseline cTnT and hsTnT Concentrations

<table>
<thead>
<tr>
<th></th>
<th>cTnT</th>
<th>hsTnT</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>&lt;0.01 ng/mL</td>
<td>≥0.01 ng/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=3633)</td>
<td>(n=420)</td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>20.5</td>
<td>13.1</td>
<td>0.0003</td>
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<tr>
<td>White, %</td>
<td>91.4</td>
<td>83.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0±4.5</td>
<td>26.7±4.8</td>
<td>0.24</td>
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<tr>
<td>Age, y</td>
<td>61.2±10.8</td>
<td>63.2±10.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NYHA III-IV, %</td>
<td>35.3</td>
<td>61.2</td>
<td>&lt;0.0001</td>
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<td>LVEF, %</td>
<td>27.1±7.1</td>
<td>24.4±7.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVIDD/BSA, cm/m²</td>
<td>3.64±0.53</td>
<td>3.66±0.54</td>
<td>0.50</td>
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<tr>
<td>Ischemic origin, %</td>
<td>57.5</td>
<td>60.7</td>
<td>0.21</td>
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<td>Diabetes mellitus, %</td>
<td>23.3</td>
<td>48.1</td>
<td>&lt;0.0001</td>
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<tr>
<td>Atrial fibrillation, %</td>
<td>10.9</td>
<td>19.5</td>
<td>&lt;0.0001</td>
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<tr>
<td>Sitting systolic blood pressure, mm Hg</td>
<td>124±18</td>
<td>121±19</td>
<td>0.025</td>
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<tr>
<td>Sitting heart rate, bpm</td>
<td>73±13</td>
<td>76±13</td>
<td>&lt;0.0001</td>
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<tr>
<td>Background therapy, %</td>
<td>Diuretics</td>
<td>83.6</td>
<td>96.4</td>
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<td></td>
<td>66.0</td>
<td>85.2</td>
<td>&lt;0.0001</td>
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<td>Angiotensin-converting enzyme inhibitors</td>
<td>93.3</td>
<td>91.2</td>
<td>0.10</td>
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<tr>
<td>β-Blockers</td>
<td>37.7</td>
<td>22.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>110.4±24.3</td>
<td>138.1±35.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bilirubin, μmol/L</td>
<td>11.2±6.1</td>
<td>14.3±9.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neurohormones, median (Q1–Q3)</td>
<td>BNP, pg/mL</td>
<td>90 (38–217)</td>
<td>229 (107–448)</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine, pg/mL</td>
<td>392 (273–567)</td>
<td>445 (323–664)</td>
</tr>
<tr>
<td></td>
<td>Plasma renin activity, ng/mL per hour</td>
<td>4.23 (1.69–15.92)</td>
<td>8.49 (2.31–25.18)</td>
</tr>
<tr>
<td></td>
<td>Aldosterone, pg/mL</td>
<td>99 (59–166)</td>
<td>133 (74–221)</td>
</tr>
<tr>
<td></td>
<td>C-reactive protein, ng/mL</td>
<td>3.09 (1.38–7.17)</td>
<td>5.94 (2.40–10.75)</td>
</tr>
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Q1–Q3 indicates quartile 1 to quartile 3.

Prognostic Value of Troponin T

Kaplan-Meier curves for all-cause mortality by cTnT (0.01< cTnT ≥0.01 ng/mL) and by quartiles of hsTnT are shown in Figure 2. The crude mortality rate after a follow-up of 24 months (median; quartile 1 to quartile 3, 18 to 29 months) was 16.5% (598/3633) and 43.3% (182/420; P<0.0001) in the patients with nonmeasurable and measurable cTnT, respectively. Mortality was 7.8% in the lowest quartile of hsTnT and 35.6% in the highest (P<0.0001). The trend for hospitalization for HF was similar (data not shown).

A progressive and significant increase occurred in the unadjusted risk of death with increasing deciles of hsTnT (from 6.2% in decile 1 to 46.3% in decile 10; decile 10 versus nondetectable) and hsTnT as continuous variable. In a model including cTnT and all demographic, clinical, and echocardiographic variables having a significant univariate relationship with outcome, this marker had the strongest
association with all-cause mortality, with an HR (95% CI) of 2.08 (1.72 to 2.52) ($\chi^2=57.2$, $P<0.0001$) followed by LVIDD (HR=1.34 [1.24 to 1.45] for each increase of 1 cm; $\chi^2=51.1$, $P<0.0001$) and ischemic origin of HF (HR=1.45 [1.24 to 1.70]; $\chi^2=21.1$, $P<0.0001$). Likewise, in a separate model including hsTnT, this marker was the first predictor of death (HR=1.05 [1.04 to 1.07] for each increase of 0.01 ng/mL; $\chi^2=53.6$, $P<0.0001$), followed by LVIDD (HR=1.30 [1.19 to 1.40] for each increase of 1 cm; $\chi^2=38.6$, $P<0.0001$) and ischemic origin of HF (HR=1.44 [1.22 to 1.67]; $\chi^2=19.3$, $P<0.0001$). cTnT and hsTnT ranked sixth and seventh, respectively, as predictors of hospitalization for HF. In the population of patients with undetectable baseline cTnT (cTnT <0.01 ng/mL; n=3633), hsTnT remained the first predictor of death (HR=1.41 [1.30 to 1.53] for each increase of 0.01 ng/mL; $\chi^2=68.2$, $P<0.0001$).

When hsTnT measurement was repeated 4 months after randomization, the first determination remained associated with all-cause mortality in a multivariable Cox model that included both measurements (Figure 4). On the other hand, the baseline measurement of hsTnT was no longer significant for the outcome of hospitalization for HF when the 4-month measurement was entered in the model.

Multiple Biomarker Approach: Prognostic Values of hsTnT and BNP

A modest correlation at baseline was present between measurable hsTnT and BNP (Spearman $r=0.441$, $P<0.0001$) and between measurable cTnT and BNP ($r=0.138$, $P=0.0048$).

The prognostic value of the combination of hsTnT and BNP was first assessed in a multivariable Cox model adjusted for clinical risk factors, in which patients were divided into 4

![Figure 1. Repeated measurements of hsTnT and BNP concentrations in clinically stable patients. Concentrations of hsTnT or BNP were compared at baseline and after 4 months in clinically stable patients stratified by NYHA class. Mean differences ($\pm$1.96 SD) were calculated according to Bland and Altman.](https://example.com/figure1.png)

![Figure 2. Kaplan-Meier cumulative curves for mortality by baseline cTnT (A) or by quartiles of hsTnT (B). For cTnT, log-rank=224, $P<0.0001$; for hsTnT, log-rank=305, $P<0.0001$.](https://example.com/figure2.png)

![Figure 3. Unadjusted HRs and 95% CIs for mortality and for hospitalization for HF by deciles of hsTnT at baseline. The concentration range for hsTnT, rate of events (death [circles], hospitalization for HF [squares]), and number of patients with detectable cTnT are reported for each decile of hsTnT. HRs and 95% CIs are reported on a logarithmic scale. Number of patients per decile=401 to 409.](https://example.com/figure3.png)
categories on the basis of baseline median concentrations of BNP (97 pg/mL) and hsTnT (0.0124 ng/mL). The reference category included 1280 patients with both markers below their respective median concentrations and a mortality rate of 8.2%. In the 658 patients with BNP above the median and hsTnT below, mortality was 14.3% (HR [95% CI] 1.28 [0.98 to 1.68]). In the 632 patients with BNP below the median and hsTnT above, mortality was 19.9% (1.57 [1.21 to 2.03]). Finally, in the 1331 patients with both markers above their respective median concentrations, mortality increased up to 32.0% (2.31 [1.85 to 2.88]). A similar trend was found for hospitalization for HF (data not shown).

To further elucidate the incremental value conferred by the biomarkers, BNP and hsTnT were added separately (models 2 and 3) or in combination (model 5) to a multivariable Cox model adjusted for clinical risk factors (model 1). Addition of BNP or hsTnT, separately or together, was statistically significant, as tested by means of the likelihood ratio test (for both markers, \( P < 0.0001 \) for mortality and \( P < 0.025 \) for hospitalization for HF; Table 2). Similarly, cTnT provided a further and significant improvement when added to the clinical model with BNP (model 4, \( P < 0.0001 \) for both outcomes; Table 2). The addition of cTnT to a model containing clinical risk factors and BNP further increased the prognostic discrimination (\( P < 0.0001 \) for both outcomes; Table 2). The addition of cTnT to a model containing clinical risk factors and BNP marginally improved the prognostic discrimination for mortality (\( P = 0.019 \)) but not for hospitalization for HF (\( P = 0.229 \); Table 2).

**Discussion**

The main findings of the present study can be summarized as follows: (1) Circulating troponin T is elevated in patients with chronic and symptomatic HF, in proportion to the severity of the disease. (2) Circulating troponin T has a high and prognostic value in these patients; an assay with improved sensitivity for troponin T shows that the circulating contractile protein retains a significant predictive value at concentrations lower than the detection limit of the traditional assay (0.01 ng/mL). (3) The circulating concentration of highly sensitive troponin T shows an incremental prognostic accuracy in the presence of the best current biohumoral marker in HF, the BNP.

**Detection and Prognostic Value of Very Low Plasma Concentration of Cardiac Troponin T in Patients With HF**

Detectable levels of circulating troponin T are rare in the general population (prevalence \( \approx 1\% \)) and associated with
underlying cardiovascular disease or with a high-risk phenotype for cardiovascular disease. Previous studies have reported elevated circulating troponin T in less than half of the patients with chronic stable or stabilized HF and reported elevated circulating troponin T in less than half of the patients with chronic stable or stabilized HF. The existing correlation between hsTnT and BNP (the active hormone was measured in the present study, but qualitatively similar results may be expected with amino-terminal probrain natriuretic peptide) did not decrease the predictive accuracy of hsTnT in multivariable analyses, suggesting that troponin T and BNP convey different and complementary clinical information. The prognostic accuracy of hsTnT is demonstrated by the fact that even in the presence of good calibration, addition of this marker to models that included clinical risk factors, with or without BNP, further improved discrimination.

Serial Measurements of Plasma Troponin T

BNP is known to have an elevated biological variability in patients with stable chronic HF. We report here that, on average, the difference in the plasma concentration of hsTnT was minimal over a period of observation of 4 months in patients with chronic HF deemed clinically stable. However, large absolute differences of concentrations could be observed, in particular in patients with higher hsTnT or BNP.

**Figure 5.** ROC curves for all-cause mortality (A) and for hospitalization for HF (B). For each outcome, curves are based on models of the prediction of risk at 24 months with clinical risk factors alone (model 1, black) or with the successive addition of BNP (model 2, red), hsTnT (model 3, blue), BNP and cTnT (model 4, brown), or BNP and hsTnT (model 5, green).
levels. Our data confirm the biological variability of these biomarkers in patients with stable chronic HF.4,5

The prognostic value of repeated determinations of BNP has been shown in patients with acute/decompensated HF undergoing optimization of therapy5 or with chronic HF.6,7 The majority of our patients had stable levels of hsTnT, and only 12.3% of them crossed either from below to above or from above to below the median value over 4 months (data not shown). Both baseline and 4-month determinations of hsTnT showed a significant association with risk, at least for all-cause mortality. These results demonstrate that serial measurements of hsTnT may be of clinical relevance for the management of patients with chronic HF.

Release of Cardiac Troponin T in Patients With Stable HF

Interpretation of the mechanism for the presence of troponin T in plasma of patients with chronic HF can only be speculative. A continuous, very slow release of troponins from the myocardium might reflect ongoing cardiac myocyte cell death, which has been reported to occur in animal models of post–myocardial infarction LV dysfunction8 and in humans with chronic HF.9,10 If ongoing cardiac damage at a very low rate is assumed to be a determinant of circulating hsTnT, this phenomenon seems to be independent of an ischemic origin of the disease. Stretch of cardiac myocytes might lead to leakage of the cytosolic pool of troponin T by transient loss of cell membrane integrity. This reversible damage may contribute to the increase of circulating TnT caused by irreversible injury of cardiac myocytes. Indeed, elevated cTnT has been found to predict adverse outcomes in patients with idiopathic cardiomyopathy.10 It is unknown to what extent, if any, apoptosis contributes to troponin T elevation in chronic HF.9,11 Several other putative causes exist, however, for elevated cardiac troponin levels, including cardiopulmonary disease and chronic renal insufficiency.4,12 Various neurohormonal systems (renin-angiotensin-aldosterone, sympathetic drive) and inflammatory responses are also chronically activated in patients with HF (Table 1) and might contribute to myocyte injury and cell death. Whatever the determinants of increased hsTnT in patients from Val-HeFT, it should be kept in mind that the group as a whole did not show much evidence of progressive worsening of cardiac function because in the whole population LVEF increased by 3.4% absolute points, and LVIDD decreased by 0.13 cm over 1-year follow-up.

These data show for the first time that previously nonmeasurable levels of troponin T can have important prognostic value in the setting of stable chronic HF.

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Disclosures

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References

Circulating cardiac troponins are sensitive and specific markers of myocardial injury routinely used in the diagnosis of acute coronary syndromes but not in heart failure (HF), in which modest and variable concentrations have been reported. The levels of cardiac troponins in patients with chronic and stable HF are generally lower, and current commercial assays are inadequate for risk stratification of these patients. A highly sensitive assay for cardiac troponin T (hsTnT), currently approved by the US Food and Drug Administration, can be used for detecting non-measurable levels of troponin T in patients with chronic HF. Lower sensitivity of troponin T can have important prognostic value in the setting of stable chronic HF.

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**CLINICAL PERSPECTIVE**

Circulating cardiac troponins are sensitive and specific markers of myocardial injury routinely used in the diagnosis of acute coronary syndromes but not in heart failure (HF), in which modest and variable concentrations have been reported. The levels of cardiac troponins in patients with chronic and stable HF are generally lower, and current commercial assays may be inadequate for risk stratification of these patients. A highly sensitive assay for cardiac troponin T (hsTnT), currently under development, allows measurement of concentrations >10-fold lower than the lower limit of the cTnT traditional assay (0.01 ng/mL). In >4000 patients with chronic HF, we found that circulating troponin T was detectable in 10.4% of the patients with the cTnT assay compared with 92.0% with hsTnT. In Cox proportional hazards models adjusting for clinical, laboratory, and echocardiographic risk factors, circulating troponins (cTnT and hsTnT) were associated with all-cause mortality (780 events) and first hospitalization for HF (655 events). Addition of hsTnT to fully adjusted multivariable models, with or without brain natriuretic peptide, significantly improved the discrimination between survivors and patients who died. Although interpretation of the mechanism for the presence of troponin T in plasma of patients with chronic HF can only be speculative, these data show for the first time that previously nonmeasurable levels of troponin T can have important prognostic value in the setting of stable chronic HF.

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for the Val-HeFT Investigators

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