Serial Measurement of Cardiac Troponin T Using a Highly Sensitive Assay in Patients With Chronic Heart Failure

Data From 2 Large Randomized Clinical Trials

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Background—Cardiac troponins are emerging as important prognostic markers in chronic cardiovascular conditions like stable coronary artery disease or chronic heart failure (HF). Less is known about the relation between serial measurements of high-sensitivity cardiac troponin T (hs-cTnT) and future events in HF. We determined the association between changes over time in hs-cTnT and outcome in patients with chronic HF.

Methods and Results—We analyzed 5284 patients with chronic HF from 2 independent randomized clinical trials, the Valsartan Heart Failure Trial (Val-HeFT) (n = 4053) and the Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca–Heart Failure (GISSI-HF) trial (n = 1231). hs-cTnT was measured at randomization and after 3 months (GISSI-HF) or 4 months of follow-up (Val-HeFT). The association between changes over time of hs-cTnT and various outcomes was tested in multivariable models. In both studies, increases in hs-cTnT levels over time were associated with age, diabetes mellitus, worsening of renal function (reduction in estimated glomerular filtration rate), and baseline and increases in N-terminal pro-brain natriuretic peptide concentrations. Increases in hs-cTnT concentrations were associated with all-cause mortality (incidence rates, 8.19 [7.51–8.88] and 6.79 [5.98–7.61] per 100 person-years in Val-HeFT and GISSI-HF, respectively, with hazard ratios [95% confidence intervals] of 1.59 [1.39–1.82] and 1.88 [1.50–2.35]) after adjustment for conventional risk factors and baseline levels of hs-cTnT and N-terminal pro-brain natriuretic peptide. Changes in hs-cTnT concentration modestly improved prognostic discrimination beyond baseline values for fatal outcomes only.

Conclusions—Despite very low circulating concentrations, changes in hs-cTnT concentrations over time are robust predictors of future cardiovascular events in patients with chronic HF but add limited prognostic discrimination.


Key Words: biomarkers ■ heart failure ■ natriuretic peptides ■ prognosis ■ troponin T

Very low circulating levels of troponin are detectable in the general population with the new generation of highly sensitive assays and are associated with adverse cardiovascular outcomes.1–3 Besides acute myocardial infarction, elevated troponin levels are also reported in several chronic disease states like coronary artery disease,4,5 diabetes mellitus,6 or chronic kidney disease.7 Troponin release in the bloodstream is low in patients with stable chronic heart failure (HF) and predicts adverse outcomes.8,9 The mechanisms of troponin release in chronic HF are not entirely clear and not only may reflect ongoing cardiac myocyte damage but also may be related to noncardiac causes such as pulmonary disease or chronic renal insufficiency that are not infrequent comorbidities in HF.10,11
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The increased sensitivity of the newly developed assays for cardiac troponins comes at the cost of decreased specificity, making clinical judgment more important in the interpretation of troponin assay results.\textsuperscript{12} Although baseline high-sensitivity cardiac troponin T (hs-cTnT) levels are strong predictors of adverse outcome, a few studies suggest that changes in hs-cTnT levels over time may convey additional prognostic information compared with a single measurement.\textsuperscript{2} In this report, we present the results from 2 large multicenter randomized clinical trials (Valsartan Heart Failure Trial [Val-HeFT] and Gruppo Italiano per lo Studio della Sopravvenienza nell’Insufficienza Cardiaca–Heart Failure [GISSI-HF]) in which we evaluated the hypothesis that changes over time in hs-cTnT concentrations provide further prognostic discrimination beyond that of a single determination in patients with chronic and stable HF.

Methods

Study Design and Selection of Patients

Data from 2 independent clinical trials, the Val-HeFT\textsuperscript{13} and the GISSI-HF trial,\textsuperscript{14,15} were used. Briefly, the Val-HeFT trial was a randomized, placebo-controlled, double-blind, parallel-arm multicenter trial that tested the effects of the angiotensin receptor antagonist valsartan versus placebo in 5010 patients with stable, symptomatic HF with left ventricular dysfunction. GISSI-HF was a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 6975 patients with clinical evidence of stable chronic HF (New York Heart Association class II to IV), irrespective of the cause and the level of left ventricular ejection fraction, and tested the effects of n-3 polyunsaturated fatty acids and losartan versus placebo. The present analyses were restricted to 4053 patients in Val-HeFT and 1231 patients in GISSI-HF HF who had hs-cTnT measured both at randomization and at first follow-up visit. Because the 2 trials differed largely in the numbers of patients with biomarkers measured, geographic origin (16 countries in Europe, North America, Australia, and South Africa for Val-HeFT and Italy and Switzerland for GISSI-HF), median follow-up (24 months [quartiles 1–3, 18–29 months] for Val-HeFT and 47 months [38–55] for GISSI-HF), and background therapy (prescription of \( \beta \)-blockers or spironolactone; see Table I in the online-only Data Supplement), the 2 samples were analyzed separately. The studies were approved by an institutional review committee, and all subjects gave informed consent. All of the events were adjudicated blindly by central ad hoc committees for both trials.\textsuperscript{13,14}

High-Sensitivity Assay of Cardiac Troponin T and Other Circulating Markers

Blood samples were collected into vacuum tubes with ethylene-diaminetetraacetic acid, and the plasma was stored at \(-70^\circ\text{C}\) in both trials until analysis in a central laboratory, as described previously.\textsuperscript{3} hs-cTnT was measured with a highly sensitive assay on an automated platform (ECLIA Elecsys 2010 analyzer, Roche Diagnostics, Germany) with a lower detection limit of 3 ng/L and a reported 99th percentile value in apparently healthy individuals of 13.5 ng/L.\textsuperscript{16} N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured as described previously.\textsuperscript{17} High-sensitivity C-reactive protein was measured with a nephelometric method in Val-HeFT (Dade Behring) and with immunoturbidimetric assay in GISSI-HF (Quantex ultra sensitive, Instrumentation Laboratory). Estimated glomerular filtration rate was calculated with the Modification of Diet in Renal Disease equation.

Statistical Methods

All analyses were performed separately for the 2 trials. Categorical variables are presented as proportions and continuous variables as mean (SD) or median (quartiles 1–3). In view of the markedly skewed distribution of hs-cTnT, changes in concentrations over time were calculated as the difference between the natural logarithm of the concentrations at follow-up and at baseline. Differences in clinical characteristics according to baseline hs-cTnT concentration below or above the upper limit of the reference value (13.5 ng/L) were analyzed with the \( \chi^2 \) test for categorical variables; continuous variables were compared by ANOVA or by the nonparametric Kruskal-Wallis test for nonnormally distributed data.

Multivariable linear regression analysis was used to identify the baseline and change variables (with univariate \( P<0.05 \)) that were independently associated with changes in hs-cTnT concentrations as a continuous variable. Kaplan-Meier plots for relative changes in hs-cTnT concentration for the outcomes of interest are presented for 3 categories of patients with either decreasing hs-cTnT concentrations over time (relative changes \(-15\%\)), stable levels (relative changes between \(-15\%\) and \(+15\%\)), or increasing levels (relative changes \(>+15\%\)). Patients were also divided into 4 groups on the basis of baseline and follow-up levels of hs-cTnT concentrations (ie, baseline and 3 or 4 months of follow-up) relative to the upper limit of the reference value (13.5 ng/L): group 1, patients with hs-cTnT below reference value at baseline and at follow-up; group 2, patients whose hs-cTnT decreased from above to below reference value; group 3, patients whose hs-cTnT increased from below to above reference value; and group 4, patients whose hs-cTnT remained above reference value at both time points.\textsuperscript{17} A Cox proportional hazards model was used to assess the risk of all-cause mortality in each group with group 1 used as the referent. The model was adjusted for baseline concentrations of hs-cTnT.

The association between changes in hs-cTnT, entered as a log-transformed continuous variable, and study end points (all-cause mortality, mortality due to worsening HF, admission to hospital for a cardiovascular reason or for HF) was first assessed with univariate Cox proportional hazards models, and data are presented as hazard ratio and 95% confidence intervals for a 1-unit increase of changes in hs-cTnT on a log scale. Gray’s tests were used for comparison of cumulative incidence curves to test whether mortality could be a competing risk for the occurrence of nonfatal outcomes.\textsuperscript{18} The proportionality and linearity of hazards were evaluated by Schoenfeld residuals and by the restricted cubic spline method,\textsuperscript{19} respectively, to test for the nonlinear component of each variable. Because neither absolute changes nor relative changes complied with the assumption of linearity, hazards, changes in hs-cTnT on a log scale were considered. Nested Cox multivariable models were used to establish the incremental prognostic value of changes in hs-cTnT concentration. The first model was adjusted for baseline concentration of hs-cTnT only. For each end point considered, all of the conventional risk factors that emerged as statistically significant at the univariate analysis (\( P<0.05 \); listed in Methods in the online-only Data Supplement) were then added to the second model. Baseline concentrations of NT-proBNP and high-sensitivity C-reactive protein (continuous log-transformed variables) were entered in the third incremental model.

The increased discriminative value of changes in hs-cTnT concentration for the end point events was assessed by the net reclassification improvement.\textsuperscript{20} This determines the difference in the probability of a patient belonging to predefined risk categories before and after the addition of a specific marker. We evaluated the contribution of changes in hs-cTnT concentration on reclassification compared with a basic model that included clinical risk factors and baseline hs-cTnT concentration (model 1) or clinical risk factors and baseline concentrations of hs-cTnT and NT-proBNP (model 2). Patients were initially classified on the basis of estimated risk tertiles. Using the same models, we assessed the integrated discrimination improvement index, which evaluates...
reclassification as a continuous outcome across the spectrum of risk.20

Statistical analysis was performed with the use of SAS software, version 9.1 (SAS Institute). A 2-sided P value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

The main baseline characteristics of the 2 study samples are presented in Table I in the online-only Data Supplement, showing clinical features of patients with mild to moderate chronic HF but some differences in racial backgrounds (9.4% of nonwhite origin in Val-HeFT and all whites in GISSI-HF), severity of symptoms (38.0% and 26.1%, respectively, in New York Heart Association class III/IV), and prescriptions of β-blockers (36.1% and 67.9%, respectively) or spironolactone (5.3% and 43.2%, respectively). The baseline concentration of hs-cTnT was lower in Val-HeFT (12.5 [5.9–22.4] ng/L; n = 4053) than in GISSI-HF (17.0 [10.3–27.8] ng/L; n = 1231), whereas that of NT-proBNP was similar (902 [378–1990] and 846 [376–1869] ng/L). There were no significant differences in the clinical characteristics of the patients with hs-cTnT measured at baseline only or at baseline and follow-up visits (Tables II and III in the online-only Data Supplement).

Table 1 shows the baseline clinical characteristics of patients stratified by baseline hs-cTnT concentration below or above the upper limit of 13.5 ng/L. More patients had high hs-cTnT at baseline in GISSI-HF (64.0%) than in Val-HeFT (47.1%). In both trials, elevated hs-cTnT was associated with the severity of the disease: Patients with higher hs-cTnT were older; were more frequently male; had worse symptoms of HF, higher heart rate, and more frequent comorbidities (diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease); and were more likely to be on diuretics and less likely to be receiving β-blockers. Patients with elevated hs-cTnT had higher circulating concentrations of serum creatinine and bilirubin and higher levels of NT-proBNP and highsensitivity C-reactive protein.

Baseline concentrations of hs-cTnT were correlated with baseline NT-proBNP (Spearman r = 0.53 in Val-HeFT and 0.57 in GISSI-HF) and with follow-up concentrations of hs-cTnT (r = 0.87 and r = 0.88, respectively; P < 0.0001 for all correlations).

Correlates of Changes in hs-cTnT Concentration

Baseline and follow-up concentrations of hs-cTnT and NT-proBNP are shown in Table 2. Relative changes in hs-cTnT were comparable in Val-HeFT (median [quartile 1 to quartile 3], 0% [−21% to +21%]) and GISSI-HF (−4% [−20% to +15%]). The same was true for NT-proBNP (−11% [−40% to +25%] in Val-HeFT and −10% [−36% to +26%] in GISSI-HF). In both studies, age, diabetes mellitus, and deterioration of renal glomerular function (reduction in estimated glomerular filtration rate) were independently associated with increases in hs-cTnT (Table 3). Low baseline hs-cTnT concentrations and baseline and increased NT-proBNP were also strongly related to increases in hs-cTnT over time.

The randomized treatments tested in Val-HeFT (valsartan versus placebo) and in GISSI-HF (n-3 polyunsaturated fatty acids versus placebo or rosuvastatin versus placebo) had no significant effect on 3-month changes in hs-cTnT concentration (data not shown).

Changes in hs-cTnT Concentration and Subsequent Events

The Kaplan-Meier curves for fatal events according to categories of changes in hs-cTnT concentration over time in both clinical trials are shown in Figure 1 (nonfatal events are presented in Figure I in the online-only Data Supplement). There was a graded increase in the probability of adverse events across these categories (decreasing, stable, or increasing levels), except for cardiovascular hospitalizations in the GISSI-HF trial (P = 0.23, log-rank test). Similar results were observed when patients were divided into tertiles of changes in hs-cTnT concentration (data not shown).

In Val-HeFT and in GISSI-HF, patients with hs-cTnT concentrations that increased from baseline to follow-up had significantly higher risk of mortality compared with those with hs-cTnT levels that remained below the reference value (13.5 ng/L) at both time points (Figure 2). Conversely, outcome tended to improve in those with decreasing hs-cTnT concentration over time.

Table 4 shows the results of Cox regression analyses for fatal events in relation to changes in hs-cTnT concentration as a continuous variable adjusted for baseline hs-cTnT (nonfatal events are presented in Table IV in the online-only Data Supplement). Changes in hs-cTnT concentration were strongly associated with subsequent events, even after adjustment for the conventional risk factors listed in Statistical Methods and for the baseline biomarkers (NT-proBNP and hs-cTnT) or for admission to the hospital for cardiovascular reasons occurring before the 2 measurements of troponin (data not shown). In the fully adjusted models (which included demographic, clinical, and echocardiographic variables, concomitant therapy, biomarkers, randomized drug therapy, and baseline concentration of hs-cTnT), hazard ratios for increasing hs-cTnT concentrations ranged from 1.40 to 2.99 depending on the trial and the outcomes considered (all with P < 0.0001). A competing risk of mortality on the occurrence of nonfatal events was excluded on the basis of the Gray’s test.

Prognostic Discrimination of Changes in hs-cTnT Concentrations

The introduction of changes in hs-cTnT concentration improved prognostic discrimination for fatal outcomes, estimated with net reclassification improvement or integrated discrimination improvement, compared with a model that included clinical risk factors and baseline concentration of hs-cTnT (Table 5; transition matrices are shown in Tables V.1 through V.16 in the online-only Data Supplement). The improvement was less marked when the baseline NT-proBNP concentration was introduced in the prognostic models and for nonfatal outcomes (except for...
Circulating Troponin Levels in Chronic HF

Discussion

Analyses of data from 2 large samples of patients with chronic HF recruited in multicenter clinical trials indicated that changes over time in the circulating levels of hs-cTnT were associated with the severity and progression of HF (increase in natriuretic peptide concentration and deterioration of renal glomerular function) and had robust prognostic value beyond that of a single measurement. These data are consistent across 2 independent samples (totaling 5284 patients) differing in geographic origin, background data are consistent across 2 independent samples (totaling 5284 patients) differing in geographic origin, background pharmacological prescriptions, and length of follow-up.

Circulating Troponin Levels in Chronic HF

There is now concordant and independent clinical evidence of a continuous release of minute amounts of cardiac enzymes in chronic HF and HF exacerbations. Serum troponin levels consistently predict adverse outcomes and clinical deterioration in chronic HF, independently of their relationship with left ventricular function. Furthermore, recent data from large-scale clinical trials also indicate that these biomarkers have predictive value for the occurrence of HF exacerbations (13). This new evidence suggests that troponin levels may serve as a sensitive marker for the diagnosis and monitoring of chronic HF and its exacerbations.

Table 1. Baseline Clinical Characteristics of Study Samples by Normal hs-cTnT level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Val-HeFT</th>
<th>GISSI-HF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;13.5 ng/L</td>
<td>≥13.5 ng/L</td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>2143 (52.9)</td>
<td>1910 (47.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>60±11</td>
<td>66±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female, %</td>
<td>24.2</td>
<td>14.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0±4.5</td>
<td>27.0±4.4</td>
<td>0.58</td>
</tr>
<tr>
<td>White, %</td>
<td>91.9</td>
<td>89.2</td>
<td>0.0098</td>
</tr>
<tr>
<td>NYHA class III/IV, %</td>
<td>30.1</td>
<td>46.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>27.8±7.0</td>
<td>25.7±7.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF &gt;0.40, %</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Comorbidities, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17.9</td>
<td>34.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8.1</td>
<td>16.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD</td>
<td>9.1</td>
<td>17.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Background therapy, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>93.2</td>
<td>93.0</td>
<td>0.85</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>43.1</td>
<td>28.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>78.2</td>
<td>92.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>4.2</td>
<td>6.6</td>
<td>0.0009</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min per 1.73 m², %</td>
<td>33.4</td>
<td>60.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum bilirubin, μmol/L</td>
<td>10.0 (6.8–12.0)</td>
<td>10.3 (8.6–15.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hs-cTnT, ng/L</td>
<td>6.2 (2.5–9.7)</td>
<td>23.3 (17.6–35.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>353 (243–1121)</td>
<td>1511 (766–3023)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>2.7 (1.2–6.6)</td>
<td>4.1 (1.9–8.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data with parentheses are shown as median (quartiles 1–3) unless indicated otherwise. hs-cTnT indicates high-sensitivity cardiac troponin T; Val-HeFT, Valsartan Heart Failure Trial; GI IsIs-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca–Heart Failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; and hs-CRP, high-sensitivity C-reactive protein.

an unexpected opposite result for cardiovascular hospitalizations in GIIsi-HF; Table VI in the online-only Data Supplement).
troponins into the bloodstream detectable with recent high-sensitivity reagents in virtually all patients with stable chronic HF. In the 2 largest samples studied to date, hs-cTnT was indeed detectable (≥3 ng/L) in 86% of the patients in Val-HeFT and 98% of those from GISSI-HF. However, the exact mechanisms for troponin release from cardiac myocytes and its clearance from the circulation remain speculative, especially in chronic HF. Mechanisms including increased wall stress, neurohormonal activation, inflammation, oxidative stress, altered calcium handling, or epicardial coronary artery disease have been advocated for troponin release in HF. We found that the strongest correlates of increases in plasma troponin concentration were increasing natriuretic peptide levels (a

Table 2. Concentrations of hs-cTnT and NT-proBNP at Baseline and Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Baseline, ng/L</th>
<th>Follow-Up, ng/L</th>
<th>RC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val-HeFT</td>
<td>3474</td>
<td>12.1 (5.6 to 21.5)</td>
<td>11.9 (5.4 to 21.7)</td>
<td>0 (−21 to 21)</td>
</tr>
<tr>
<td>GISSI-HF</td>
<td>1066</td>
<td>16.8 (10.2 to 27.2)</td>
<td>15.8 (9.4 to 24.9)</td>
<td>−4 (−20 to +15)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>3474</td>
<td>859 (363 to 1873)</td>
<td>725 (294 to 1667)</td>
<td>−11 (−40 to +25)</td>
</tr>
<tr>
<td>GISSI-HF</td>
<td>1066</td>
<td>814 (367 to 1683)</td>
<td>703 (291 to 1620)</td>
<td>−10 (−36 to +26)</td>
</tr>
</tbody>
</table>

Data are shown as median (quartiles 1 to 3). hs-cTnT indicates high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; RC, relative changes calculated as marker concentration at follow-up minus baseline concentration divided by baseline concentration and expressed as a percentage; Val-HeFT, Valsartan Heart Failure Trial; and GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca—Heart Failure. Follow-up concentrations 4 months after randomization in Val-HeFT and 3 months in GISSI-HF are shown. Analysis is restricted to patients with hs-cTnT and NT-proBNP measured at baseline and at follow-up.

Table 3. Independent Correlates of Changes in hs-cTnT Concentration

<table>
<thead>
<tr>
<th>Variable</th>
<th>Val-HeFT</th>
<th>GISSI-HF t</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression Coefficient (SE)</td>
<td>P</td>
</tr>
<tr>
<td>Log baseline hs-cTnT</td>
<td>−0.248 (0.012)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Absolute changes in NT-proBNP</td>
<td>5.8×10⁻⁶ (0.6×10⁻⁶)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Absolute changes in eGFR</td>
<td>−0.0076 (0.0012)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.0076 (0.0012)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.18 (0.03)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>0.0048 (0.0009)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.129 (0.025)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.015 (0.03)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Baseline NT-proBNP</td>
<td>2.9×10⁻⁵ (0.6×10⁻⁵)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Absolute changes in hs-CRP</td>
<td>0.0032 (0.0009)</td>
<td>0.004</td>
</tr>
<tr>
<td>β-blockers (no)</td>
<td>0.064 (0.023)</td>
<td>0.006</td>
</tr>
<tr>
<td>Absolute changes in serum bilirubin</td>
<td>0.0066 (0.0025)</td>
<td>0.008</td>
</tr>
<tr>
<td>LVEF</td>
<td>−0.0040 (0.0015)</td>
<td>0.008</td>
</tr>
<tr>
<td>COPD</td>
<td>0.085 (0.032)</td>
<td>0.009</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.093 (0.030)</td>
<td>0.002</td>
</tr>
<tr>
<td>Absolute changes in body mass index</td>
<td>−0.029 (0.014)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

hs-cTnT indicates high-sensitivity cardiac troponin T; Val-HeFT, Valsartan Heart Failure Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca—Heart Failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; and NYHA, New York Heart Association. Multivariable linear regression analysis to identify the clinical correlates associated with changes in hs-cTnT concentration, considered as a continuous variable, is shown. For GISSI-HF (R²=0.23), the variables entered in the model were log₂-transformed baseline concentration of hs-cTnT, baseline and absolute changes in NT-proBNP (ng/L), baseline and absolute changes in eGFR (mL/min per 1.73 m²), age, absolute changes in hSCRP (mg/L), absolute changes in body mass index (kg/m²), absolute changes in heart rate (bpm), baseline diastolic blood pressure (mm Hg), diabetes mellitus, NYHA class (III or IV), and ischemic etiology of heart failure.
marker of ventricular wall stress), diabetes mellitus (a metabolic state characterized by chronic inflammation, oxidative stress, and vascular injury and the progressive loss of cardiac myocytes\textsuperscript{24,25}), and reduced renal filtration rate (estimated glomerular filtration rate). Reduced clearance of troponin molecules or their fragments by dysfunctional kidneys contributes to elevated circulating concentrations of immune-like troponin in hemodialysis patients\textsuperscript{26} and in patients with chronic HF.\textsuperscript{27} In the 2 samples examined in the present study, ischemic etiology of HF and body mass index were not significant correlates of increasing troponin levels. Our data agree with a recent investigation in the general population (Dallas Heart Study) in which the main variables associated with detectable levels of hs-cTnT (≥3 ng/L) were male sex, age, diabetes mellitus, and estimated glomerular filtration rate.\textsuperscript{1}

**Prognostic Value of Changes Over Time in Troponin Concentration**

A single measurement of circulating troponin at any time during the natural progression of HF provides robust, independent prognostic information, irrespective of the clinical presentation (acute or chronic), etiology (ischemic or nonischemic), troponin form (I or T), and generation of reagents (traditional or high sensitivity).\textsuperscript{12,23} We show here for the first time in patients with chronic HF a strong

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**Figure 1.** Kaplan-Meier curves for fatal events in the Valsartan Heart Failure Trial (Val-HeFT) and Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca–Heart Failure (GISSI-HF). Cumulative probabilities by categories of percent changes in high-sensitivity cardiac troponin T concentration over time are shown: increase (I, relative changes >15%), stable (S, relative changes from −15% to +15%), and decrease (D, relative changes <−15%). Time equal to 0 reported on the x-axis corresponds to 3 months for GISSI-HF and 4 months for Val-HeFT. HF indicates heart failure.

**Figure 2.** Hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality according to categories of changes of high-sensitivity cardiac troponin T (hs-cTnT) over time. Patients were divided into 4 categories according to hs-cTnT concentration at baseline and follow-up relative to the upper limit of the reference value (13.5 ng/L). A Cox proportional hazards model was used to compare the risk of death among the 4 categories of patients with the group with hs-cTnT below the threshold at both time points used as referent, after adjustment for baseline concentration of hs-cTnT. Val-HeFT indicates Valsartan Heart Failure Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca–Heart Failure.
Table 4. Association of Changes in hs-cTnT Concentrations With Fatal Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Val-HeFT</th>
<th>GISSI-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with event</td>
<td>554</td>
<td>266</td>
</tr>
<tr>
<td>Incidence rate (95% CI, per 100 person-years)</td>
<td>8.19 (7.51–8.88)</td>
<td>6.79 (5.98–7.61)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.69 (1.49–1.92)</td>
<td>2.23 (1.86–2.69)</td>
</tr>
<tr>
<td>Adjusted for risk factors*</td>
<td>1.60 (1.41–1.82)</td>
<td>1.97 (1.58–2.46)</td>
</tr>
<tr>
<td>Adjusted for risk factors* and baseline NT-proBNP and hs-CRP</td>
<td>1.59 (1.39–1.82)</td>
<td>1.88 (1.50–2.35)</td>
</tr>
<tr>
<td>Mortality for worsening heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with event</td>
<td>148</td>
<td>81</td>
</tr>
<tr>
<td>Incidence rate (95% CI, per 100 person-years)</td>
<td>2.19 (1.84–2.54)</td>
<td>2.07 (1.62–2.52)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.32 (1.90–2.82)</td>
<td>2.99 (2.30–3.89)</td>
</tr>
<tr>
<td>Adjusted for risk factors*</td>
<td>2.26 (1.78–2.86)</td>
<td>2.90 (2.08–4.03)</td>
</tr>
<tr>
<td>Adjusted for risk factors* and baseline NT-proBNP and hs-CRP</td>
<td>2.23 (1.75–2.86)</td>
<td>2.60 (1.86–3.64)</td>
</tr>
</tbody>
</table>

hs-cTnT indicates high-sensitivity cardiac troponin T; Val-HeFT, Valsartan Heart Failure Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca–Heart Failure; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide; and hs-CRP, high-sensitivity C-reactive protein. Changes in hs-cTnT are considered as a continuous variable; hazard ratios refer to 1-unit increment in hs-cTnT concentrations on a log scale, with P<0.0001 for all Cox models.

*Selection of risk factors, reported in Methods in the online-only Data Supplement, is based on the statistically significant association (univariate analysis, P<0.05) with each end point.

increase in the risk of future fatal and nonfatal events associated with changes over time in hs-cTnT concentrations. This observation was replicated in 2 large, independent samples of well-studied patients enrolled in multicenter clinical trials. In the absence of methodologically sound data on the biological variability of high-sensitivity troponin concentrations in patients with chronic and stable HF, such as those obtained in healthy individuals for defining clinically useful diagnostic criteria for myocardial infarction,28,29 our data suggest that even small changes in troponin have prognostic significance and may help to identify patients at long-term risk for adverse events. These results are consistent with reports of worsening outcomes with increasing circulating troponin concentrations in community-dwelling older adults,2 in ambulatory patients with chronic HF,30 or in patients with chest pain.31 Although such changes may reflect normal biological variation, their relation with future adverse events regardless of baseline concentrations suggests that they may truly reflect dynamic changes in disease progression.

Study Limitations

Although the present study is the largest thus far to address the prognostic value of changes over time of circulating cardiac troponins in patients with chronic and symptomatic HF, it has several limitations. First, the patients were selected according to strict inclusion criteria and may not reflect the clinical diversity of real-life patients; for instance, we do not have a sufficient number of patients with preserved left ventricular ejection fraction to draw robust conclusions on the prognostic value of troponin in this relevant group. Second, we have investigated only short-term (3–4 months) variations in troponin concentration, although it may be more clinically relevant to have insights on changes over longer periods (6–12 months) in stable ambulatory patients. Third, elevation of troponin release is explained in part by several noncardiac causes that may have not been examined carefully in the present report.

In conclusion, the prognostic value of changes in hs-cTnT concentration was independent of the benchmark center clinical trials. In the absence of methodologically sound data on the biological variability of high-sensitivity troponin concentrations in patients with chronic and stable HF, such as those obtained in healthy individuals for defining clinically useful diagnostic criteria for myocardial infarction, our data suggest that even small changes in troponin have prognostic significance and may help to identify patients at long-term risk for adverse events. These results are consistent with reports of worsening outcomes with increasing circulating troponin concentrations in community-dwelling older adults, in ambulatory patients with chronic HF, or in patients with chest pain. Although such changes may reflect normal biological variation, their relation with future adverse events regardless of baseline concentrations suggests that they may truly reflect dynamic changes in disease progression.

Table 5. Prognostic Discrimination of Changes in hs-cTnT Concentrations for Fatal Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Val-HeFT</th>
<th>GISSI-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 + changes in hs-cTnT</td>
<td>1.86 (1.17 to 2.56)</td>
<td>&lt;0.0001 5.57 (2.09 to 9.05)</td>
</tr>
<tr>
<td>Model 2 + changes in hs-cTnT</td>
<td>1.76 (1.08 to 2.43)</td>
<td>&lt;0.0001 2.50 (0.85 to 5.85)</td>
</tr>
<tr>
<td>Mortality for worsening heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 + changes in hs-cTnT</td>
<td>3.00 (1.25 to 4.75)</td>
<td>0.0008 7.59 (2.22 to 12.96)</td>
</tr>
<tr>
<td>Model 2 + changes in hs-cTnT</td>
<td>2.88 (1.13 to 4.64)</td>
<td>0.001 5.47 (0.00 to 10.99)</td>
</tr>
</tbody>
</table>

hs-cTnT indicates high-sensitivity cardiac troponin T; Val-HeFT, Valsartan Heart Failure Trial; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca–Heart Failure; IDI, integrated discrimination improvement; CI, confidence interval; and NRI, net reclassification improvement. Model 1 includes conventional risk factors as listed in Methods in the online-only Data Supplement, selected on their statistically significant association (univariate analysis, P<0.05) with each end point and baseline hs-cTnT concentrations; model 2 is model 1 and baseline N-terminal pro-brain natriuretic peptide concentration. Boundaries of estimated risk tertiles for model 1 are as follows: Val-HeFT, all-cause mortality (tertile 1, <16%; tertile 2, 16–26%; tertile 3, >26%); mortality for worsening heart failure (tertile 1, <2%; tertile 2, 2–6%; tertile 3, >6%); GISSI-HF, all-cause mortality (tertile 1, <16%; tertile 2, 16–34%; tertile 3, >34%); mortality for worsening HF (tertile 1, <3%; tertile 2, 3–9%; tertile 3 >9%).
biomarker NT-proBNP, suggesting that the 2 markers convey slightly different prognostic information in chronic HF. Compared with baseline, changes over time in hs-cTnT slightly improved risk discrimination for fatal outcomes only after adjustment for clinical risk factors. The improvement was modest or no longer statistically significant when NT-proBNP was also considered among the predictive values. In essence, the information in serial troponin measurements appears to be relevant mainly in those patients whose levels rise or decrease over time, although it does not add much to baseline in the majority of patients with stable troponin.

Acknowledgments
The authors are grateful to Dr Dietmar Zdunek (Roche Diagnostics Ltd, Rotkreuz, Switzerland) for continuous support and to Dr Luca Porcu (Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy) for his helpful statistical advice. Reagents for measuring hs-cTnT and NT-proBNP in Val-HeFT and GISSI-HF were kindly provided by Roche Diagnostics.

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Disclosures
The sponsors had no role in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript. Dr Masson has received honoraria from Roche Diagnostics. Drs Anand and Barlera have received research grants from Novartis Pharma. Dr Bertocchi is an employee of Novartis Pharma, the company that funded Val-HeFT. Drs Maggioni and Tavazzi have received research grants from SPA, Sigma Tau, Pfizer, and AstraZeneca. Dr Latini has received grant support and honoraria from Roche Diagnostics and Novartis Pharma.

References


**CLINICAL PERSPECTIVE**

Validation of biomarkers requires large cohorts reflecting a broad range of contemporary patients. In 5284 patients with chronic heart failure from 2 independent randomized clinical trials, the Valsartan Heart Failure Trial (Val-HeFT) and the Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca–Heart Failure (GISSI-HF), changes over time in circulating high-sensitivity cardiac troponin T were related to fatal and nonfatal outcomes. In both studies, increases in high-sensitivity cardiac troponin T levels over 3 to 4 months were associated with age, diabetes mellitus, and reduction in estimated glomerular filtration rate. Despite very low baseline levels, increases in high-sensitivity cardiac troponin T concentration were strongly associated with clinical outcome, even after adjustment for conventional risk factors and benchmark circulating biomarkers of cardiac function (N-terminal pro-brain natriuretic peptide) or inflammation (C-reactive protein). The discriminative value of changes in high-sensitivity cardiac troponin T was limited, however. The strength of these observations lies in the fact that the data were obtained in 2 independent samples that differed with respect to the origin of patients, length of follow-up, and prescription rate of comediations (with β-blockers and aldosterone receptor antagonists more frequent in GISSI-HF). These results are consistent with reports of worsening outcomes with increasing circulating troponin concentrations in community-dwelling older adults, in ambulatory patients with chronic heart failure, or in patients with chest pain. Although such changes may reflect normal biological variation, their relation with future adverse events regardless of baseline concentrations suggests that they may truly reflect dynamic changes in disease progression. Given the limited variability of troponin levels over time, the potential for using their changes to guide therapy of chronic heart failure is questionable.
Serial Measurement of Cardiac Troponin T Using a Highly Sensitive Assay in Patients With Chronic Heart Failure: Data From 2 Large Randomized Clinical Trials

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http://circ.ahajournals.org/content/suppl/2011/12/02/CIRCULATIONAHA.111.044149.DC1

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SUPPLEMENTAL MATERIAL
Supplemental Methods: Covariates (with \( p < 0.05 \) at the univariate analysis) entered in the second model of the nested Cox proportional hazard models (Tables 4 and 5, Supplemental Tables 4 and 5).

**All-cause mortality** Val-HeFT: age (year), sex (male), BMI (kg/m\(^2\)), LVEF (%), NYHA class (III or IV), ischemic etiology of HF, systolic and diastolic blood pressures (mmHg), heart rate (bpm), diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease (COPD), prescription of diuretics, beta-blockers or spironolactone, serum bilirubin (mg/dL), serum creatinine (mg/dL), log baseline hs-cTnT. GISSI-HF: age, BMI, LVEF, NYHA class, ischemic etiology of HF, systolic and diastolic pressures, heart rate, diabetes mellitus, atrial fibrillation, COPD, prescription of diuretics or beta-blockers, serum bilirubin, serum creatinine, log baseline hs-cTnT.

**Mortality for worsening HF** Val-HeFT: age, BMI, LVEF, NYHA class, ischemic etiology of HF, systolic and diastolic blood pressures, prescription of diuretics, beta-blockers or spironolactone, serum creatinine, log baseline hs-cTnT. GISSI-HF: age, BMI, LVEF, NYHA class, ischemic etiology of HF, systolic and diastolic blood pressures, heart rate, diabetes mellitus, atrial fibrillation, COPD, prescription of diuretics or beta-blockers, serum bilirubin, serum creatinine, log baseline hs-cTnT.

**Cardiovascular hospitalization** Val-HeFT: age, LVEF, NYHA class, ischemic etiology of HF, systolic and diastolic blood pressures, diabetes mellitus, atrial fibrillation, COPD, prescription of diuretics, beta-blockers or spironolactone, serum bilirubin, serum creatinine, log baseline hs-cTnT. GISSI-HF: age, LVEF, NYHA class, ischemic etiology of HF, systolic and diastolic blood pressures, diabetes mellitus, atrial fibrillation, COPD, prescription of diuretics, beta-blockers or ACE inhibitors, serum creatinine, log baseline hs-cTnT.

**Hospitalization for worsening of HF** Val-HeFT: age, LVEF, NYHA class, ischemic etiology, systolic and diastolic blood pressures, heart rate, diabetes mellitus, atrial fibrillation, COPD, prescription of diuretics, beta-blockers, spironolactone, serum creatinine, serum bilirubin, log baseline hs-cTnT. GISSI-HF: age, NYHA class, systolic and diastolic blood pressures, heart rate, diabetes mellitus, atrial fibrillation, COPD, prescription of diuretics or beta-blockers, serum creatinine, log baseline hs-cTnT.
### Supplemental Table 1: Baseline characteristics of study populations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Val-HeFT</th>
<th>GISSI-HF</th>
</tr>
</thead>
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<tr>
<td>No.</td>
<td>4053</td>
<td>1231</td>
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<tr>
<td>Age (year)</td>
<td>63±11</td>
<td>67±11</td>
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<tr>
<td>Female (%)</td>
<td>19.7</td>
<td>19.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0±4.5</td>
<td>26.8±4.4</td>
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<tr>
<td>Caucasians (%)</td>
<td>90.6</td>
<td>100</td>
</tr>
<tr>
<td>NYHA III-IV (%)</td>
<td>38.0</td>
<td>26.1</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26.8±7.2</td>
<td>33.3±9.6</td>
</tr>
<tr>
<td>LVEF &gt; 0.40 (%)</td>
<td>0</td>
<td>11.3</td>
</tr>
<tr>
<td>Ischemic etiology of HF (%)</td>
<td>57.9</td>
<td>50.9</td>
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<tr>
<td>SBP (mmHg)</td>
<td>124±18</td>
<td>125±19</td>
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<td>DBP (mmHg)</td>
<td>76±10</td>
<td>77±10</td>
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<td>HR (bpm)</td>
<td>73±13</td>
<td>71±14</td>
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<td>Comorbidities (%)</td>
<td></td>
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<tr>
<td>Diabetes</td>
<td>25.9</td>
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<tr>
<td>Atrial fibrillation</td>
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<td>18.8</td>
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<td>COPD</td>
<td>13.0</td>
<td>18.6</td>
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<td>Background therapy (%)</td>
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<td></td>
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<td>81.5</td>
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<td>36.1</td>
<td>67.9</td>
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<tr>
<td>Diuretics</td>
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<tr>
<td>Spironolactone</td>
<td>5.3</td>
<td>43.2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.28±0.31</td>
<td>1.19±0.41</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>61.7±15.8</td>
<td>68.8±23.2</td>
</tr>
<tr>
<td>eGFR&lt;60 mL/min/1.73 m² (%)</td>
<td>46.3</td>
<td>36.9</td>
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<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>0.67±0.38</td>
<td>0.84±0.54</td>
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<tr>
<td>Hs-cTnT (ng/L)</td>
<td>12.5 [5.9-22.4]</td>
<td>17.0 [10.3-27.8]</td>
</tr>
<tr>
<td>Hs-cTnT &lt; 3 ng/L</td>
<td>14.5</td>
<td>1.6</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>902 [378-1990]</td>
<td>846 [376-1869]</td>
</tr>
<tr>
<td>Hs-CRP (mg/L)</td>
<td>3.3 [1.4-7.6]</td>
<td>2.3 [1.1-5.5]</td>
</tr>
<tr>
<td>Outcomes (incidence rate per 100 person-years)</td>
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</tr>
<tr>
<td>All-cause mortality</td>
<td>10.28</td>
<td>7.46</td>
</tr>
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<td>Mortality for worsening HF</td>
<td>2.57</td>
<td>2.33</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular reasons</td>
<td>19.51</td>
<td>23.63</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>11.68</td>
<td>10.50</td>
</tr>
</tbody>
</table>

Abbreviations: BMI: body-mass index, LVEF: left ventricular ejection fraction, HR: heart rate, SBP/DBP, systolic and diastolic blood pressures, ARBs: angiotensin II type 1 receptor blockers, eGFR: estimated glomerular filtration rate, hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal probrain natriuretic peptide, hs-CRP: high sensitivity C-reactive protein.
Supplemental Table 2: Baseline characteristics of Val-HeFT patients with hs-cTnT measured at baseline only (n=4053) or at baseline and 4 months (n=3474)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline only</th>
<th>Baseline and 4 months</th>
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</thead>
<tbody>
<tr>
<td>No.</td>
<td>4053</td>
<td>3474</td>
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<tr>
<td>Age (year)</td>
<td>63±11</td>
<td>63±11</td>
</tr>
<tr>
<td>Female (%)</td>
<td>19.7</td>
<td>19.5</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.0±4.5</td>
<td>27.0±4.4</td>
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<tr>
<td>Caucasians (%)</td>
<td>90.6</td>
<td>91.3</td>
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<tr>
<td>NYHA III-IV (%)</td>
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<tr>
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<td>0</td>
<td>0</td>
</tr>
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<td>Ischemic etiology of HF (%)</td>
<td>57.9</td>
<td>57.7</td>
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<td>Serum creatinine (mg/dL)</td>
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<td>1.27±0.30</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
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<td>61.9±15.5</td>
</tr>
<tr>
<td>eGFR&lt;60 mL/min/1.73 m² (%)</td>
<td>46.3</td>
<td>45.4</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>0.67±0.38</td>
<td>0.67±0.37</td>
</tr>
<tr>
<td>Hs-cTnT (ng/L)</td>
<td>12.5 [5.9-22.4]</td>
<td>12.1 [5.6-21.5]</td>
</tr>
<tr>
<td>Hs-cTnT &lt; 3 ng/L (%)</td>
<td>14.5</td>
<td>14.8</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>902 [378-1990]</td>
<td>857 [363-1873]</td>
</tr>
<tr>
<td>Hs-CRP (mg/L)</td>
<td>3.3 [1.4-7.6]</td>
<td>3.2 [1.4-7.3]</td>
</tr>
<tr>
<td>Outcomes (incidence rate per 100 person-years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>10.28</td>
<td>8.19</td>
</tr>
<tr>
<td>Mortality for worsening HF</td>
<td>2.57</td>
<td>2.19</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular reasons</td>
<td>19.51</td>
<td>19.50</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>11.68</td>
<td>11.59</td>
</tr>
</tbody>
</table>

Abbreviations: BMI: body-mass index, LVEF: left ventricular ejection fraction, HR: heart rate, SBP/DBP, systolic and diastolic blood pressures, ARBs: angiotensin II type 1 receptor blockers, eGFR: estimated glomerular filtration rate, hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal probrain natriuretic peptide, hs-CRP: high sensitivity C-reactive protein.
## Supplemental Table 3: Baseline characteristics of GISSI-HF patients with hs-cTnT measured at baseline only (n=1231) or at baseline and 3 months (n=1065)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline only</th>
<th>Baseline and 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>1231</td>
<td>1065</td>
</tr>
<tr>
<td>Age (year)</td>
<td>67±11</td>
<td>67±11</td>
</tr>
<tr>
<td>Female (%)</td>
<td>19.5</td>
<td>20.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8±4.4</td>
<td>26.7±4.3</td>
</tr>
<tr>
<td>Caucasians (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>NYHA III-IV (%)</td>
<td>26.1</td>
<td>24.8</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>33.3±9.6</td>
<td>33.0±9.8</td>
</tr>
<tr>
<td>LVEF &gt; 0.40 (%)</td>
<td>11.3</td>
<td>12.1</td>
</tr>
<tr>
<td>Ischemic etiology of HF (%)</td>
<td>50.9</td>
<td>49.6</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>125±19</td>
<td>126±19</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77±10</td>
<td>77±11</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>71±14</td>
<td>71±13</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>26.2</td>
<td>25.6</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>18.8</td>
<td>18.9</td>
</tr>
<tr>
<td>COPD</td>
<td>18.6</td>
<td>18.9</td>
</tr>
<tr>
<td>Background therapy (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>81.5</td>
<td>82.2</td>
</tr>
<tr>
<td>ARBs</td>
<td>17.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>67.9</td>
<td>67.7</td>
</tr>
<tr>
<td>Diuretics</td>
<td>92.9</td>
<td>92.8</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>43.2</td>
<td>43.2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.19±0.41</td>
<td>1.19±0.39</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>68.8±23.2</td>
<td>69.0±22.7</td>
</tr>
<tr>
<td>eGFR&lt;60 mL/min/1.73 m² (%)</td>
<td>36.9</td>
<td>36.4</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>0.84±0.54</td>
<td>0.84±0.56</td>
</tr>
<tr>
<td>Hs-cTnT (ng/L)</td>
<td>17.0 [10.3-27.8]</td>
<td>16.8 [10.2-27.2]</td>
</tr>
<tr>
<td>Hs-cTnT &lt; 3 ng/L (%)</td>
<td>1.6</td>
<td>1.9</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>846 [376-1869]</td>
<td>813 [367-1681]</td>
</tr>
<tr>
<td>Hs-CRP (mg/L)</td>
<td>2.3 [1.1-5.5]</td>
<td>2.2 [1.1-5.4]</td>
</tr>
<tr>
<td>Outcomes (incidence rate per 100 person-years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>7.46</td>
<td>6.77</td>
</tr>
<tr>
<td>Mortality for worsening HF</td>
<td>2.33</td>
<td>2.07</td>
</tr>
<tr>
<td>Hospitalization for cardiovascular reasons</td>
<td>23.63</td>
<td>23.57</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td>10.50</td>
<td>10.32</td>
</tr>
</tbody>
</table>

Abbreviations: BMI: body-mass index, LVEF: left ventricular ejection fraction, HR: heart rate, SBP/DBP, systolic and diastolic blood pressures, ARBs: angiotensin II type 1 receptor blockers, eGFR: estimated glomerular filtration rate, hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal probrain natriuretic peptide, hs-CRP: high sensitivity C-reactive protein.
Supplemental Table 4: Association of changes in hs-cTnT concentrations with non-fatal events

<table>
<thead>
<tr>
<th></th>
<th>Val-HeFT</th>
<th>GISSI-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with event</td>
<td>1137</td>
<td>579</td>
</tr>
<tr>
<td>Incidence rate (95% CI, per 100 person-years)</td>
<td>19.50 (18.37-20.64)</td>
<td>21.19 (19.46-22.91)</td>
</tr>
<tr>
<td>Hazard ratio HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.51 (1.37-1.66)</td>
<td>1.74 (1.43-2.11)</td>
</tr>
<tr>
<td>Adjusted for risk factors*</td>
<td>1.41 (1.28-1.55)</td>
<td>1.56 (1.27-1.90)</td>
</tr>
<tr>
<td>Adjusted for risk factors*, and baseline NT-proBNP and hs-CRP</td>
<td>1.40 (1.27-1.54)</td>
<td>1.50 (1.23-1.85)</td>
</tr>
<tr>
<td><strong>Hospitalization for worsening HF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with event</td>
<td>727</td>
<td>322</td>
</tr>
<tr>
<td>Incidence rate (95% CI, per 100 person-years)</td>
<td>11.59 (10.75-12.43)</td>
<td>9.63 (8.58-10.68)</td>
</tr>
<tr>
<td>Hazard ratio HR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.74 (1.55-1.96)</td>
<td>1.85 (1.52-2.25)</td>
</tr>
<tr>
<td>Adjusted for risk factors*</td>
<td>1.63 (1.45-1.84)</td>
<td>1.66 (1.35-2.05)</td>
</tr>
<tr>
<td>Adjusted for risk factors*, and baseline NT-proBNP and hs-CRP</td>
<td>1.61 (1.42-1.82)</td>
<td>1.55 (1.25-1.93)</td>
</tr>
</tbody>
</table>

Changes in hs-cTnT are considered as a continuous variable; hazard ratios refer to one-unit increment in hs-cTnT concentrations on a log scale, with p<0.0001 for all Cox models. * selection of risk factors, reported in the online supplemental methods, is based on the statistically significant association (univariate analysis, p <0.05) with each endpoint.
Supplemental Tables 5: Transition matrices for net reclassification improvement (NRI)

Supplemental Table 5.1: Val-HeFT, all-cause mortality, model 1 (clinical risk factors)

<table>
<thead>
<tr>
<th>Patients with event</th>
<th>Model 1 (clinical risk factors)</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;16%</td>
<td>16-28%</td>
<td>&gt;28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;16%</td>
<td>57 (82.6%)</td>
<td>11 (15.9%)</td>
<td>1 (1.5%)</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>16-28%</td>
<td>15 (9.4%)</td>
<td>109 (68.1%)</td>
<td>36 (22.5%)</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>&gt;28%</td>
<td>2 (0.6%)</td>
<td>16 (5.0%)</td>
<td>302 (94.4%)</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>136</td>
<td>339</td>
<td></td>
<td>549</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net correct reclassification (%)</strong></td>
<td>2.73</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients without event</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16%</td>
<td>1015 (92.4%)</td>
<td>77 (7.0%)</td>
<td>7 (0.6%)</td>
<td>1099</td>
<td></td>
</tr>
<tr>
<td>16-28%</td>
<td>126 (12.9%)</td>
<td>780 (79.7%)</td>
<td>72 (7.4%)</td>
<td>978</td>
<td></td>
</tr>
<tr>
<td>&gt;28%</td>
<td>6 (0.7%)</td>
<td>106 (13.1%)</td>
<td>697 (86.2%)</td>
<td>809</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1147</td>
<td>963</td>
<td>776</td>
<td>2886</td>
<td></td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>156</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>238</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net correct reclassification (%)</strong></td>
<td>2.84</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRI = 5.57 (2.09-9.05)%; p=0.002
### Supplemental Table 5.2: Val-HeFT, all-cause mortality, model 2 (clinical risk factors + baseline NT-proBNP)

<table>
<thead>
<tr>
<th>Model 2 (clinical risk factors + NT-proBNP)</th>
<th>&lt;16%</th>
<th>16-28%</th>
<th>&gt;28%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16%</td>
<td>55 (83.3%)</td>
<td>9 (13.7%)</td>
<td>2 (3.0%)</td>
<td>66</td>
</tr>
<tr>
<td>16-28%</td>
<td>13 (9.2%)</td>
<td>102 (71.8%)</td>
<td>27 (19.0%)</td>
<td>142</td>
</tr>
<tr>
<td>&gt;28%</td>
<td>0 (0.0%)</td>
<td>21 (6.2%)</td>
<td>320 (93.8%)</td>
<td>341</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>68</strong></td>
<td><strong>132</strong></td>
<td><strong>349</strong></td>
<td><strong>549</strong></td>
</tr>
</tbody>
</table>

Reclassified to higher risk (n) | 38
Reclassified to lower risk (n) | 34
**Net correct reclassification (%)** | 0.73

<table>
<thead>
<tr>
<th>Model 2 (clinical risk factors + NT-proBNP)</th>
<th>&lt;16%</th>
<th>16-28%</th>
<th>&gt;28%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16%</td>
<td>978 (90.8%)</td>
<td>92 (8.6%)</td>
<td>7 (0.6%)</td>
<td>1077</td>
</tr>
<tr>
<td>16-28%</td>
<td>146 (14.3%)</td>
<td>785 (76.9%)</td>
<td>90 (8.8%)</td>
<td>1021</td>
</tr>
<tr>
<td>&gt;28%</td>
<td>6 (0.8%)</td>
<td>88 (11.2%)</td>
<td>694 (88.1%)</td>
<td>788</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1130</strong></td>
<td><strong>965</strong></td>
<td><strong>791</strong></td>
<td><strong>2886</strong></td>
</tr>
</tbody>
</table>

Reclassified to higher risk (n) | 189
Reclassified to lower risk (n) | 240
**Net correct reclassification (%)** | 1.77

NRI = 2.50 (-0.85-5.85)%, p=0.14
# Supplemental Table 5.3: Val-HeFT, mortality for worsening HF, model 1 (clinical risk factors)

<table>
<thead>
<tr>
<th>Model 1 (clinical risk factors)</th>
<th>&lt;1.7%</th>
<th>1.7-5.8%</th>
<th>&gt;5.8%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.7%</td>
<td>2 (66.7%)</td>
<td>0 (0.0%)</td>
<td>1 (33.3%)</td>
<td>3</td>
</tr>
<tr>
<td>1.7-5.8%</td>
<td>0 (0.0%)</td>
<td>10 (55.6%)</td>
<td>8 (44.4%)</td>
<td>18</td>
</tr>
<tr>
<td>&gt;5.8%</td>
<td>0 (0.0%)</td>
<td>6 (4.8%)</td>
<td>119 (95.2%)</td>
<td>125</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>16</td>
<td>128</td>
<td>146</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td></td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td></td>
<td></td>
<td></td>
<td>2.06</td>
</tr>
<tr>
<td>Patients without event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.7%</td>
<td>1066 (93.2%)</td>
<td>68 (5.9%)</td>
<td>10 (0.9%)</td>
<td>1144</td>
</tr>
<tr>
<td>1.7-5.8%</td>
<td>206 (18.5%)</td>
<td>830 (74.6%)</td>
<td>76 (6.8%)</td>
<td>1112</td>
</tr>
<tr>
<td>&gt;5.8%</td>
<td>6 (0.6%)</td>
<td>124 (12.0%)</td>
<td>903 (87.4%)</td>
<td>1033</td>
</tr>
<tr>
<td>Total</td>
<td>1278</td>
<td>1022</td>
<td>989</td>
<td>3289</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td></td>
<td></td>
<td></td>
<td>154</td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td></td>
<td></td>
<td></td>
<td>336</td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td></td>
<td></td>
<td></td>
<td>5.53</td>
</tr>
</tbody>
</table>

\[ \text{NRI} = 7.59 \ (2.22-12.96)\% , \ p=0.006 \]
Supplemental Table 5.4: Val-HeFT, mortality for worsening HF, model 2 (clinical risk factors + baseline NT-proBNP)

<table>
<thead>
<tr>
<th></th>
<th>Model 2 (clinical risk factors + NT-proBNP)</th>
<th>Model 2 and changes in hs-cTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1.8%</td>
<td>1.8-6.2%</td>
</tr>
<tr>
<td>Patients with event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.8%</td>
<td>2 (100.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>1.8-6.2%</td>
<td>0 (0.0%)</td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td>&gt;6.2%</td>
<td>0 (0.0%)</td>
<td>8 (6.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Net correct reclassification (%)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without event</td>
<td>1341</td>
<td>965</td>
</tr>
<tr>
<td>&lt;1.8%</td>
<td>1132 (93.4%)</td>
<td>73 (6.0%)</td>
</tr>
<tr>
<td>1.8-6.2%</td>
<td>199 (19.1%)</td>
<td>772 (74.2%)</td>
</tr>
<tr>
<td>&gt;6.2%</td>
<td>10 (1.0%)</td>
<td>120 (11.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>1341</td>
<td>965</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Net correct reclassification (%)</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRI = 5.47 (0.00-10.99)%, p=0.05
## Supplemental Table 5.5: Val-HeFT, cardiovascular hospitalization, model 1 (clinical risk factors)

<table>
<thead>
<tr>
<th>Patients with event</th>
<th>Model 1 (clinical risk factors)</th>
<th>Model 1 and changes in hs-cTnT</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;58%</td>
<td>58-76%</td>
<td>&gt;76%</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;58%</td>
<td>153 (80.5%)</td>
<td>33 (17.4%)</td>
<td>4 (2.1%)</td>
<td>190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>58-76%</td>
<td>38 (10.1%)</td>
<td>284 (75.8%)</td>
<td>53 (14.1%)</td>
<td>375</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;76%</td>
<td>2 (0.3%)</td>
<td>29 (5.2%)</td>
<td>531 (94.5%)</td>
<td>562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>193</td>
<td>346</td>
<td>588</td>
<td>1127</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td>1.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without event</td>
<td>&lt;58%</td>
<td>58-76%</td>
<td>&gt;76%</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;58%</td>
<td>859 (91.0%)</td>
<td>79 (8.4%)</td>
<td>6 (0.6%)</td>
<td>944</td>
<td></td>
<td></td>
</tr>
<tr>
<td>58-76%</td>
<td>100 (13.2%)</td>
<td>586 (77.4%)</td>
<td>71 (9.4%)</td>
<td>757</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;76%</td>
<td>3 (0.5%)</td>
<td>75 (12.4%)</td>
<td>529 (87.1%)</td>
<td>607</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>962</td>
<td>740</td>
<td>606</td>
<td>2308</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>156</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>178</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRI= 2.82 (0.13-5.51)%, p=0.04
**Supplemental Table 5.6: Val-HeFT, cardiovascular hospitalization, model 2 (clinical risk factors + baseline NT-proBNP)**

<table>
<thead>
<tr>
<th>Model 2 (clinical risk factors + NT-proBNP)</th>
<th>&lt;58%</th>
<th>58-77%</th>
<th>&gt;77%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;58%</td>
<td>152 (84.4%)</td>
<td>25 (13.9%)</td>
<td>3 (1.7%)</td>
<td>180</td>
</tr>
<tr>
<td>58-77%</td>
<td>41 (10.8%)</td>
<td>288 (75.8%)</td>
<td>51 (13.4%)</td>
<td>380</td>
</tr>
<tr>
<td>&gt;77%</td>
<td>1 (0.2%)</td>
<td>36 (6.3%)</td>
<td>530 (93.5%)</td>
<td>567</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>194</td>
<td>349</td>
<td>584</td>
<td>1127</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net correct reclassification (%)</strong></td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients without event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;58%</td>
<td>874 (91.4%)</td>
<td>76 (8.0%)</td>
<td>6 (0.6%)</td>
<td>956</td>
</tr>
<tr>
<td>58-77%</td>
<td>97 (12.7%)</td>
<td>603 (78.6%)</td>
<td>67 (8.7%)</td>
<td>767</td>
</tr>
<tr>
<td>&gt;77%</td>
<td>4 (0.7%)</td>
<td>61 (10.4%)</td>
<td>520 (88.9%)</td>
<td>585</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>975</td>
<td>740</td>
<td>593</td>
<td>2308</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>149</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>162</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net correct reclassification (%)</strong></td>
<td>0.56</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

NRI = 0.65 (-1.99-3.29)%, p=0.63
### Supplemental Table 5.7: Val-HeFT, hospitalization for worsening HF, model 1 (clinical risk factors)

<table>
<thead>
<tr>
<th>Model 1 (clinical risk factors)</th>
<th>&lt;24%</th>
<th>24-39%</th>
<th>&gt;39%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 and changes in hs-cTnT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24%</td>
<td>71 (77.2%)</td>
<td>18 (19.6%)</td>
<td>3 (3.3%)</td>
<td>92</td>
</tr>
<tr>
<td>24-39%</td>
<td>21 (10.3%)</td>
<td>140 (68.6%)</td>
<td>43 (21.1%)</td>
<td>204</td>
</tr>
<tr>
<td>&gt;39%</td>
<td>2 (0.5%)</td>
<td>18 (4.2%)</td>
<td>404 (95.3%)</td>
<td>424</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>176</td>
<td>450</td>
<td>720</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td></td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td></td>
<td>3.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24%</td>
<td>925 (89.1%)</td>
<td>107 (10.3%)</td>
<td>6 (0.6%)</td>
<td>1038</td>
</tr>
<tr>
<td>24-39%</td>
<td>128 (13.8%)</td>
<td>694 (75.0%)</td>
<td>104 (11.2%)</td>
<td>926</td>
</tr>
<tr>
<td>&gt;39%</td>
<td>4 (0.5%)</td>
<td>77 (10.3%)</td>
<td>670 (89.2%)</td>
<td>751</td>
</tr>
<tr>
<td>Total</td>
<td>1057</td>
<td>878</td>
<td>780</td>
<td>2715</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td></td>
<td>217</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td></td>
<td>209</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td></td>
<td>-0.29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRI = 2.90 (-0.26-6.06)%, \( p=0.07 \)
### Supplemental Table 5.8: Val-HeFT, hospitalization for worsening HF, model 2 (clinical risk factors + baseline NT-proBNP)

<table>
<thead>
<tr>
<th>Model 2 (clinical risk factors + NT-proBNP)</th>
<th>&lt;24%</th>
<th>24-40%</th>
<th>&gt;40%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24%</td>
<td>79 (81.4%)</td>
<td>13 (13.4%)</td>
<td>5 (5.2%)</td>
<td>97</td>
</tr>
<tr>
<td>24-40%</td>
<td>17 (9.0%)</td>
<td>137 (72.1%)</td>
<td>36 (18.9%)</td>
<td>190</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>3 (0.7%)</td>
<td>18 (4.2%)</td>
<td>412 (95.2%)</td>
<td>433</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>168</td>
<td>453</td>
<td>720</td>
</tr>
</tbody>
</table>

Reclassified to higher risk (n) 54
Reclassified to lower risk (n) 38
Net correct reclassification (%) 2.22

<table>
<thead>
<tr>
<th>Model 2 and changes in hs-cTnT</th>
<th>&lt;24%</th>
<th>24-40%</th>
<th>&gt;40%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24%</td>
<td>954 (90.5%)</td>
<td>90 (8.5%)</td>
<td>10 (1.0%)</td>
<td>1054</td>
</tr>
<tr>
<td>24-40%</td>
<td>129 (13.8%)</td>
<td>722 (77.2%)</td>
<td>84 (9.0%)</td>
<td>935</td>
</tr>
<tr>
<td>&gt;40%</td>
<td>6 (0.8%)</td>
<td>78 (10.8%)</td>
<td>642 (88.4%)</td>
<td>726</td>
</tr>
<tr>
<td>Total</td>
<td>1089</td>
<td>890</td>
<td>736</td>
<td>2715</td>
</tr>
</tbody>
</table>

Reclassified to higher risk (n) 184
Reclassified to lower risk (n) 213
Net correct reclassification (%) 1.07

NRI= 3.29 (0.31-6.27)%, p=0.03
Supplemental Table 5.9: GISSI-HF, all-cause mortality, model 1 (clinical risk factors)

<table>
<thead>
<tr>
<th>Model 1 (clinical risk factors)</th>
<th>&lt;16%</th>
<th>16-33%</th>
<th>&gt;33%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;16%</td>
<td>22 (73.3%)</td>
<td>8 (26.7%)</td>
<td>0 (0.0%)</td>
<td>30</td>
</tr>
<tr>
<td>16-33%</td>
<td>2 (3.2%)</td>
<td>51 (80.9%)</td>
<td>10 (15.9%)</td>
<td>63</td>
</tr>
<tr>
<td>&gt;33%</td>
<td>0 (0.0%)</td>
<td>10 (6.3%)</td>
<td>148 (93.7%)</td>
<td>158</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>69</td>
<td>158</td>
<td>251</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td>2.39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;16%</td>
<td>301 (93.2%)</td>
<td>22 (6.8%)</td>
<td>0 (0.0%)</td>
<td>323</td>
</tr>
<tr>
<td>16-33%</td>
<td>32 (11.9%)</td>
<td>218 (81.3%)</td>
<td>18 (6.7%)</td>
<td>268</td>
</tr>
<tr>
<td>&gt;33%</td>
<td>2 (1.1%)</td>
<td>23 (12.9%)</td>
<td>153 (86.0%)</td>
<td>178</td>
</tr>
<tr>
<td>Total</td>
<td>335</td>
<td>263</td>
<td>171</td>
<td>769</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td>2.21</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

NRI = 4.60 (-0.36-9.56)%, p=0.07
Supplemental Table 5.10: GISSI-HF, all-cause mortality, model 2 (clinical risk factors + baseline NT-proBNP)

<table>
<thead>
<tr>
<th></th>
<th>Model 2 (clinical risk factors + NT-proBNP)</th>
<th>Model 2 and changes in hs-cTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;15%</td>
</tr>
<tr>
<td>Patients with event</td>
<td>&lt;15%</td>
<td>21 (77.8%)</td>
</tr>
<tr>
<td></td>
<td>15-23%</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td></td>
<td>&gt;23%</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Reclassified to higher risk (n)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Reclassified to lower risk (n)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Net correct reclassification (%)</td>
<td>1.59</td>
</tr>
<tr>
<td>Patients without event</td>
<td>&lt;15%</td>
<td>299 (94.6%)</td>
</tr>
<tr>
<td></td>
<td>15-23%</td>
<td>30 (10.7%)</td>
</tr>
<tr>
<td></td>
<td>&gt;23%</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>329</td>
</tr>
<tr>
<td></td>
<td>Reclassified to higher risk (n)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Reclassified to lower risk (n)</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Net correct reclassification (%)</td>
<td>3.12</td>
</tr>
</tbody>
</table>

NRI= 4.71 (0.25-9.17)% , p=0.04
Supplemental Table 5.11: GISSI-HF, mortality for worsening HF, model 1 (clinical risk factors)

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (clinical risk factors)</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with event</strong></td>
<td><strong>&lt;2.6%</strong></td>
<td>2.6-9.0%</td>
<td>&gt;9.0%</td>
<td></td>
</tr>
<tr>
<td>&lt;2.6%</td>
<td>1 (25.0%)</td>
<td>3 (75.0%)</td>
<td>0 (0.0%)</td>
<td>4</td>
</tr>
<tr>
<td>2.6-9.0%</td>
<td>1 (6.7%)</td>
<td>11 (73.3%)</td>
<td>3 (20.0%)</td>
<td>15</td>
</tr>
<tr>
<td>&gt;9.0%</td>
<td>0 (0.0%)</td>
<td>3 (5.3%)</td>
<td>54 (94.7%)</td>
<td>57</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2</td>
<td>17</td>
<td>57</td>
<td>76</td>
</tr>
<tr>
<td><strong>Reclassified to higher risk (n)</strong></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reclassified to lower risk (n)</strong></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net correct reclassification (%)</strong></td>
<td>2.64</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>Patients without event</strong></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.6%</td>
<td>355 (96.2%)</td>
<td>14 (3.8%)</td>
<td>0 (0.0%)</td>
<td>369</td>
</tr>
<tr>
<td>2.6-9.0%</td>
<td>51 (17.4%)</td>
<td>222 (75.8%)</td>
<td>20 (6.8%)</td>
<td>293</td>
</tr>
<tr>
<td>&gt;9.0%</td>
<td>5 (1.8%)</td>
<td>36 (12.8%)</td>
<td>241 (85.4%)</td>
<td>282</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>411</td>
<td>272</td>
<td>261</td>
<td>944</td>
</tr>
<tr>
<td><strong>Reclassified to higher risk (n)</strong></td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reclassified to lower risk (n)</strong></td>
<td>92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net correct reclassification (%)</strong></td>
<td>6.14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRI= 8.78 (0.29-17.27)%, p=0.04
Supplemental Table 5.12: GISSI-HF, mortality for worsening HF, model 2 (clinical risk factors + baseline NT-proBNP)

<table>
<thead>
<tr>
<th>Model 2 (clinical risk factors + NT-proBNP)</th>
<th>&lt;2.3%</th>
<th>2.3-8.6%</th>
<th>&gt;8.6%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.3%</td>
<td>1 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1</td>
</tr>
<tr>
<td>2.3-8.6%</td>
<td>0 (0.0%)</td>
<td>14 (93.3%)</td>
<td>1 (6.7%)</td>
<td>15</td>
</tr>
<tr>
<td>&gt;8.6%</td>
<td>0 (0.0%)</td>
<td>3 (5.0%)</td>
<td>57 (95.0%)</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>17</td>
<td>58</td>
<td>76</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td>-2.63</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2 and changes in hs-cTnT</th>
<th>&lt;2.3%</th>
<th>2.3-8.6%</th>
<th>&gt;8.6%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.3%</td>
<td>269 (93.7%)</td>
<td>18 (6.3%)</td>
<td>0 (0.0%)</td>
<td>287</td>
</tr>
<tr>
<td>2.3-8.6%</td>
<td>62 (16.0%)</td>
<td>304 (78.3%)</td>
<td>22 (5.7%)</td>
<td>388</td>
</tr>
<tr>
<td>&gt;8.6%</td>
<td>1 (0.4%)</td>
<td>44 (16.4%)</td>
<td>224 (83.2%)</td>
<td>269</td>
</tr>
<tr>
<td>Total</td>
<td>332</td>
<td>366</td>
<td>246</td>
<td>944</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>107</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td>7.10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRI= 4.47 (-1.27-10.21)%, p=0.13
Supplemental Table 5.13: GISSI-HF, cardiovascular hospitalization, model 1 (clinical risk factors)

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (clinical risk factors)</th>
<th>Model 1 and changes in hs-cTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;54%</td>
<td>54-71%</td>
</tr>
<tr>
<td>Patients with event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;54%</td>
<td>117 (89.3%)</td>
<td>14 (10.7%)</td>
</tr>
<tr>
<td>54-71%</td>
<td>22 (10.8%)</td>
<td>152 (74.9%)</td>
</tr>
<tr>
<td>&gt;71%</td>
<td>0 (0.0%)</td>
<td>11 (4.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
<td>177</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td>1.72</td>
<td></td>
</tr>
</tbody>
</table>

|                              |                                |                                |      |       |
| Patients without event       |                                |                                |      |       |
| <54%                         | 210 (92.5%)                    | 17 (7.5%)                      | 0 (0.0%) | 227   |
| 54-71%                       | 25 (16.2%)                     | 110 (71.4%)                    | 19 (12.3%) | 154   |
| >71%                         | 1 (0.9%)                       | 11 (10.5%)                     | 93 (88.6%) | 105   |
| Total                        | 236                            | 138                            | 112   | 486   |
| Reclassified to higher risk (n) | 36                             |                                |       |       |
| Reclassified to lower risk (n) | 37                             |                                |       |       |
| Net correct reclassification (%) | 0.21                           |                                |       |       |

NRI = 1.93 (-2.60 to 6.46)%, p=0.40
Supplemental Table 5.14: GISSI-HF, cardiovascular hospitalization, model 2 (clinical risk factors + baseline NT-proBNP)

<table>
<thead>
<tr>
<th>Model 2 (clinical risk factors + NT-proBNP)</th>
<th>&lt;54%</th>
<th>54-72%</th>
<th>&gt;72%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;54%</td>
<td>113 (86.3%)</td>
<td>18 (13.7%)</td>
<td>0 (0.0%)</td>
<td>131</td>
</tr>
<tr>
<td>54-72%</td>
<td>18 (8.7%)</td>
<td>163 (79.1%)</td>
<td>25 (12.1%)</td>
<td>206</td>
</tr>
<tr>
<td>&gt;72%</td>
<td>0 (0.0%)</td>
<td>13 (5.4%)</td>
<td>229 (94.6%)</td>
<td>242</td>
</tr>
<tr>
<td>Total</td>
<td>131</td>
<td>194</td>
<td>254</td>
<td>579</td>
</tr>
</tbody>
</table>

Reclassified to higher risk (n) | 43
Reclassified to lower risk (n) | 31
Net correct reclassification (%) | 2.07

<table>
<thead>
<tr>
<th>Patients without event</th>
<th>&lt;54%</th>
<th>54-72%</th>
<th>&gt;72%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;54%</td>
<td>209 (94.1%)</td>
<td>13 (5.9%)</td>
<td>0 (0.0%)</td>
<td>222</td>
</tr>
<tr>
<td>54-72%</td>
<td>27 (17.0%)</td>
<td>116 (73.0%)</td>
<td>16 (10.0%)</td>
<td>159</td>
</tr>
<tr>
<td>&gt;72%</td>
<td>1 (1.0%)</td>
<td>16 (15.2%)</td>
<td>88 (83.8%)</td>
<td>105</td>
</tr>
<tr>
<td>Total</td>
<td>237</td>
<td>145</td>
<td>104</td>
<td>486</td>
</tr>
</tbody>
</table>

Reclassified to higher risk (n) | 29
Reclassified to lower risk (n) | 44
Net correct reclassification (%) | 3.09

NRI= 5.16 (0.65-9.67)%; p=0.03
Supplemental Table 5.15: GISSI-HF, hospitalization for worsening HF, model 1 (clinical risk factors)

<table>
<thead>
<tr>
<th>Model 1 (clinical risk factors)</th>
<th>&lt;26%</th>
<th>26-43%</th>
<th>&gt;43%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26%</td>
<td>39 (90.7%)</td>
<td>4 (9.3%)</td>
<td>0 (0.0%)</td>
<td>43</td>
</tr>
<tr>
<td>26-43%</td>
<td>6 (5.7%)</td>
<td>86 (81.1%)</td>
<td>14 (13.2%)</td>
<td>106</td>
</tr>
<tr>
<td>&gt;43%</td>
<td>0 (0.0%)</td>
<td>9 (5.2%)</td>
<td>164 (94.8%)</td>
<td>322</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>99</td>
<td>178</td>
<td>322</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td></td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients without event</th>
<th>&lt;26%</th>
<th>26-43%</th>
<th>&gt;43%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26%</td>
<td>300 (89.6%)</td>
<td>23 (7.1%)</td>
<td>0 (0.0%)</td>
<td>323</td>
</tr>
<tr>
<td>26-43%</td>
<td>34 (14.2%)</td>
<td>188 (78.7%)</td>
<td>17 (7.1%)</td>
<td>239</td>
</tr>
<tr>
<td>&gt;43%</td>
<td>1 (0.5%)</td>
<td>15 (8.3%)</td>
<td>165 (91.2%)</td>
<td>181</td>
</tr>
<tr>
<td>Total</td>
<td>335</td>
<td>226</td>
<td>182</td>
<td>743</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td></td>
<td></td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td></td>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td></td>
<td></td>
<td></td>
<td>1.35</td>
</tr>
</tbody>
</table>

NRI = 2.28 (-2.02-6.58)%, p=0.30
Supplemental Table 5.16: GISSI-HF, hospitalization for worsening HF, model 2 (clinical risk factors + baseline NT-proBNP)

<table>
<thead>
<tr>
<th></th>
<th>Model 2 (clinical risk factors + NT-proBNP)</th>
<th>Model 2 and changes in hs-cTnT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25%</td>
<td>25-44%</td>
</tr>
<tr>
<td>Patients with event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25%</td>
<td>35 (87.5%)</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>25-44%</td>
<td>4 (3.8%)</td>
<td>92 (86.8%)</td>
</tr>
<tr>
<td>&gt;44%</td>
<td>0 (0.0%)</td>
<td>11 (6.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>108</td>
</tr>
<tr>
<td>Reclassified to higher risk (n)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Reclassified to lower risk (n)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Net correct reclassification (%)</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

|                     |                                            |                               |               |          |
| Patients without event |                                          |                               |               |          |
| <25%                | 294 (93.6%)                                | 20 (6.4%)                     | 0 (0.0%)      | 314      |
| 25-44%              | 29 (11.8%)                                 | 203 (82.9%)                   | 13 (5.3%)     | 245      |
| >44%                | 1 (0.5%)                                   | 14 (7.6%)                     | 169 (91.9%)   | 184      |
| Total               | 324                                        | 237                           | 182           | 743      |
| Reclassified to higher risk (n) | 33                                      |                               |               |          |
| Reclassified to lower risk (n) | 44                                      |                               |               |          |
| Net correct reclassification (%) | 1.48                                    |                               |               |          |

NRI= 1.48 (-2.58-5.54)%, \(p=0.47\)

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Supplemental Table 6: Prognostic discrimination of changes in hs-cTnT concentrations for non-fatal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Val-HeFT</th>
<th>GISSI-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDI (95% CI), %</td>
<td>P value for IDI</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 + changes in hs-cTnT</td>
<td>1.15 (0.69-1.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2 + changes in hs-cTnT</td>
<td>1.08 (0.64-1.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospitalization for worsening HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 + changes in hs-cTnT</td>
<td>2.10 (1.42-2.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2 + changes in hs-cTnT</td>
<td>2.02 (1.34-2.69)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Model 1 includes conventional risk factors as listed in the supplemental methods, selected on their statistically significant association (univariate analysis, p<0.05) with each endpoint and baseline hs-cTnT concentrations; model 2 is model 1 and baseline NT-proBNP concentration. Boundaries of estimated risk tertiles for model 1 as follows: Val-HeFT, cardiovascular hospitalization (T1<58, T2 58-76, T3>76%), hospitalization for worsening HF (T1<24, T2 24-40, T3>40%); GISSI-HF, cardiovascular hospitalization (T1<54, T2 54-71, T3>71%), hospitalization for worsening HF (T1<26, T2 26-43, T3>43%). IDI, integrated discrimination improvement; NRI, net reclassification improvement.
Supplemental Figure 1: Kaplan-Meier curves for non-fatal events in Val-HeFT and GISSI-HF

Cumulative probabilities by categories of percent changes in hs-cTnT concentration over time: increase (I, relative changes >15%), stable (S, relative changes from -15% to +15%), decrease (D, relative changes < -15%). Time equal to 0 reported on the X-axis corresponds to 3 months for GISSI-HF and to 4 months for Val-HeFT.