**Troponin T Measurements by High-Sensitivity vs Conventional Assays for Risk Stratification in Acute Dyspnea**

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**BACKGROUND:** Cardiac troponin T measured by a high-sensitivity assay (hs-cTnT) recently proved to be of prognostic value in several populations. The hs-cTnT assay may also improve risk stratification in acute dyspnea.

**METHODS:** We prospectively studied the prognostic value of hs-cTnT in 678 consecutive patients presenting to the emergency department with acute dyspnea. On the basis of conventional cardiac troponin T assay (cTnT) and hs-cTnT assay measurements, patients were divided into 3 categories: (1) neither assay increased (cTnT <0.03 μg/L, hs-cTnT <0.016 μg/L), (2) only hs-cTnT increased ≥0.016 μg/L (cTnT <0.03 μg/L), and (3) both assays increased (cTnT ≥0.03 μg/L, hs-cTnT ≥0.016 μg/L). Moreover, the prognostic value of hs-cTnT was investigated if cTnT was not detectable (<0.01).

**RESULTS:** One hundred seventy-two patients were in the lowest, 282 patients in the middle, and 223 patients in the highest troponin category. Patients in the second and third categories had significantly higher mortality compared to those in the first category (90-day mortality rate 2%, 10%, and 26% in groups 1, 2, and 3, respectively, P < 0.001; 1-year mortality rate 9%, 21%, and 39%, P < 0.001). Importantly, in patients with undetectable cTnT (n = 347, 51%), increased hs-cTnT indicated worse outcome [90-day mortality, odds ratio 4.26 (95% CI 1.19–15.21); 1-year mortality, hazard ratio 2.27 (1.19–4.36), P = 0.013], whereas N-terminal pro–brain-type natriuretic peptide (NT-proBNP) was not predictive of short-term outcome.

**CONCLUSIONS:** hs-cTnT is associated with mortality in patients presenting with acute dyspnea. hs-cTnT concentrations provide additional prognostic information to cTnT and NT-proBNP testing in patients with cTnT concentrations below the detection limit. In particular, the hs-cTnT cutoff of 0.016 μg/L enables identification of low-risk patients.

Cardiac troponins are sensitive markers of cardiac injury and are the preferred biochemical markers for the diagnosis of acute coronary syndrome (ACS)² (1, 2). It has been recognized for some years, however, that cardiac troponin T (cTnT) may also be detected in the absence of ACS (3, 4), for example in heart failure (HF) (5, 6), end-stage renal disease (ESRD) (7, 8), atrial fibrillation (9), and pulmonary embolism (10). In these conditions, troponin concentrations were found to be associated with disease severity and worse outcome. Recently, high-sensitivity assays with the ability to accurately measure very low troponin concentrations, even in healthy individuals, have been developed (11, 12). These high-sensitivity cardiac troponin T (hs-cTnT) assays enable detection of circulating troponin in the majority of patients with chronic HF and stable coronary artery disease and were found to be prognostic in these patients (13, 14). Although the hs-cTnT assay seems to increase the prognostic power of troponin measurement, few direct comparisons have been made between the conventional and the high-sensitivity assays (10, 15, 16). In particular, it is unclear...
hs-cTnT is of added value where conventional cardia-c troponin T is not detectable. Also, it is not yet known whether the prognostic value of hs-cTnT measurements can be extended to patients presenting with acute dyspnea, one of the most common and challenging presentations at the emergency department (17, 18). Despite recent advances in the evaluation of patients with dyspnea, particularly by using brain natriuretic peptide and N-terminal pro–brain-type natriuretic peptide (NT-proBNP) (19–21), assessing individual risk remains difficult. To provide best management, it is important to accurately stratify risk in these patients. With the upcoming clinical introduction of the hs-cTnT assay, it is important for clinicians to be aware of the prevalence and prognostic value of increased hs-cTnT in the emergency setting of acute dyspnea. Therefore, we investigated the prognostic value of hs-cTnT in addition to several well-known prognostic factors, including NT-proBNP, for short- and long-term mortality and assessed whether the hs-cTnT assay has additional value beyond the conventional cTnT assay.

Materials and Methods

STUDY POPULATION AND STUDY DESIGN

Between June 2007 and October 2009, 678 patients >18 years old who presented to the cardiac emergency department of the Maastricht University Medical Center with dyspnea as their main complaint were consecutively enrolled in this prospective study. Exclusion criteria were ST-elevation myocardial infarction (STEMI) and dyspnea resulting from chest trauma. Blood samples were obtained within 30 min after arrival at the emergency department. Baseline characteristics including the final cause of dyspnea were based on the clinical record. Left ventricular ejection fraction (LVEF) was obtained from echocardiography when available with a range of 1 year before presentation to 1 month after presentation. Coronary artery disease was defined as having a history of coronary artery bypass grafting, percutaneous coronary intervention, or acute myocardial infarction or as having coronary artery disease on coronary angiography or computed tomography angiography. Patients were followed for 1 year. We obtained follow-up data via chart review and, if necessary, from the general practitioner or by enquiry of the municipal register. The primary outcome measure was 90-day all-cause mortality, and the secondary outcome, 1-year all-cause mortality. All investigational procedures involved in this study have been approved by the institutional review board (medical ethics committee, Maastricht University Medical Center) and comply with the Declaration of Helsinki.

LABORATORY ANALYSIS

Measurements of routine laboratory parameters [NT-proBNP, cTnT, C-reactive protein (CRP), creatinine, and hemoglobin] were performed immediately after blood collection. Excess of collected serum sample was frozen and stored at −80 °C. hs-cTnT concentrations were measured at a later time point (1 freeze-thaw cycle). In this study, we refer to the conventional, fourth-generation troponin T assay as “cTnT” and the highly sensitive, fifth-generation troponin T assay as “hs-cTnT.” We measured cTnT concentrations with the cTnT and hs-cTnT assays, using the Elecsys 2010 analyzer (Roche Diagnostics). The conventional assay has a limit of detection (LOD) of 0.01 µg/L, a 99th percentile upper reference limit (URL) of <0.01 µg/L, and a 10% CV value at 0.03 µg/L, as specified by the manufacturer. The high-sensitivity assay has an LOD of 0.003 µg/L, a 99th percentile URL of 0.016 µg/L, and a 10% CV at 0.009 µg/L, as recently described (22, 23). In agreement with recent guidelines, troponin concentrations were considered increased when exceeding the 99th percentile URL, with the prerequisite that the assay has a CV <10% (1, 2). In keeping with these guidelines, increased concentrations were defined as ≥0.016 µg/L for the hs-cTnT assay and ≥0.03 µg/L for the cTnT assay. We measured NT-proBNP concentrations using the NT-proBNP assay for the Elecsys 2010 and used the prospectively defined cutoff of 900 pg/mL (21).

STATISTICAL ANALYSIS

Data are presented as frequencies, mean (SD), or median (interquartile range). We performed comparisons between groups using χ² tests for categorical data and 1-way ANOVA or the Kruskal–Wallis H-test for continuous data, as appropriate. We used ROC analysis to assess prognostic accuracy and logistic regression analysis to test the association between troponin T concentrations and 90-day mortality. For 1-year mortality, we performed Cox proportional-hazard regression analysis. Clinical covariates associated with outcome were added in a stepwise fashion with P < 0.1 as the cutoff for entry or retention. The final clinical model included age, sex, history of HF, creatinine concentration, dyspnea (New York Heart Association class IV or less), systolic blood pressure, and LVEF. Biomarkers were subsequently added to the clinical model. In these models, troponin concentrations below the detection limit were substituted with a concentration of 50% of the LOD. We checked for collinearity and interactions among covariates and found none of significance. Continuous variables not fulfilling linearity assumption were transformed before entry into the models. Calibration of the models was visualized and tested by the Hosmer–Lemeshow statistic. We evaluated model...
accuracy and discrimination by (a) c statistic, a measure of the area under the curve (AUC), (b) integrated discrimination improvement (IDI), and (c) net reclassification index (NRI), as recently suggested (24), following the method of Pencina et al. (25). For calculation of the NRI, we used risk categories of <5%, 5%–10%, and >10%. Kaplan–Meier curve plots were estimated and compared by the log-rank test. For time-dependent analysis, data were censored at the time of last contact. Finally, we performed sensitivity analyses that excluded the patients with final diagnosis of ACS. Tests were 2-sided with a level of significance of \( P < 0.05 \). Calculations used SPSS 16.0 (SPSS). Comparison of ROC curves was performed using the STAR (Statistical Technique for Analytical Review) online application (26).

Results

DISTRIBUTION OF TROPONIN T CONCENTRATIONS

Fig. 1 shows the distribution of troponin T values measured with the hs-cTnT assay in this dyspnea population (\( n = 678 \)) and in a reference population of 477 apparently healthy individuals described previously (22, 23). Troponin T was detectable in almost all patients with the hs-cTnT assay (\( n = 648, 96\% \)), whereas fewer than half of the patients had detectable concentrations with the conventional assay (\( n = 331, 49\% \)). An increased troponin according to the hs-cTnT cutoff of 0.016 \( \mu \)g/L was found in 506 patients (75%), whereas troponin was increased in only 223 patients (33%) according to the cTnT cutoff of 0.03 \( \mu \)g/L (see Supplemental Fig. 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol58/issue1).

PATIENT CHARACTERISTICS BY TROPONIN CATEGORIES

Patients were divided into 3 categories based on troponin concentrations: (1) troponin T not increased by either assay (hs-cTnT <0.016 \( \mu \)g/L and cTnT <0.03 \( \mu \)g/L); (2) troponin T increased by the hs-cTnT assay only (hs-cTnT \( \geq \)0.016 \( \mu \)g/L and cTnT <0.03 \( \mu \)g/L); and (3) troponin T increased by both assays (hs-cTnT \( \geq \)0.016 \( \mu \)g/L and cTnT \( \geq \)0.03 \( \mu \)g/L). Baseline characteristics by troponin categories are shown in Table 1. Overall, patients with increased cTnT concentrations were older and more likely to be male; have a history of HF, coronary artery disease, or diabetes mellitus; and be on diuretics before presentation. In addition, these patients had more highly increased NT-proBNP and creatinine concentrations, lower LVEF, and more severe dyspnea at presentation. Considering the final diagnosis of dyspnea, patients with increased cTnT concentrations more often had a diagnosis of acutely
Table 1. Baseline characteristics by baseline troponin categories.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Category 1 (cTnT &lt;0.03 μg/L and hs-cTnT &lt;0.016 μg/L)</th>
<th>Category 2 (cTnT &lt;0.03 μg/L and hs-cTnT ≥0.016 μg/L)</th>
<th>Category 3 (cTnT ≥0.03 μg/L and hs-cTnT ≥0.016 μg/L)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>678</td>
<td>172</td>
<td>283</td>
<td>223</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>75 (12)</td>
<td>67 (15)</td>
<td>77 (10)</td>
<td>78 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>373 (55)</td>
<td>88 (51)</td>
<td>143 (51)</td>
<td>142 (64)</td>
<td>0.006</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>241 (36)</td>
<td>43 (25)</td>
<td>103 (36)</td>
<td>95 (43)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>157 (65)% (n = 241)</td>
<td>23 (53) (n = 43)</td>
<td>68 (66) (n = 103)</td>
<td>66 (69) (n = 95)</td>
<td>0.182</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>146 (22)</td>
<td>29 (17) (n = 170)</td>
<td>63 (22)</td>
<td>54 (24) (n = 221)</td>
<td>0.206</td>
</tr>
<tr>
<td>Hypertension</td>
<td>386 (58)</td>
<td>85 (60) (n = 142)</td>
<td>175 (75) (n = 233)</td>
<td>126 (69) (n = 183)</td>
<td>0.008</td>
</tr>
<tr>
<td>Mean LVEF, % (SD)</td>
<td>43 (17) (n = 401)</td>
<td>48 (16) (n = 86)</td>
<td>42 (16) (n = 174)</td>
<td>39 (17) (n = 141)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median hs-cTnT, μg/L (range)</td>
<td>0.033 (0.017–0.061) (n = 648)</td>
<td>0.010 (0.007–0.013) (n = 142)</td>
<td>0.026 (0.021–0.037)</td>
<td>0.080 (0.057–0.158)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean hemoglobin, mmol/L (SD)</td>
<td>7.9 (1.8) (n = 673)</td>
<td>8.4 (1.0) (n = 170)</td>
<td>7.8 (1.3) (n = 280)</td>
<td>7.7 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean CRP, mg/L (range)</td>
<td>15 (5.6–42) (n = 612)</td>
<td>9.5 (3.4–28) (n = 142)</td>
<td>14 (5.0–36) (n = 267)</td>
<td>25 (9.20–57) (n = 203)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median NT-proBNP, pg/mL (range)</td>
<td>3174 (989–8350) (n = 674)</td>
<td>788 (180–2476) (n = 168)</td>
<td>3177 (1186–7153)</td>
<td>7525 (2797–16 864)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Diagnosis at presentation

<table>
<thead>
<tr>
<th>Diagnosis at presentation</th>
<th>Overall</th>
<th>Category 1 (cTnT &lt;0.03 μg/L and hs-cTnT &lt;0.016 μg/L)</th>
<th>Category 2 (cTnT &lt;0.03 μg/L and hs-cTnT ≥0.016 μg/L)</th>
<th>Category 3 (cTnT ≥0.03 μg/L and hs-cTnT ≥0.016 μg/L)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute decompensated HF</td>
<td>389 (57)%</td>
<td>52 (30)</td>
<td>178 (63)</td>
<td>159 (71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-STEMI or angina pectoris</td>
<td>51 (8)</td>
<td>10 (6)</td>
<td>13 (5)</td>
<td>28 (13)</td>
<td>0.003</td>
</tr>
<tr>
<td>Inflammatory pulmonary disease</td>
<td>35 (5)</td>
<td>16 (9)</td>
<td>14 (5)</td>
<td>5 (2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Rhythm/conduction disturbances</td>
<td>48 (7)</td>
<td>16 (9)</td>
<td>19 (7)</td>
<td>13 (6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Other</td>
<td>55 (8)</td>
<td>23 (13)</td>
<td>20 (7)</td>
<td>12 (5)</td>
<td>0.192</td>
</tr>
<tr>
<td>Dyspnea of unknown cause</td>
<td>100 (15)</td>
<td>55 (32)</td>
<td>39 (14)</td>
<td>6 (3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 1. Baseline characteristics by baseline troponin categories.**

*Data are n (%) unless noted otherwise.

*Parenthetical n values refer to the subset of the cohort having data for the given characteristic.

P < 0.05, category 1 vs 2.

P < 0.05, category 1 vs 3.

P < 0.05, category 2 vs 3.
decompensated heart failure and ACS or stable angina pectoris.

HIGH-SENSITIVITY AND CONVENTIONAL TROPONIN T ASSAYS FOR PREDICTING 90-DAY MORTALITY

Ninety-day follow-up was completed in all patients. After 90 days, 89 patients (13.1%) died, 68 (76%) from cardiovascular causes. The 90-day mortality rate increased over the troponin categories, from 2% in the lowest category and 10% in the second category to 26% in the highest category ($P < 0.001$ for all between-group comparisons). Event rates per troponin category including initial admission rate, length of stay, and in-hospital mortality are shown in online Supplemental Table 1. hs-cTnT and cTnT were both strongly and independently associated with 90-day mortality, even after correction for clinical risk factors and after correction for clinical risk factors plus NT-proBNP and CRP (Table 2). hs-cTnT and cTnT had incremental value in predicting 90-day mortality beyond the clinical risk model according to the $c$ statistic, NRI, and IDI (Table 3). The incremental value of hs-cTnT and cTnT, when added to the clinical model, was similar to that of NT-proBNP. The combination of any 2 biomarkers did not further improve model performance (data not shown). The cutoff value of 0.016 $\mu$g/L for hs-cTnT showed a higher prognostic sensitivity (96%) and negative predictive value (98%) than when the cTnT cutoff of 0.03 $\mu$g/L was used (65% and 93%, respectively), at the expense of lower specificity and positive predictive value (Table 3). The exclusion of patients with a final diagnosis of ACS (n = 51, 8%) did not alter the results for 90-day mortality (see online Supplemental File 3).

hs-cTnT FOR PREDICTING LONG-TERM MORTALITY

Complete 1-year follow-up data were available for 606 patients (89.3%). Of the remaining 72 patients, 70 patients had a follow-up of at least 6 months (2 patients emigrated, leaving no means of contact). At 1 year, 162 patients (24%) had died, 118 (73%) from cardiovascular causes. The 1-year mortality rate increased over the troponin categories, from 2% in the lowest category and 10% in the second category to 26% in the highest category ($P < 0.001$ for all between-group comparisons). Event rates per troponin category including initial admission rate, length of stay, and in-hospital mortality are shown in online Supplemental Table 1. hs-cTnT and cTnT were both strongly and independently associated with 1-year mortality, even after correction for clinical risk factors and after correction for clinical risk factors plus NT-proBNP and CRP (Table 2). hs-cTnT and cTnT had incremental value in predicting 1-year mortality beyond the clinical risk model according to the $c$ statistic, NRI, and IDI (Table 3). The incremental value of hs-cTnT and cTnT, when added to the clinical model, was similar to that of NT-proBNP. The combination of any 2 biomarkers did not further improve model performance (data not shown). The cutoff value of 0.016 $\mu$g/L for hs-cTnT showed a higher prognostic sensitivity (96%) and negative predictive value (98%) than when the cTnT cutoff of 0.03 $\mu$g/L was used (65% and 93%, respectively), at the expense of lower specificity and positive predictive value (Table 3). The exclusion of patients with a final diagnosis of ACS (n = 51, 8%) did not alter the results for 90-day mortality (see online Supplemental File 3).

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Table 2. Prognostic value of hs-cTnT and cTnT for 90-day and 1-year mortality.a

<table>
<thead>
<tr>
<th>Marker</th>
<th>Cutoff</th>
<th>AUC (95% CI)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>c Statistic, %</th>
<th>NRI, %</th>
<th>IDI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-cTnT</td>
<td>0.016 $\mu$g/L</td>
<td>0.753 (0.705–0.802)</td>
<td>96 (88–99)</td>
<td>29 (25–32)</td>
<td>17 (14–20)</td>
<td>98 (94–99)</td>
<td>3.1</td>
<td>12.9</td>
<td>4.2</td>
</tr>
<tr>
<td>cTnT</td>
<td>0.03 $\mu$g/L</td>
<td>0.729 (0.674–0.785)</td>
<td>65 (54–75)</td>
<td>72 (68–76)</td>
<td>26 (20–32)</td>
<td>93 (90–95)</td>
<td>3.1</td>
<td>13.7</td>
<td>4.4</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>900 pg/mL</td>
<td>0.729 (0.673–0.784)</td>
<td>94 (87–98)</td>
<td>26 (23–30)</td>
<td>16 (13–20)</td>
<td>97 (92–99)</td>
<td>2.1</td>
<td>17.1</td>
<td>3.9</td>
</tr>
</tbody>
</table>

a $c$ Statistic, NRI and IDI are measures of model discrimination and represent the additive value of single biomarkers to the clinical model.

b PPV, positive predictive value; NPV, negative predictive value.

c $P < 0.001$ vs clinical model.

d $P < 0.05$ vs clinical model.

Table 3. Predictive accuracy of hs-cTnT, cTnT, and NT-proBNP for 90-day mortality.a

<table>
<thead>
<tr>
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<th>Cutoff</th>
<th>AUC (95% CI)</th>
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<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
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c $P < 0.001$ vs clinical model.
d $P < 0.05$ vs clinical model.
lar causes. Both hs-cTnT and cTnT concentrations were independently associated with mortality over the long term (Table 2), although this association was less strong than for short-term outcome. Cumulative survival rates over time, shown in Fig. 2A, show significantly reduced survival in the second and third troponin category compared with the lowest troponin category (log-rank \( P < 0.001 \)), with 1-year mortality rates ranging from 9\% in the first category to 21\% in the second and 39\% in the third category. As shown in Table 4, the relationship between troponin and mortality was most appreciated in patients with a final diagnosis of acutely decompensated heart failure but was also present in patients with other diagnoses (e.g., inflammatory pulmonary disease, anemia, rhythm disorders). The relationship between troponin and mortality was less distinct in patients with ACS, although this was a small subset of the study population (n = 51, 8\%). In addition, exclusion of patients with a final diagnosis of ACS did not affect the long-term results for hs-cTnT and cTnT (see online Supplemental File 3), although the fully adjusted hazard ratio failed to reach significance.

hs-cTnT IN PATIENTS WITH UNDETECTABLE cTnT
Three hundred forty-seven patients (51.2\%) had undetectable cTnT concentrations (<0.01 \( \mu g/L \)) with the conventional assay (Fig. 2); hs-cTnT was detectable in most of them and increased (i.e., \( \geq 0.016 \mu g/L \)) in 180 patients (51.9\%) (Fig. 2B). Patients with increased hs-cTnT had higher mortality rates at 90-day (3/167 vs 13/180, \( P \) for trend = 0.02) and 1-year (13/167 vs 30/180, \( P \) for trend = 0.01) follow-up. Concentrations above the hs-cTnT cutoff identified patients at risk of 90-day [odds ratio (OR) 4.26, 95\% CI: 1.19–15.21, \( P = 0.026 \)] and long-term (hazard ratio 2.27, 95\% CI 1.19–

### Table 4. Kaplan–Meier event rates for 1-year all-cause mortality across troponin categories, stratified by diagnostic categories.\(^a\)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Overall, n (%)</th>
<th>Category 1 (cTnT &lt;0.03 ( \mu g/L ) and hs-cTnT &lt;0.016 ( \mu g/L ))</th>
<th>Category 2 (cTnT &lt;0.03 ( \mu g/L ) and hs-cTnT ( \geq 0.016 ) ( \mu g/L ))</th>
<th>Category 3 (cTnT ( \geq 0.03 ) ( \mu g/L ) and hs-cTnT ( \geq 0.016 ) ( \mu g/L ))</th>
<th>( P ) (log rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute decompensated HF</td>
<td>389 (51)</td>
<td>9/52 (17)</td>
<td>41/178 (23)</td>
<td>73/159 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACS</td>
<td>51 (8)</td>
<td>0/10 (0)</td>
<td>1/13 (8)</td>
<td>6/28 (21)</td>
<td>0.18</td>
</tr>
<tr>
<td>Other</td>
<td>176 (26)</td>
<td>3/55 (6)</td>
<td>10/53 (19)</td>
<td>9/30 (30)</td>
<td>0.007</td>
</tr>
<tr>
<td>Unknown</td>
<td>100 (15)</td>
<td>3/55 (6)</td>
<td>6/39 (15)</td>
<td>1/6 (17)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

\(^a\) Data are n (%). “Other” includes inflammatory pulmonary disease, rhythm/conduction disturbances, anemia, and other final diagnoses. \( P \) values are for the trend across troponin categories.
4.36, \( P = 0.013 \)) mortality (Fig. 2B) even in this group of patients with undetectable cTnT by the conventional assay. Furthermore, hs-cTnT was the only biomarker independently associated with 90-day mortality (OR 3.63, 95% CI 1.21–10.89, \( P = 0.02 \) corrected for clinical risk factors, per logarithmic unit increase) and the only biomarker with a significant prognostic accuracy for 90-day mortality (AUC 0.733, 95% CI 0.617–0.849, \( P = 0.002 \)), whereas NT-proBNP and CRP were not predictive of 90-day mortality in this subgroup. For 1-year mortality, hs-cTnT had prognostic value similar to that of NT-proBNP and CRP in this subgroup (see online Supplemental Table 2).

**Discussion**

In our cohort of 678 patients presenting with dyspnea to the emergency department, we found that (a) troponin concentrations were measurable in virtually all patients with the high-sensitivity assay in contrast to the conventional assay, (b) hs-cTnT was associated with both 90-day and 1-year mortality, independent of clinical risk factors including NT-proBNP and CRP, (c) the hs-cTnT and cTnT assays had similar prognostic value in the concentration range in which troponin T is measurable by both assays, (d) hs-cTnT had additional prognostic value beyond conventional cTnT and NT-proBNP in the concentration range in which troponin T was not detectable when using the conventional assay, and (e) the hs-cTnT cutoff of 0.016 \( \mu \)g/L enabled identification of low-risk individuals.

Our data show that hs-cTnT is a good prognostic marker in acute dyspnea, thereby confirming the results of previous studies showing that cTnT portends risk independent of diagnosis. For instance, very low troponin T concentrations measured by the high-sensitivity assay have recently been shown to be a powerful predictor of outcome in patients with ESRD (27), stable HF (13), stable coronary artery disease (14), and non–high-risk pulmonary embolism (10), even in community-dwelling populations (28, 29). This study extends these results to a more heterogeneous population with acute dyspnea seen at the emergency department. As expected, the relationship between troponin categories and mortality was most distinct in patients with acutely decompensated heart failure. Interestingly, the association between troponin and mortality was also present in the patients with other diagnoses, including inflammatory pulmonary disease and anemia. In patients with unknown cause of dyspnea, there was no consistent increase in mortality over the troponin categories. It should be mentioned, however, that both the number of events and the number of increased troponin concentrations were very low in patients with unknown causes of dyspnea, making it difficult to demonstrate an association. The relationship between troponin and mortality was less distinct in patients with ACS, which is probably due to the low number of patients with a final diagnosis of ACS (n = 51, 8%). Importantly, exclusion of patients with ACS did not alter overall results of the present study.

Acute dyspnea is one of the most common conditions encountered in the emergency department (17, 18). This is a population in which making a quick and safe risk stratification is of particular importance. Brain natriuretic peptides are currently the most widely used biomarkers for risk stratification in patients with acute dyspnea (19–21). We could confirm the excellent prognostic value of NT-proBNP in this setting. Even so, we found a prognostic performance of hs-cTnT that was overall similar to that of NT-proBNP. Moreover, hs-cTnT was associated with 90-day mortality in the 347 patients with undetectable cTnT, whereas NT-proBNP and CRP were not of short-term prognostic value in this patient group. Thus, the prognostic performance of hs-cTnT exceeded that of NT-proBNP and CRP in patients with cTnT concentrations below the detection limit by the conventional assay, which represented half of the patients in our cohort.

The hs-cTnT and cTnT assays had similar prognostic value in the range in which troponin T is measurable by both assays. This comes as no surprise, because the assays are well calibrated in this range. Therefore, the additive value of the high-sensitivity assay over the conventional assay was difficult to show in the whole patient population. Nonetheless, we were curious to learn if hs-cTnT measurement is of value in individuals with troponin T concentrations below the detection range of currently available assays. In fact, in patients with undetectable cTnT concentrations (<0.01 \( \mu \)g/L), hs-cTnT was the only biomarker predicting short-term outcome. Interestingly, hs-cTnT was increased \( \geq 0.016 \) \( \mu \)g/L in more than half of the patients with undetectable cTnT concentrations, showing the discrepancy of the assays in the low range. This discrepancy can be explained by a mismatch in the calibration between the conventional and the hs-cTnT assay at very low concentrations (11), at which the hs-cTnT assay was of added value. This is shown by the excellent prognostic sensitivity and negative predictive value of the hs-cTnT cutoff of 0.016 \( \mu \)g/L in our study. This cutoff allowed identification of patients with a low risk of 90-day and 1-year mortality. Patients with undetectable or nonincreased cTnT values according to the conventional assay, on the other hand, do not necessarily have a benign prognosis. The hs-cTnT assay enabled further prognostic stratification in the overall study population (Fig. 2A), and hs-cTnT concentrations above the cutoff identified patients at risk of 90-
hs-cTnT Assay in Acute Dyspnea

day and 1-year mortality in the subgroup of patients with undetectable cTnT (Fig. 2B). Thus, the hs-cTnT assay can help to stratify risk in patients with acute dyspnea. However, one must take into consideration that as a result of using a more sensitive assay, specificity and positive predictive value are severely reduced and overall poor (Table 3). This makes the interpretation of an increased troponin concentration difficult, because the high-sensitivity assay will give a higher rate of true-positive tests but also a higher rate of false-positive results. Still, an increased hs-cTnT concentration should raise clinical vigilance and trigger physicians to perform a thorough clinical evaluation, because patients with such values are obviously at risk. Increased troponin concentrations are known to have several etiologies (10, 13, 14, 27), and therefore, no standard or immediate treatment for an increased troponin exists. In our opinion, it is not necessary per se to admit all dyspneic patients with increased hs-cTnT concentrations, but a short-term reevaluation seems warranted. Serial measures of troponin might be of help in this regard (30), but we do not have the data to support this. On the other hand, the negative predictive value of the hs-cTnT assay is excellent in our cohort, which makes the high-sensitivity assay best used as a test for exclusion of serious pathology in the setting of acute dyspnea. This may help clinicians to quickly discharge truly low-risk patients. Still, there is an urgent need for further evaluation of the implications of using hs-cTnT for clinical decision-making in the emergency setting of dyspnea.

There were some limitations to our study. First, our study was performed in a single center emergency department and results might be different in other centers, although this is unlikely. Second, the number of patients and events was relatively small, especially in the subgroup of patients with undetectable cTnT, making multivariate analysis challenging. Nonetheless, we corrected for 7 traditional risk factors in multivariate analysis and found no influence on our results. Altogether, it will be of interest to validate our findings in another, preferably larger cohort. Also, our study did not directly assess the impact of hs-cTnT measurements on the management of patients. Therefore, the therapeutic consequences of using the hs-cTnT assay in clinical practice for stratifying patients with dyspnea need prospective evaluation.

In conclusion, cTnT concentrations measured with the hs-cTnT assay are associated with 90-day and 1-year mortality in patients presenting with acute dyspnea, independent of clinical risk factors including NT-proBNP and CRP. The high-sensitivity and the conventional cTnT assays have similar prognostic value in the range in which troponin T is measurable by both assays. hs-cTnT concentrations below the detection range of conventional cTnT assays provide additional prognostic information beyond conventional cTnT and NT-proBNP testing. In particular, regarding clinical decision making, results of hs-cTnT below the cutoff of 0.016 μg/L enable identification of low-risk patients, whereas patients with results above this cutoff have a substantial risk even if conventional cTnT is not detectable.

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