Impact of Serial Troponin Release on Outcomes in Patients With Acute Heart Failure
Analysis From the PROTECT Pilot Study

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Background—Cardiac troponin T (cTnT) elevation is common and is a predictor of outcomes in patients with acute heart failure (AHF). The degree and progression of cTnT release during hospitalization of patients with AHF is unclear. We evaluated the incidence of cTnT release during AHF hospitalization and the relationship of cTnT release with outcomes.

Methods and Results—The Placebo-controlled Randomized study of the selective A(1) adenosine receptor antagonist rolodylline for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal funcTion (PROTECT) pilot study was a multicenter, double-blind study of patients with AHF. Measurements of cTnT were collected at randomization and days 2, 3, 4, and 7. Patients were classified on the basis of their serum cTnT levels at baseline: positive (>0.03 ng/mL), detectable (>0.01 ng/mL), and negative (≤0.01 ng/mL). A detectable cTnT level developed during the study (after baseline) was classified as cTnT conversion: 288 patients were included; 172 (60%) patients had detectable cTnT levels and 97 (34%) had positive values (>0.03 ng/mL) at baseline. Of the 116 patients with negative troponin at baseline, 24 (21%) had elevated cTnT levels by day 7. On multivariable analysis, positive cTnT at baseline was an independent predictor of the composite end point of cardiovascular/renal rehospitalization or death at 60 days (hazard ratio, 1.84; 95% confidence interval, 1.04–3.26; P=0.036). Kaplan-Meier curves showed similar worse outcomes in patients with troponin conversion and positive troponin at baseline.

Conclusions—There was a high prevalence of baseline cTnT elevation in this cohort; 21% of those negative at baseline converted to detectable levels by day 7. Positive troponin at baseline, and conversion to positive levels, were associated with worse outcomes at 60 days.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00328692 and NCT00354458.

Clinical Perspective on p 732

The mechanism of troponin release in patients with HF is multifactorial. Abnormal hemodynamics with high left ventricular end-diastolic pressure and low aortic and coronary perfusion pressure, adrenergic stimulation, increased inflammatory cytokines, and excessive tachycardia due to arrhyth-
mias such as rapid atrial fibrillation may all favor myocardial ischemia, loss of cell membrane integrity, and myocardial cell death with the mechanisms of necrosis and apoptosis. Concomitant therapy with inotropic and vasodilating agents, especially when administered in combination or by use of agents that have both pharmacological effects, such as milrinone or levosimendan, may exacerbate all of these factors and lead to increased mortality. Recent data suggest that elevated troponin concentrations are a predictor of poor outcomes in patients with AHF. However, this study only assessed the role of troponin concentrations at the time of admission with respect to the prediction of in-hospital mortality. Serial measurements of troponin plasma levels during hospitalization were assessed in 2 studies to date, which demonstrated that troponin release commonly occurs and is associated with poor outcome in these clinical settings. In both studies, approximately 8–10% of patients who were negative at baseline had an elevated troponin during hospitalization. The recently conducted PROTECT pilot study tested the effects of the selective adenosine A1 receptor antagonist rolol sufficiently in patients with AHF and renal insufficiency. In the present analysis, we evaluated the magnitude and time sequence of troponin release during initial hospitalization of patients with AHF and the relationship of this troponin release with subsequent short-term outcomes.

Methods

Trial Design and Patient Population

The PROTECT pilot study was a multicenter, double-blinded study, randomly assigning patients with AHF and renal insufficiency, defined as a creatinine clearance between 20 to 80 mL/min using the Cockcroft-Gault formula, to intravenous rolol sufficiently or placebo within 24 hours of admission. The details of the design, results, and conclusions of this trial have been previously published. Eligible patients were ≥18 years of age and admitted with a primary diagnosis of AHF. A diagnosis of AHF required the following before participation in the study.

Serum Troponin T Measurements

Blood sample measurements of cardiac troponin T (cTnT) were collected at time of enrollment (day 1) and on days 2, 3, 4, and 7. Serum was stored at −7 °C and shipped to the central core laboratory for analysis. Troponin levels were measured with a commercially available high sensitivity assay (Elecsys Troponin T STAT assay, Roche Diagnostics, Indianapolis, IN).

Patients were classified based on their serum cardiac troponin T levels at baseline: positive (>0.03 ng/mL), detectable (>0.01 ng/mL), and negative (≤0.01 ng/mL). Cardiac troponin conversion was defined as going from undetectable cTnT at baseline to having any detectable level during the hospitalization.

Plasma cTnT levels were measured after completion of the study, and patients’ treatments or follow-ups were not influenced by their knowledge. Patient demographics, baseline characteristics, medical history, and medications were collected at time of random assignment.

End Points

The primary end point of the PROTECT trial was a composite trichotomous end point, designed to capture improvement of dyspnea and adverse events that occurred after admission, including worsening HF despite treatment or worsening renal function. Patient were classified as success, failure, or unchanged. Treatment success was defined as improvement in dyspnea (reported by the patient, using a 7-point Likert scale, as moderately or markedly better compared with study start) determined at 24 and 48 hours after the start of study drug and not meeting criteria for treatment failure. Treatment failure was defined as death; worsening HF, defined as physician-determined assessment (based on history, physical examination, and chart review) of worsening symptoms or signs of HF occurring >24 hours after the start of study drug to day 7 or discharge, whichever occurred first; early HF readmission (occurring within 7 days of study drug initiation); or persistent renal impairment defined as an increase in serum creatinine of ≥0.3 mg/dL at day 7 and day 14. Patients were classified as unchanged if neither criteria for success or failure were met.

In this post hoc analysis, the PROTECT primary end point was calculated on the basis of baseline cTnT level, using logistic regression with a 3-level outcome and the proportional odds assumption. We also evaluated the association of baseline cTnT level or conversion to detectable troponin T during hospitalization with the short-term end point of in-hospital worsening HF or death by day 7, based on troponin at baseline and conversion to any detectable level. Finally, we evaluated a composite of cardiovascular (CV)/renal rehospitalization or death by 60 days, based on troponin at baseline and conversion to any detectable level.

Statistical Analysis

Continuous variables with normal distribution were expressed as mean±SD and medians (25th, 75th percentile) for other continuous variables. Comparisons of demographic and clinical baseline characteristics, medical history, and medications were evaluated by the Student t test for continuous variables and the χ² test for categorical variables. Multivariate analysis for the primary end point was performed using multiple logistic regression with positive and detectable troponin T variables analyzed as dichotomous variables. The model was adjusted for baseline clinical and laboratory characteristics. For the clinical end points, models were developed using candidate sets of predictor variables for possible model inclusion. The candidate variables represented a broad range of characteristics, which were classified as baseline characteristics, medical history, and laboratory values. A Cox proportional hazards backward selection algorithm was applied using a nominal 0.25 critical value for model inclusion. A candidate predictor was included in the model if it met the 0.25 critical significance value.

All reported probability values are 2-sided, and a probability value <0.05 was considered statistically significant.

The present study was conducted according to the principles stated in the Declaration of Helsinki. The study protocol was approved by the ethics committee and institutional review boards for each participating site, and all patients signed the informed consent form before participation in the study.

Results

Patient Population

Of 301 patients enrolled in the PROTECT pilot study, 288 had troponin T levels evaluable for inclusion into this study. There were no clinically important differences in the baseline characteristics of the excluded patients. The demographics and baseline characteristics of the population are shown in Table 1. The mean age of the overall cohort was 70.6 years, and 59% were male. The clinical profile of the patients was similar to large acute HF registries. Most patients received optimal medical treatment, as recommended by international guidelines, before hospitalization.
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=288)</th>
<th>Negative, (\leq 0.01) ng/mL (n=116)</th>
<th>Detectable, (&gt; 0.01) ng/mL (n=172*)</th>
<th>Positive, (&gt; 0.03) ng/mL (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (25th, 75th), y</td>
<td>73.00 (65.00, 77.50)</td>
<td>74.00 (65.00, 78.00)</td>
<td>71.00 (64.00, 77.00)</td>
<td>71.00 (63.00, 77.00)</td>
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<td>Male</td>
<td>171 (59.38)</td>
<td>59 (50.86)</td>
<td>112 (65.12)</td>
<td>67 (69.07)</td>
</tr>
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<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
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<td>2 (2.22)</td>
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<tr>
<td>2</td>
<td>43 (15.75)</td>
<td>13 (11.93)</td>
<td>30 (18.29)</td>
<td>17 (18.89)</td>
</tr>
<tr>
<td>3</td>
<td>114 (41.76)</td>
<td>44 (40.37)</td>
<td>70 (42.68)</td>
<td>35 (38.89)</td>
</tr>
<tr>
<td>4</td>
<td>110 (40.29)</td>
<td>49 (44.95)</td>
<td>61 (37.20)</td>
<td>36 (40.00)</td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>211 (73.78)</td>
<td>87 (75.00)</td>
<td>124 (72.94)</td>
<td>64 (67.37)</td>
</tr>
<tr>
<td>History of MI</td>
<td>157 (54.51)</td>
<td>62 (53.45)</td>
<td>95 (55.23)</td>
<td>44 (45.36)</td>
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<tr>
<td>History of hypertension</td>
<td>237 (82.29)</td>
<td>98 (84.48)</td>
<td>139 (80.81)</td>
<td>75 (77.32)</td>
</tr>
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<td>History of diabetes</td>
<td>150 (52.08)</td>
<td>47 (40.52)</td>
<td>103 (59.88)</td>
<td>60 (61.86)</td>
</tr>
<tr>
<td>History of AF/flutter</td>
<td>133 (46.34)</td>
<td>62 (53.91)</td>
<td>71 (41.28)</td>
<td>33 (34.02)</td>
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<tr>
<td>Day 1 creatinine, mean±SD, mg/dL</td>
<td>1.53±0.659</td>
<td>1.23±0.406</td>
<td>1.72±0.719</td>
<td>1.79±0.728</td>
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<tr>
<td>CrCl, mean±SD, mL/min</td>
<td>57.16±26.36</td>
<td>64.31±27.29</td>
<td>52.37±24.665</td>
<td>50.91±24.839</td>
</tr>
<tr>
<td>Median (25th, 75th)</td>
<td>52.43±38.02, 72.42</td>
<td>62.11±46.25, 77.83</td>
<td>47.84±35.24, 66.85</td>
<td>46.27±32.99, 62.20</td>
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<tr>
<td>Screening BNP, mean±SD, pg/mL</td>
<td>1527.1±1469.13</td>
<td>955.17±858.422</td>
<td>1746.3±1596.42</td>
<td>1842.4±1899.17</td>
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<tr>
<td>Screening NT proBNP, mean±SD, pg/mL</td>
<td>4009.4±5069.87</td>
<td>2693.0±1590.06</td>
<td>5104.4±6520.18</td>
<td>4904.9±6625.14</td>
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<td>BMI, median (25th, 75th), kg/m²</td>
<td>28.86±(25.52, 33.10)</td>
<td>29.20±(25.51, 32.82)</td>
<td>28.85±(25.55, 33.21)</td>
<td>28.73±(25.47, 32.67)</td>
</tr>
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<td>History of ICD</td>
<td>49 (17.01)</td>
<td>17 (14.66)</td>
<td>32 (18.60)</td>
<td>13 (14.40)</td>
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<tr>
<td>History of pacemaker</td>
<td>33 (11.46)</td>
<td>16 (13.79)</td>
<td>17 (9.98)</td>
<td>8 (8.52)</td>
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<tr>
<td>ACE inhibitor at admission</td>
<td>165 (57.49)</td>
<td>75 (65.22)</td>
<td>90 (52.33)</td>
<td>50 (51.55)</td>
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<tr>
<td>ARB at admission</td>
<td>37 (13.07)</td>
<td>17 (15.04)</td>
<td>20 (11.76)</td>
<td>8 (8.25)</td>
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<tr>
<td>Aldosterone antagonist at admission</td>
<td>98 (34.63)</td>
<td>41 (35.96)</td>
<td>57 (33.73)</td>
<td>29 (29.90)</td>
</tr>
<tr>
<td>Hydralazine/oral nitrate combination at admission</td>
<td>10 (3.51)</td>
<td>0 (0.00)</td>
<td>10 (5.88)</td>
<td>6 (6.19)</td>
</tr>
<tr>
<td>Intravenous nitrates at admission</td>
<td>33 (11.56)</td>
<td>15 (13.04)</td>
<td>18 (10.59)</td>
<td>11 (11.34)</td>
</tr>
<tr>
<td>Digoxin at admission</td>
<td>75 (26.60)</td>
<td>31 (27.19)</td>
<td>44 (26.19)</td>
<td>23 (24.21)</td>
</tr>
<tr>
<td>Baseline sodium, mean±SD, mEq/L</td>
<td>138.98±4.31</td>
<td>139.98±3.62</td>
<td>138.31±4.61</td>
<td>137.92±5.11</td>
</tr>
<tr>
<td>Median (25th, 75th)</td>
<td>140.00±(137.00, 142.00)</td>
<td>140.00±(138.00, 142.00)</td>
<td>139.00±(136.00, 141.00)</td>
<td>138.00±(135.00, 142.00)</td>
</tr>
<tr>
<td>Baseline hemoglobin, mean±SD, g/dL</td>
<td>12.78±1.98</td>
<td>13.16±1.99</td>
<td>12.53±1.94</td>
<td>12.18±1.77</td>
</tr>
<tr>
<td>Median (25th, 75th)</td>
<td>12.60±(11.50, 14.30)</td>
<td>13.20±(11.80, 14.50)</td>
<td>12.40±(11.10, 13.90)</td>
<td>12.10±(10.95, 13.20)</td>
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<tr>
<td>Baseline BUN, mean±SD, mg/dL</td>
<td>32.87±17.01</td>
<td>25.59±11.78</td>
<td>37.73±18.22</td>
<td>41.26±19.35</td>
</tr>
<tr>
<td>Median (25th, 75th)</td>
<td>28.00±(20.00, 40.00)</td>
<td>21.50±(17.00, 31.00)</td>
<td>34.00±(24.00, 48.00)</td>
<td>37.00±(26.00, 55.00)</td>
</tr>
<tr>
<td>Systolic blood pressure, median (25th, 75th), mm Hg</td>
<td>130.00±(110.00, 140.00)</td>
<td>130.00±(111.00, 145.00)</td>
<td>128.00±(110.00, 140.00)</td>
<td>126.00±(110.00, 140.00)</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>127.04±15.61</td>
<td>129.32±15.17</td>
<td>125.51±18.57</td>
<td>124.19±15.95</td>
</tr>
<tr>
<td>Heart rate, median (25th, 75th), bpm</td>
<td>78.00±(68.00, 90.00)</td>
<td>75.50±(65.50, 90.00)</td>
<td>80.00±(70.00, 90.00)</td>
<td>78.00±(70.00, 90.00)</td>
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<tr>
<td>Mean±SD</td>
<td>79.82±15.61</td>
<td>78.95±17.16</td>
<td>80.41±14.49</td>
<td>80.52±14.86</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; bpm, beats per minute; BUN, blood urea nitrogen; CrCl, creatinine clearance; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; and NYHA, New York Heart Association.

*Includes group of patients positive (>0.03) at baseline. Values are presented as n (%) unless otherwise indicated.

Prevalence of Troponin Release

One hundred seventy-two (60%) patients had detectable (>0.01 ng/mL) cTnT levels, and 97 (34%) patients had positive values of cTnT (>0.03 ng/mL) at baseline. By day 7, 196 patients (68%) had detectable troponin T, and 92 (32%) remained negative.

Of the 116 patients with negative troponin T at baseline, 24 (21%) had a detectable cTnT level >0.01 ng/mL by day 7.
The characteristics of those who were converters and those who did not convert are shown in Table 2. There were no important differences in clinical characteristics between those who converted to any detectable levels of troponin T by day 7 compared with those who remained negative, except that patients with detectable troponin T by day 7 were more often diabetic ($P=0.046$) and more often had an automatic implantable cardioverter-defibrillator without recent firing ($P=0.02$). Of note, no patient with detectable cTnT at baseline dropped to having undetectable levels after baseline.

<table>
<thead>
<tr>
<th>Table 2. Clinical Characteristics of Converters</th>
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<tbody>
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<td></td>
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<tr>
<td>Age, median (25th, 75th), y</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>NYHA class</td>
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<tr>
<td>1</td>
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<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
</tr>
<tr>
<td>History of MI</td>
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<tr>
<td>History of hypertension</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
</tr>
<tr>
<td>Day 1 creatinine value, median (25th, 75th)</td>
</tr>
<tr>
<td>CrCl (calculated), median (25th, 75th)</td>
</tr>
<tr>
<td>Screening BNP, median (25th, 75th), pg/mL</td>
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<tr>
<td>Screening NT proBNP, median (25th, 75th), pg/mL</td>
</tr>
<tr>
<td>BMI, median (25th, 75th), kg/m²</td>
</tr>
<tr>
<td>History of AICD</td>
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<tr>
<td>History of pacemaker</td>
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<tr>
<td>ACE inhibitor at admission</td>
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<tr>
<td>ARB at admission</td>
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<tr>
<td>ß-Blocker at admission</td>
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<td>Aldosterone antagonist at admission</td>
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<td>Hydralazine/oral nitrate combination at admission</td>
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<tr>
<td>Intravenous nitrates at admission</td>
</tr>
<tr>
<td>Digoxin at admission</td>
</tr>
<tr>
<td>Sodium, median (25th, 75th), mg/dL</td>
</tr>
<tr>
<td>HGB, median (25th, 75th), g/dL</td>
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<tr>
<td>BUN, median (25th, 75th), mg/dL</td>
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<td>Systolic BP, median (25th, 75th), mm Hg</td>
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<td>Pulse, median (25th, 75th), bpm</td>
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<tr>
<td>Randomized treatment</td>
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<tr>
<td>Rolofylline, 10 mg</td>
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<tr>
<td>Rolofylline, 20 mg</td>
</tr>
<tr>
<td>Rolofylline, 30 mg</td>
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</table>

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; AICD, automatic implantable cardioverter-defibrillator; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CrCl, creatinine clearance; HGB, hemoglobin; MI, myocardial infarction; and NYHA, New York Heart Association.

*Conversion to any detectable troponin by day 7.
†Comparison between converters and negative troponin at day 7.

Values presented as n (%) unless otherwise indicated.
There was no difference in worsening of creatinine clearance by day 7 in the converter group and no propensity of converters to have worse renal function. Additionally, we examined patients with coronary artery disease as a subset of interest, defined as patients with a history of myocardial infarction, coronary artery bypass surgery, or percutaneous coronary intervention. There was no difference in the incidence of troponin T release, conversion, or outcomes in this subset of patients compared with the overall study cohort.

There was no statistical evidence that rolofylline was associated with an increased risk of troponin T release compared with placebo. Although the numbers were small, the number of converters decreased as the dose of rolofylline increased, a finding that contradicts evidence suggesting adenosine A1 receptor stimulation is cardioprotective.24

Outcomes

Composite Trichotomous End Point

In patients with either detectable troponin T or positive troponin T at baseline, there was no difference in the results observed for the trichotomous end point (Tables 3 and 4) compared with patients who were negative at baseline. Those patients who had positive troponin T levels at baseline or converted to any detectable level of troponin T were more often treatment failures and less often had treatment success (Table 5).

Short-Term End Point

On univariable analysis, any detectable troponin T at baseline was associated with a nearly 3-fold (hazard ratio [HR], 2.94;
increase in the risk of the short-term outcome of death or in-hospital worsening HF by day 7 (Table 3). Positive troponin T at baseline conferred a doubling risk of this end point, which occurred in 14% of patients with positive troponin T compared with 6% of patients with troponin T \( < 0.03 \) ng/mL at baseline (HR, 2.4; \( P = 0.03 \); Table 4).

On multivariable analysis, both detectable and positive troponin T at baseline indicated a greater risk for the short-term end point compared with those who were negative, but this difference did not achieve statistical significance (Table 6).

Those who converted to any detectable level of troponin T did not appear to have an increased risk of in-hospital mortality or worsening HF compared with those who were negative at baseline (\( P = 0.29 \)).

**CV/Renal Rehospitalization or Death at 60 Days**

On univariable analysis, detectable troponin T (\( > 0.01 \) ng/mL) at baseline conferred a doubling of the risk (HR, 2.01; \( P = 0.005 \)) for the composite end point of CV/renal rehospitalization or death at 60 days, compared with patients with negative troponin T at baseline. In particular, these patients had a 3.5-fold increased risk of death at 60 days (\( P = 0.023 \)). Likewise, positive troponin T at baseline was associated with a doubling of the risk for cardiovascular/renal hospitalization or death at 60 days (HR, 2.19; \( P < 0.001 \)), with a 4-fold increased risk of death at 60 days (HR, 4.25; \( P = 0.001 \)).

On multivariable analysis, positive levels of cardiac troponin T at baseline were confirmed to be an independent predictor of the composite end point of CV/renal rehospitalization or death at 60 days (HR, 1.84; 95% confidence interval [CI], 1.04–3.26; \( P = 0.036 \)), whereas detectable troponin T at baseline was not associated with a statistically significant increase in risk for this end point (HR, 1.23; 95% CI, 0.64–2.35; \( P = 0.54 \), Table 7). In the group that converted to any detectable troponin T, there was a higher incidence of the composite end point compared with those who remained negative throughout hospitalization (33% versus 13%, \( P = 0.019 \)), which was similar to those who were detectable at baseline (33%).

Kaplan-Meier curves showed similar worse outcomes in patients with troponin T conversion and positive troponin T levels at baseline, compared with those who were negative (Figures 1 and 2).

**Discussion**

To our knowledge, this study represents the largest cohort to date of AHF patients in which serial troponin T levels were correlated with outcomes. This analysis confirms that troponin T elevation at baseline is common in patients with AHF and mild-to-moderate renal dysfunction and is related to poor

### Table 5. Outcomes by Troponin T Conversion

<table>
<thead>
<tr>
<th>Troponin T</th>
<th>Total (n=288)</th>
<th>All Negative (n=92)</th>
<th>Converter* (n=24)</th>
<th>Detectable at Baseline (n=172)</th>
<th>( P ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Success</td>
<td>129 (44.79)</td>
<td>46 (50.00)</td>
<td>8 (33.33)</td>
<td>75 (43.60)</td>
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</tr>
<tr>
<td>Unchanged</td>
<td>97 (33.68)</td>
<td>36 (39.13)</td>
<td>9 (37.50)</td>
<td>52 (30.23)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>62 (21.53)</td>
<td>10 (10.87)</td>
<td>7 (29.17)</td>
<td>45 (26.16)</td>
<td></td>
</tr>
<tr>
<td>Day 60 CV/renal rehospitalization or death</td>
<td>76 (26.39)</td>
<td>12 (13.04)</td>
<td>8 (33.33)</td>
<td>56 (32.56)</td>
<td>0.02</td>
</tr>
<tr>
<td>In-hospital (up to day 7) worsening HF or death</td>
<td>26 (9.03)</td>
<td>3 (3.26)</td>
<td>2 (8.33)</td>
<td>21 (12.21)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

*Baseline, \( P < 0.01 \); after baseline, \( P > 0.01 \). †\( P \) value for converter versus negative troponin.

Values are presented as n (%) unless otherwise indicated.

**Table 6. In-Hospital (Up to Day 7) Worsening HF or Death: Multivariable Analysis**

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>( P ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline troponin &gt;0.01*</td>
<td>2.63 (0.84, 8.22)</td>
<td>0.10</td>
</tr>
<tr>
<td>Baseline troponin &gt;0.03*</td>
<td>1.96 (0.71, 5.45)</td>
<td>0.20</td>
</tr>
<tr>
<td>Age of subject</td>
<td>1.02 (0.97, 1.08)</td>
<td>0.45</td>
</tr>
<tr>
<td>Male</td>
<td>1.52 (0.50, 4.62)</td>
<td>0.46</td>
</tr>
<tr>
<td>Baseline weight</td>
<td>1.02 (0.99, 1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>3.16 (0.64, 15.67)</td>
<td>0.16</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.85 (0.31, 2.38)</td>
<td>0.76</td>
</tr>
<tr>
<td>History of asthma, bronchitis, or COPD</td>
<td>2.48 (1.04, 5.94)</td>
<td>0.04</td>
</tr>
<tr>
<td>History of AF/flutter</td>
<td>0.59 (0.23, 1.53)</td>
<td>0.28</td>
</tr>
<tr>
<td>History of stroke, beyond 2 y</td>
<td>0.52 (0.07, 4.13)</td>
<td>0.53</td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>1.37 (0.47, 4.01)</td>
<td>0.56</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.98 (0.95, 1.01)</td>
<td>0.16</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.02 (0.98, 1.05)</td>
<td>0.35</td>
</tr>
<tr>
<td>Screening BNP &gt;500 or NT proBNP &gt;2000</td>
<td>1.10 (0.35, 3.43)</td>
<td>0.87</td>
</tr>
<tr>
<td>BUN</td>
<td>1.03 (1.00, 1.06)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.97 (0.76, 1.28)</td>
<td>0.91</td>
</tr>
<tr>
<td>Sodium</td>
<td>1.09 (0.97, 1.24)</td>
<td>0.15</td>
</tr>
<tr>
<td>Day 1 creatinine value</td>
<td>0.24 (0.06, 0.95)</td>
<td>0.04</td>
</tr>
<tr>
<td>Randomized treatment†</td>
<td>1.00 (0.65, 1.54)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

†Relative to negative troponin group. Models were run separately with “baseline troponin >0.01” and “baseline troponin >0.03.” Because results for other variables were very similar in the 2 models, only those for the model with “baseline troponin >0.01” are presented.

†Linear dose trend in the order of placebo, 10 mg, 20 mg, and 40 mg.
prognosis. Univariate analysis showed the same high event rates in patients with positive and detectable cardiac troponin T levels at baseline. In multivariate analysis, only positive troponin T level was an independent predictor of mortality or CV/renal rehospitalization at 60 days. Conversion to detectable levels during hospitalization was also associated with statistically significant higher event rates at 60 days.

There are several important findings of this analysis. First, there was a high prevalence (60%) of baseline troponin T elevation in this cohort. The reported prevalence has varied widely in other trials and registries; however, direct comparisons are difficult due to differences in the population being studied, different cutoff values, and variation in the assay used.

Second, 8% of the total cohort of patients (21% of those who were negative at baseline) converted to detectable levels of troponin T by day 7 of hospitalization. Finally, positive troponin T at baseline, and conversion to positive levels, were associated with worse outcomes at 60 days.

Cardiac troponin T is a marker of myocardial injury and the prognostic significance of elevated troponin levels in the evaluation and risk stratification of patients with AHF has been demonstrated.7,11,17,26,27 Several studies have shown that the release of troponin T is a predictor of short- and long-term prognosis in patients with AHF.28–32 In 84 872 subjects randomized to AHF, Peacock et al analyzed in-hospital outcomes and reported that a positive cardiac troponin was associated with greater in-hospital mortality (95% CI, 2.24–2.89; P<0.001), a longer hospitalization, and greater use of resources.7 In a large cohort of patients with stable chronic HF from the Valsartan Heart Failure Trial (Val-HeFT), detectable cardiac troponin T (>0.001 ng/mL) was found in 10.4% of 4053 patients and was associated with death (HR, 2.08; 95% CI, 1.72–2.52; P<0.001) and first hospitalization for HF (HR, 1.55; 95% CI, 1.25–1.93; P<0.001).8 Other studies in stable outpatients with HF have shown a significant association between elevated levels of troponin and outcomes.29

Of note is that there appeared to be similar risk of major cardiac events between converters and the patients with positive troponin T levels at baseline group. These elevations probably reflect ongoing injury after admission.

Our results suggest that postadmission cTnT measurements in addition to baseline measurements may be useful in understanding patients who have an unfavorable hospital course, particularly when those patients are initially troponin negative. The association between troponin T release and subsequent outcome suggests that myocardial injury occurs at some point during the hospitalization. Our study confirmed that the presence of troponin T at baseline and the persistent release of troponin T are correlated with a poor outcome.

Previous studies have shown the magnitude of troponin elevation is correlated with the severity of HF and worse outcomes.8,27–30 Indeed, in our study the magnitude of troponin T at baseline predicted worse long-term outcomes. This evidence also suggests that a single measurement of cardiac...
troponin T at baseline is a strong predictor of risk for all-cause mortality and cardiovascular events, specifically worsening of HF.

Clinical Implications

Our study confirms that patients who present with positive troponin T levels at baseline may have a worse prognosis. Serial measurements may identify additional patients who may be at risk. Troponin may be an emerging biomarker useful for assessing safety and efficacy of HF therapies, and the finding that serial troponin release occurs throughout the hospitalization may provide a target for novel therapeutics to mitigate the risk of morbidity and mortality. Our findings suggest that myocardial injury is a frequent event in AHF patients and the release of troponin, particularly as it relates to current treatments and investigational therapies, should be examined. It is yet to be seen whether the greater sensitivity of new troponin assays will afford greater clinical utility in predicting outcomes, given the fact that >90% of acute decompensated HF (ADHF) patients have detectable troponin on these new assays.

Limitations

Our study was limited by the relatively modest number of patients, short follow-up period, and modest number of events. The small subgroup of patients with conversion from negative to positive troponin T after admission is of particular interest, but the association with poorer subsequent outcomes must be viewed as hypothesis-generating rather than conclusive. In addition, the analysis was carried out as a post hoc evaluation from the PROTECT pilot, of which the primary objective was to evaluate the effects of rolofylline on outcome in AHF with renal impairment. There could be a risk of overfitting the model, as the number of variables in the model was based on the primary end point of the trial. Our findings should be interpreted in the context of these limitations.

Conclusion

Our study confirms that troponin release is common in patients with AHF and cardiorenal impairment and that myocardial injury may continue to occur throughout hospitalization. In addition, our data show that positive troponin T at baseline is associated with worse outcomes at 60 days and conversion to any detectable level of troponin T may increase 60-day risk to the same extent as positive troponin T at baseline. These findings suggest that serial troponin measurements may be useful in assessing the safety and efficacy of existing and investigational therapies for AHF. Further prospective research is necessary to confirm these observations.

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Disclosures

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References

Heart failure continues to be a major health burden, with a high incidence of acute hospital admission. One of the limitations of broad-based therapies in the patients with acute decompensated heart failure is the heterogeneity of patients presenting with this syndrome. Traditional risk factor prediction models have only limited accuracy in this population to identify those at highest risk for worsening outcomes. A growing body of evidence suggests that measurement of troponin levels proves an accurate predictor of deterioration in heart failure. However, few studies have looked at the serial trend of troponin release in these patients. In our study, we evaluated the incidence of troponin release during heart failure hospitalization and the relationship of troponin release with outcomes. Serial measurements were used to determine whether patients who had a conversion from a troponin negative measurement to a detectable level had adverse outcomes similar to those presenting with an elevation of troponin at baseline. Measurements were collected at randomization and days 2, 3, 4, and 7. The study included 288 patients and showed a high incidence of baseline cardiac troponin T elevation in this cohort; 21% of those negative at baseline converted to detectable levels by day 7. Positive troponin at baseline and conversion to positive levels were associated with worse outcomes at 60 days. Thus, the findings from this study suggest that serial measurements of troponin should be considered in the evaluation of patients with acute decompensated heart failure and that these findings should be confirmed in a large, prospective study.
Impact of Serial Troponin Release on Outcomes in Patients With Acute Heart Failure: Analysis From the PROTECT Pilot Study

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